Gene 698 (2019) 179–185

Contents lists available at ScienceDirect

Gene

journal homepage: www.elsevier.com/locate/gene

Research paper

The effect of ginger supplementation on some immunity and inflammation intermediate genes expression in patients with active Rheumatoid Arthritis

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ARTICLE INFO

Keywords:
Ginger
Immunity
Inflammation
Rheumatoid Arthritis
Zingiber officinale Roscoe

ABSTRACT

Objective: Rheumatoid Arthritis (RA) is an autoimmune disease. The aim of this study was to investigate the effect of ginger supplementation on the expression of some immunity and inflammation intermediate genes in patients who suffer from RA.

Methods: In this randomized double-blind placebo-controlled clinical trial, seventy active RA patients were allocated randomly into two groups who either received 1500 mg ginger powder or placebo daily for 12 weeks. Disease activity score and gene expression of NF-κB, PPAR-γ, FoxP3, T-bet, GATA-3, and RORγt as immunity and inflammation intermediate factors were measured using quantitative real-time PCR before and after the intervention.

Results: After the intervention, FoxP3 genes expression increased significantly within ginger group and between the two groups (P-value = 0.02). Besides, T-bet and RORγt genes expression decreased significantly between the two groups (P-value < 0.05). In ginger group, PPAR-γ genes expression increased significantly (P-value = 0.047) but the difference between the two groups wasn't statistically significant (P-value = 0.12). The reduction in disease activity score was statistically significant within ginger group and between the two groups after the intervention.

Conclusion: It seems that ginger can improve RA by decreasing disease manifestations via increasing FoxP3 genes expression and by decreasing RORγt and T-bet genes expression.

1. Introduction

Rheumatoid Arthritis is an autoimmune-inflammatory disease that causes proliferation of synovial tissue and destructive lesions in joint cartilage and bone. The disease is caused by both genetic and environmental factors, with a prevalence of 0.33% to 2% around the world. In Iran, the prevalence of the disease is 0.33%, which is higher than other autoimmune disorders (Davatchi et al., 2008).

It is evident that the severity of illness and pain are closely associated with inflammation and oxidative stress (Fauci et al., 2008). Autoimmunity and activation of the innate immune system are in synergy for disease progression (Boissier et al., 2012). An imbalance

Abbreviations: ACR, American College of Rheumatology; APC, antigen presenting cell; cDNA, complementary DNA; CRP, C - reactive protein; DAS 28, Disease Activity Score 28; ESR, erythrocyte sedimentation rate in mm/first hour; FDA, Food and Drug Administration RA, Rheumatoid Arthritis; FoxP3, forkhead box P3; GATA-3, GATA binding protein 3; GH, general health or patient's global assessment of disease; IPAQ, International Physical Activity Questionnaire; MMPs, matrix metallo proteinases; MCP-1, monocyte chemo-attractant protein-1; NCCAM, National Center for Complementary and Alternative Medicine; NF-κB, nuclear factor-kappa-light-chain-enhancer of activated B cells; NK cells, natural killer cells; NO, nitric oxide; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E2; PPAR-γ, peroxisome proliferator-activated receptor-gamma; RORγt, RAR-related orphan receptor γt; ROS, reactive oxygen species; RAI, number of painful joints calculated with the Ritchie Articular Index; RANTES, regulated on activation, normal T cell expressed and secreted; STAT, signal transducer and activator of transcription; Swollen, number of swollen joints from 44 joints; sw28, number of swollen joints from 28 joints; T-bet, T-box transcription factor TBX; Th, T helper; TNF-α, tumor necrosis factor-alpha; Treg, regulatory T cells; t28, number of painful joints from 28 joints

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https://doi.org/10.1016/j.gene.2019.01.048
Received 11 November 2018; Received in revised form 30 December 2018; Accepted 22 January 2019
Available online 04 March 2019
0378-1119/

between Th1 and Th2 cells activity ratio, increased Th17 cells activity and increased level of cytokines secreted from Th0 or Th1 in peripheral blood and joint tissue have been observed in patients who suffer from active rheumatoid arthritis (Feldmann and Maini, 2008; Kawashima and Miossec, 2005). The elevation in the serum levels of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), IL-1β, and IL-6 is evident in active RA patients and thus some of immune system factors, including nuclear factor- kappa-B (NF-κB), peroxisome proliferator-activated receptor-gamma (PPAR-γ), forkhead box P3 (FoxP3), T-box transcription factor TBX (T-bet), GATA binding protein 3(GATA-3), and RAR-related orphan receptor γt (RORγt), are changed in RA patients (Boissier et al., 2012). High level of inflammatory cytokines is due to the increased NF-κB pathway activity (Feldmann and Maini, 2008). PPAR-γ is expressed in most human tissues. It is known as an important immune marker that inhibits the production of matrix metallo proteinases (MMPs), inflammatory cytokines, and reactive oxygen species (ROS). It also prevents the pro-inflammatory gene expression (Shahin et al., 2011).

RA is characterized by a significant increase in Th1 phenotype, which plays a major role in inflammation, with overproduction of IFN-γ and inadequate production of Th2 cytokines such as IL-4, IL-5 and IL-13. The over production of Th1 results from the expression of transcription factors such as T-bet and signal transducer and activator of transcription 4 (STAT4) (Boissier et al., 2012), that are essential for production of IFN-γ and induction of Th1 production (Feldmann and Maini, 2008) and inhibition of Th2 differentiation (Kawashima and Miossec, 2005), whereas the Th2 phenotype results from the expression of STAT6 and GATA3 that regulate Th2 cytokines gene expression (Boissier et al., 2012; Kawashima and Miossec, 2005).

Several studies have shown that Th17 cells play pro-inflammatory roles in cancer and autoimmune diseases. The differentiation of naive T cells to Th17 depends on the nuclear transcription factor RORγt (Boissier et al., 2012). RORγt is required for the induction of transcription of IL-17, and Th17 related autoimmune disease in mice (Huh and Littman, 2012). IL-17 induces the expression of inflammatory cytokines IL-1, IL-6, and TNF-α, inducible nitric oxide (NO) synthase, metalloproteinases, and chemokines and thus increases RA development (Boissier et al., 2012).

Regulatory T cells (Treg) are essential for the modulation of Th1/Th2 ratio and the activity of Th17, and innate immunity (Nazari et al., 2013). Tregs express the transcription factor FoxP3. It was shown that Treg function decreases during RA progression, thereby FoxP3 expression reduces. The decreased level of FoxP3 affects the ability of Treg cells to suppress effector T-cell proliferation and cytokine secretion (Boissier et al., 2009).

Ginger, "*Zingiber officinale* Roscoe" is a medicinal plant from Zingiberaceae family. To date, > 40 antioxidants have been isolated from ginger rhizome. The major pharmacological activity of ginger is related to its phenolic ingredients such as gingerols and shogaols (Feldmann and Maini, 2008). These compounds have anti-emetic, anti-fever, anti-cough, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, and anti-cancer properties (Ali et al., 2008; Aryaeian and Tavakkoli, 2015).Ginger is known as a traditional treatment for relieving stiffness and pain in patients with osteoarthritis (Manusirivithaya et al., 2004). Ginger is a safe ingredient and is well tolerated in doses up to 2 g daily (Gregory et al., 2008).

However, there is insufficient evidence for the efficacy of ginger in the treatment of RA. According to the American National Institute of Health, the National Center for Complementary and Alternative Medicine (NCCAM), and the Food and Drug Administration (FDA) (2012) to date, there has been no sufficient evidence and clinical trials to determine the effect of ginger on patients with rheumatoid arthritis, osteoarthritis, and other muscular and joint pains (Blog RL, n.d.).

Due to the pivotal role of the mentioned immunity factors on the progression and development of RA and also because to the best of our knowledge, there is no study regarding the effect of ginger on inflammatory and immunity markers expression in active RA patients, the present study was conducted to investigate the effect of ginger supplementation on NF-κB, PPAR-γ, FoxP3, T-bet, GATA-3, and RORγt genes expression in active RA patients.

2. Methods and materials

2.1. Study design

The present study was a randomized double blind placebo-controlled clinical trial that was approved by the medical ethics committee of Iran University of Medical Sciences. The mentioned committee confirms to the provision of Helsinki in 1995 (as revised in 2000) and recorded by the identification code of IRCT201403109472N6 in clinical trials registry of Iran. A written informed consent was obtained from all the participants, at the beginning of the study.

2.2. Study population and intervention

This study is a double blind, placebo-controlled clinical trial that was conducted during 25 months. Participants of the study were seventy 19–69 year-old active RA patients, referred to the Rheumatology Research Center, Shariati Hospital and diagnosed as active rheumatoid arthritis patients based on American College of Rheumatology (ACR) criteria, (Neogi et al., 2010). Other inclusion criteria were at least two years of disease duration, being under treatment with disease modifying anti-rheumatic drugs (DMARDs: Methotrexate, Hydroxychloroquine and Prednisolone < 10 mg/day), and not receiving anti-inflammatory drugs (NSAIDs) as far as possible.

The exclusion criteria were the history of myocardial infarction, hyperlipidemia, abnormal renal or hepatic function, taking vitamins and/or mineral supplements and drugs such as thyroid hormones, anti-hypertensive drugs, contraceptives, diuretics, and β-blockers, and also alcohol use, smoking, pregnancy, and lactation.

A written informed consent was obtained from all the participants. The participants were asked not to alter their usual diet, physical activity, and prescribed drugs throughout the study. Data on their dietary habits, dietary supplements, smoking, and drug history were obtained by conducting interview.

The patients were assigned randomly into two groups to receive either ginger or placebo. Ginger prescribed 1500 mg daily as 2 capsules (each containing 750 mg of ginger powder). Placebos, containing wheat flour were produced in similar shape, size, smell, and color. Placebo groups received similar capsules contained of fried wheat powder that had served two weeks in Ginger powder box for getting Ginger smell.

The intervention period was 12 weeks and started after the patients were divided randomly into two groups to receive either Ginger or placebo. The method of assigning patients to groups was by using random numbers; if the number was even, the person was in group A and the next would be in group B, and conversely. None of the patients, as well as the researcher, was aware of the group in which the patients were assigned to and the type of intervention received (ginger or placebo supplements). The codes were stored in the database of the pharmacist and were broken after the completion of the study and the statistical analysis.

Compliance was estimated by intake of > 90% of the supplements throughout the study. Patients were checked regularly by contacting them and reminding them to consume the supplement. Dose of drugs were obtained from patients medical records.

2.3. Analytical procedures

Body weight was measured in fasting state with light clothing and without shoes, using Seca scale (Seca, Hamburg, Germany), and height was measured without shoes using a Stadiometer attached to the scale. BMI was calculated by dividing the weight in kilogram by the square of

height in meter. Dietary intakes were estimated using 24-hour dietary recall questionnaire for three consecutive days (two weekdays and a weekend day), before and after the intervention. The intakes were analyzed using USA Food Processor (version 4). Physical activity was evaluated by validated International Physical Activity Questionnaire (IPAQ).

The disease activity score-28 (DAS28-ESR) was measured by a rheumatologist concerning information from swollen joints, tender joints, acute phase response and patient self-report of general health of 28 joints (van Riel and Fransen, 2005). ESR was measured using Convergent apparatus Westergren method (van Riel and Fransen, 2005).

2.4. Quantitative real-time PCR analysis

To assay gene expression, 15 ml heparinized blood was obtained and plasma was isolated using a centrifuge. Then, peripheral blood mononuclear cells (PBMC) were separated using a standard protocol (Schmittgen and Livak, 2008), at baseline and the end. The expression of PPARγ and other mentioned genes were measured in PBMC.

First, total RNA was isolated using High Pure RNA Isolation Kit (Roche, Nutley, NJ) according to the instructions of the manufacturer. Then complementary DNA (cDNA) was synthesized from 1 μg of total RNA using the Revert Aid First Strand cDNA Synthesis Kit (Thermo scientific, Wilmington, DE). NanoDrop 2000c (Thermo scientific) was used to quantify the concentrations of cDNA. The relative expression levels of mRNA were measured by SYBR Green Takara gene expression master mix. The values were expressed as the difference in Ct values normalized to β2-microglobulin for each sample, using the following formula: relative RNA expression = $(2 - \Delta Ct) \times 103$ (Schmittgen and Livak, 2008).

PCR Primers are shown in Table 1.

2.5. Statistical analysis

Statistical analysis was carried out using SPSS software version 18 (SPSS, Chicago, IL, USA).

The Kolmogorov–Smirnov test was utilized to ensure the normal distribution of data. Quantitative variables were compared between the two groups at baseline and at the end of the study using an independent samples *t*-test. Quantitative variables before and after treatment within each group were compared by paired samples *t*-test. Qualitative variables were analyzed by chi-square test. All values were reported based on mean ± SE. P-value < 0.05 was considered as the statistical significance level.

Table 1
Primers used for quantitative real-time PCR analysis.

Gene	Type	Sequence	Gene ID
NF-κB	Forward	5′-GAAGCACGAATGACAGAGGC-3′	4790
	Reverse	5′-GCTTGGCGGATTAGCTCTTTT-3′	
PPARγ	Forward	5′-GGGATCAGCTCCGTGGATCT-3′	5468
	Reverse	5′-TGCACTTTGGTACTCTTGAAGTT-3′	
FoxP3	Forward	5′-GTGGCCCGGATGTGAGAAG-3′	50943
	Reverse	5′-GGAGCCCTTGTCGGATGATG-3′	
T-bet	Forward	5′-GTCCAACAATGTGACCCAGAT-3′	30009
	Reverse	5′-ACCTCAACGATATGCAGCCG-3′	
GATA3	Forward	5′-GCCCCTCATTAAGCCCAAG-3′	2625
	Reverse	5′-TTGTGGTGGTCTGACAGTTCG-3′	
RORγt	Forward	5′-GTGGGGACAAGTCGTCTGG-3′	6097
	Reverse	5′-AGTGCTGGCATCGGTTTCG-3′	

a) Nuclear factor-kappa-light-chain-enhancer of activated B cells; b) Peroxisome proliferator-activated receptor gamma; c) Forkhead box P3; d) T-box transcription factor TBX; e) GATA binding protein 3; f) RAR-related orphan receptor γt.

3. Results

Seventy patients with active RA entered the study. Seven patients were excluded from the study due to incomplete supplement intake and change in their medication (3 in ginger group and 4 in the placebo group). Finally 63 patients completed the study (Fig. 1).

Baseline characteristics of the participants are presented in Table 2. Comparisons showed no significant difference in sex, age, duration of disease, weight, BMI, use of DMARDs (percent usage Hydroxychloroquine and Methotrexate in patients) and corticosteroids at the beginning of the study (Table 2).

Also, there was no significant difference in medications between the two groups during the study (Data not shown). There were no significant differences in patients' dietary intake and physical activities between the two groups before and after the intervention (Data not shown).

Fig. 2 shows the mean and standard error of NF-κB, PPAR-γ, FoxP3, T-bet, GATA-3, and RORγt genes expression. Change of NF-κB gene expression was nonsignificant between the two groups (P-value = 0.06) and decreased nonsignificantly in Ginger group (P-value = 0.07). In ginger group, FoxP3 and PPAR-γ genes expression significantly increased (P-value < 0.05), in contrast with PPAR-γ (P-value = 0.12), this increase in FoxP3 gene expression was statistically significant between the two groups (P-value < 0.05).

T-bet gene expression reduced significantly within ginger group after the intervention (P-value = 0.045). Moreover, the decrease was significant between the two groups after the intervention (P-value = 0.04). The expression of GATA3 gene increased nonsignificantly within the ginger group (P-value = 0.065), and the changes between the two groups after the intervention wasn't significant (P-value = 0.061). RORγt gene expression reduced in the ginger group not significantly (P-value = 0.07) while it increased nonsignificantly in the placebo group (P-value = 0.055), but the difference between the two groups was statistically significant (P-value = 0.02) (Fig. 2).

Results showed the significant reduction of DAS-28 within the ginger group and between the two groups after the intervention (P-value = 0.001 and P-value = 0.003 respectively) (Table 3).

4. Discussion

In the present study, 12 weeks supplementation with 1500 mg ginger powder per day in active RA patients caused significant decrease in das-28 score and RORγt, and T-bet genes expression. In addition, ginger caused statistically significant increase in FoxP3 genes expression. Also, the expression of PPAR-γ gene within the ginger group increased significantly.

So far, according to our knowledge, the present study is the first study to evaluate the effect of ginger on the expression of genes involved in Th1, Th2, Th17, and Treg cells activity in RA patients.

Some studies have shown that ginger has reduced pain and inflammation in patients with osteoarthritis and muscle discomfort and also, ginger consumption is recommended in patients with arthritis muscle pain such as osteoarthritis and rheumatoid arthritis in the traditional medicine (Srivastava and Mustafa, 1992; Altman and Marcussen, 2001; Haghighi et al., 2005).

Some human and animal studies have shown that anti-inflammatory effect of ginger is due to the inhibition of pro-inflammatory cytokines and chemokines production. In a clinical trial on type 2 diabetic patients, supplementation with 1600 mg ginger per day for 12 weeks caused significant reduction in serum prostaglandin E2 (PGE2) and C-reactive protein (CRP) compared with placebo; however, the reduction in serum TNFα was not statistically significant between ginger and placebo groups (Arablou et al., 2014).

In a study on rats with arthritis, red ginger ethanolic extract reduced inflammation by decreasing PGE2 and nitric oxide production

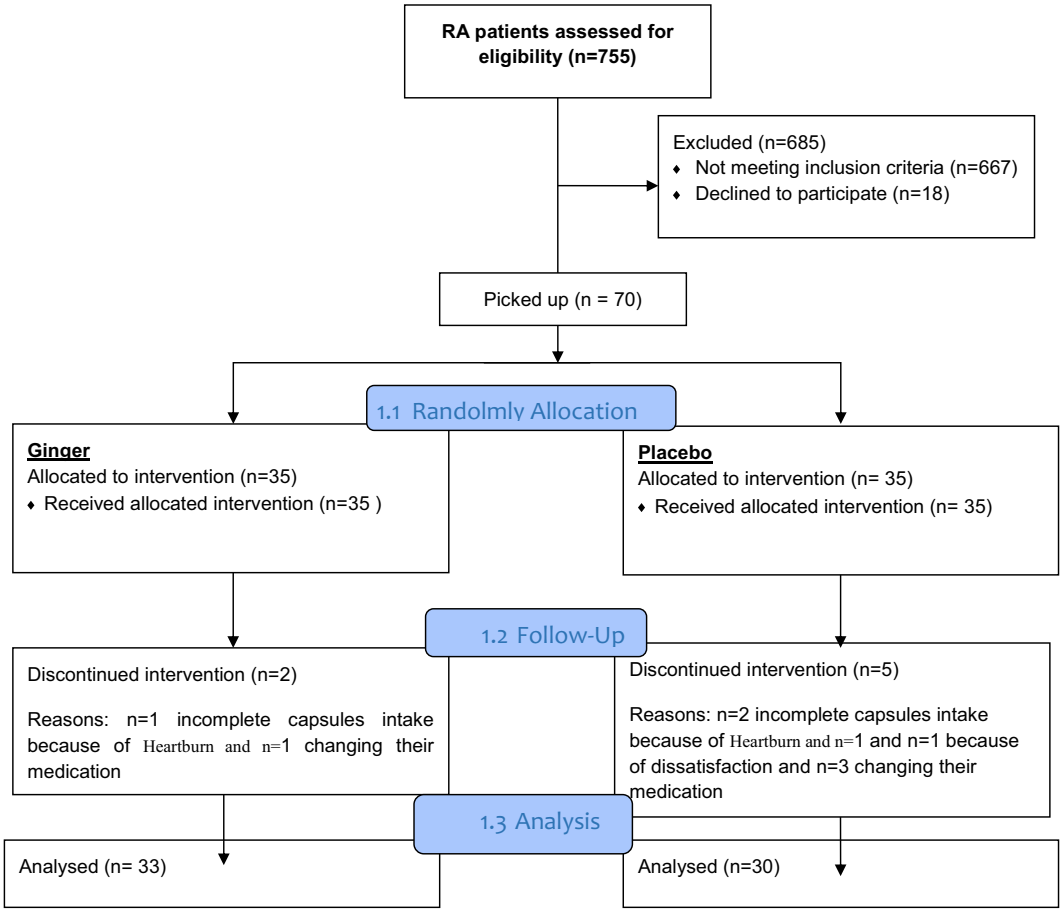

Fig. 1. Overview of the study in summary form.

Table 2
Baseline characteristics of the study participants.

Variable	Ginger group N = 33	Placebo group N = 30	P-value
Male/female	4/29	3/27	0.50$^{\gamma}$
Age (years)†	48.63 ± 2.38	46.67 ± 1.94	0.77*
Disease duration (years)†	18.12 ± 4.13	14.87 ± 4.13	0.57*
Weight (kg)†	73.45 ± 2.13	74.49 ± 2.03	0.62*
BMI (kg/m^2)†	29.23 ± 0.83	29.59 ± 1.12	0.79*
Corticosteroids^{a} (mg/d)	8.10 ± 0.7	8.48 ± 0.65	0.88$^{\gamma}$
Hydroxychloroquine (%)	29(80)	22(73)	0.35$^{\gamma}$
Methotrexate (%)	32(91)	29(96)	0.38$^{\gamma}$

P* Between group comparison (Independent *t*-test).
P$^{\gamma}$ Chi-squared test.
P-value < 0.05 is significant.
† Data are presented as mean ± SE.
^{a} Equivalent dose of Prednisolone.

(Shimoda et al., 2010). Another study on murine (C57BL/6) peritoneal macrophages showed that ginger reduced the production of pro-inflammatory cytokines TNF-α, IL-12, IL-1β and pro-inflammatory chemokines, monocyte chemoattractant protein-1(MCP-1) and regulated on activation, normal T cell expressed and secreted (RANTES) in vitro. Besides, ginger down regulated the expression of $B7_1$, $B7_2$, and MHC class II molecules. In addition, a significant reduction in IFN-γ and IL-2 production by T cells was observed. Therefore, ginger extract decreased macrophages activity as antigen presenting cell (APC) and inhibited T cells activity indirectly (Tripathi et al., 2008).

In our study the reduction of NF-κB between groups wasn't significant (P = 0.069). Several studies have shown the effect of ginger on alleviation of inflammation by reducing NF-κB pathway. Lee et al. demonstrated that 6-gingerol isolated from Zingiber Officinal exhibited anti-inflammatory effect by blocking NF-κB signaling pathway. 6-Gingerol significantly suppressed IκBα phosphorylation, and NF-κB nuclear activation (Lee et al., 2009). Recently, it has been reported that 1-dehydro-10-gingerdione, one of the ginger compounds, showed anti-inflammatory effect by suppressing the NF-κB regulated inflammatory genes expression (Lee et al., 2012). This discrepancy may be due to difference in the methodology of studies. They were done on mice and cell culture.

The present study showed that ginger increased PPAR-γ gene expression within the ginger group. So far, potential anti-inflammatory characteristics of ligands of PPAR-γ on the activity of rheumatoid arthritis in several arthritis experimental models have been observed (Shahin et al., 2011). PPAR-γ agonists inhibit translation of genes involved in joint inflammation such as TNF-α, IL-1, MMP-9 and MMP-13 (Palma et al., 2012). Ligands of PPAR-γ have been shown as inducers of apoptosis in T lymphocytes and macrophages. Expression of PPAR-γ in monocytes and monocyte-derived macrophages can be an indicator of disease activity and treatment efficacy in rheumatoid arthritis (Nammi et al., 2009). Some previous studies have shown that ginger components act as PPAR-γ agonists and can up regulate PPAR-γ target genes expression (Isa et al., 2008; Wohlfert et al., 2011). The results of these studies are consistent with the present study.

In RA as an autoimmune disease, the immune system is impaired and it seems that ginger can improve immune function in Patients with this disease and other autoimmune diseases. The results showed that ginger decreased the expression of T-bet gene significantly. T-bet is Th1 cells transcription factor that induces the proliferation of Th1 and is essential for the production of IFN-γ (Feldmann and Maini, 2008). It

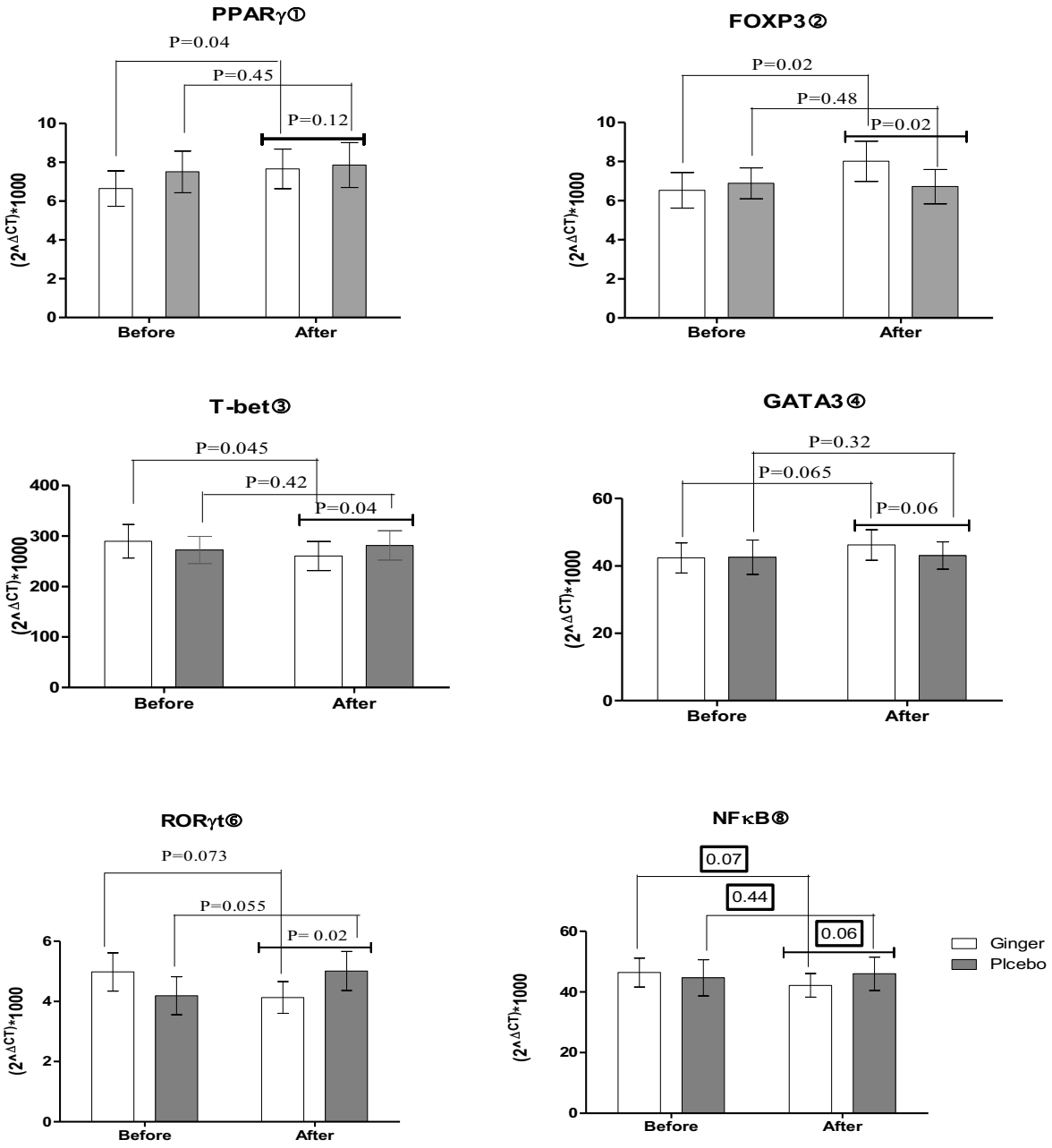

Fig. 2. Immunity and inflammation intermediate genes expression levels in ginger and placebo groups before and after intervention.
Data are presented as mean ± SE.P Within group comparison (Paired *t*-test).
P Between group comparisons (Independent *t*-test), *P* value < 0.05 is significant.
1) Peroxisome proliferator-activated receptor gamma; 2) Forkhead box P3; 3) T-box transcription factor TBX; 4) GATA binding protein 3; 5) RAR-related orphan receptor γt; 6) Nuclear factor- kappa-light-chain-enhancer of activated B cells.

also inhibits Th2 differentiation (Kawashima and Miossec, 2005). The reduction of T-bet by ginger indicated the anti-inflammatory property of ginger.

In the present study, ginger caused a non-significant increase in GATA-3 gene expression. The transcription factor GATA-3 is essential for early T cell development and differentiation of naive $CD4^+$ T cells into Th2 effector cells and inhibition of Th1 differentiation. GATA-3 strongly transactivates the IL-5 promoter, but appears to have only limited effects on IL-4 gene transcription (Nawijn et al., 2001; van Hamburg et al., 2009). A study in contrary of our research showed that GATA-3 expression protects against severe joint inflammation and bone erosion in mice (Zhou et al., 2006).

The present study showed that RORγt gene expression increased nonsignificantly in the placebo group, and reduced in the ginger group nonsignificantly, but the differences between the two groups was statistically significant. It means that ginger could prevent the increase of this factor in RA patients. It is evident that Th17 cells have pro-inflammatory effects in autoimmune diseases. Some studies have shown a link between genes involved in cell differentiation and function of Th17 with the risk of Crohn's disease, arthritis and Psoriasis (Huh and Littman, 2012). The results showed that ginger can prevent the increase in RORγt in the intervention group and thus can reduce pro-inflammatory conditions in RA patients.

In the present study, the augment in the expression of FoxP3 in the ginger group shows the immune-modulatory effects of the plant. FoxP3 is the transcription factor in Treg cells and its increase causes an

Table 3
DAS28 values in ginger and placebo groups before and after intervention.
Data are presented as mean ± SE.

DAS-28[a]	Ginger group N = 33	Placebo group* N = 30	P-value$^{\Psi}$
Before	4.73 ± 0.27	4.51 ± 0.27	0.003
After	3.44 ± 0.30	4.30 ± 0.33	
P-value*	0.001	0.18	

P* Within group comparison (Paired *t*-test).
P$^{\Psi}$ Between group comparisons (Independent *t*-test).
P value < 0.05 is significant.
[a] Disease Activity Score ESR (van Riel and Fransen, 2005) (DAS28 ESR = 0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln (ESR) + 0.014 * GH) (van Riel and Fransen, 2005).

increase in Tregs function and modulation of the immune system and prevents from autoimmune diseases (Nazari et al., 2013).

According to our knowledge, there are limited studies that investigated the effect of ginger on T cells proliferation and function. Some in vitro studies showed that ginger and its main gingerols can inhibit T cell proliferation and activation. In an in vitro study, the volatile oil of ginger inhibited the proliferation of helper T cells ($P < 0.01$), but increased the percentage of T suppressor cells to total T lymphocytes ($P < 0.01$) (Zhou et al., 2006). On the other hand, the inhibitory effect of gingerols on IFN-γ production besides no effects on IL-4 production in one study showed that ginger inhibits Th1 responses that contribute to the development of certain autoimmune diseases (Schoenknecht et al., 2016). In another study on rats, low doses of ginger increased the activity of total T cells and natural killer cells (NK cells) and high doses increased the activity of Treg cells in a dose dependent trend (Mojani et al., 2014). The increase in Treg cells activity in the mentioned studies is consistent with the present study.

The present study indicated that ginger caused significant reduction in DAS28-ESR in RA patients. DAS-28-ESR is a continuous measure of RA disease activity (van Riel and Renskers, 2016; Matsui et al., 2007); and its reduction by ginger supplementation showed the ability of the plant to improve disease symptoms.

The present study has some limitations: It would have been better if we could have assessed the level of transcription factors protein and also some other inflammatory and immune markers which play important roles in the autoimmune disease initiation and progression such as TNF-α, and its receptors, IL-1β, IL-6 and IL-17.

In conclusion, the present study showed that ginger can reduce RA manifestations and improve immune system function by decreasing NF-κB, RORγt, and T-bet genes expression as factors involved in inflammation and autoimmunity and increasing FoxP3, PPAR-γ, and GATA3 genes expression as factors involved in tolerance and can be considered as a therapeutic agent in RA patients. However, because of the limited number of studies in this field, further studies are suggested to investigate the effect of ginger consumption on autoimmunity, inflammation, and clinical manifestations in RA patients.

Conflicting interests

None of the authors report conflicting interests.

Acknowledgment

This study was funded by a research grant from the Research Deputy of Iran University of Medical Sciences; No 92032723598. We appreciate the Research Center for Traditional Medicine (Iran) that provided ginger supplements.

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