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Original article

The effect of *chamomile* tea consumption on inflammation among rheumatoid arthritis patients: randomized clinical trial

Saeed Pirouzpanah[1], Soltanali Mahboob[2], Mahzad Sanayei[3], Mehrzad Hajaliloo[4], Abdolrasoul Safaeiyan[5]

[1]Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran; [2]Department of Biochemistry and Clinical Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran; [3]Department of Biochemistry and Nutrition, Faculty of Health and Nutrition, Tabriz University of Medical Science, Tabriz, Iran, E-mail: mahzad.sanayei@gmail.com, [4]Connective Tissue Diseases Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran; Department of Vital Statistics and Epidemiology, Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran.

Summary. *Background:* Rheumatoid arthritis (RA) is a joint inflammatory disease, which proinflammatory cytokines and oxidant spices accelerate inflammatory response in patients. Drugs and supplements which can modulate the inflammation can slow the disease progression, and minimize the joints destruction. Anti inflammatory effect of Chamomile on severity of disease was measured by Disease Activity Score (DAS-28) tool in the study. *Patients and method:* The study was a randomized, placebo-controlled, double blind clinical trial. The participants were selected from Tabriz university rheumatology clinic clients. According to rheumatologist diagnosis, 44 patients have the inclusion criteria in this study which fulfilled the American college of rheumatology (ACR-2010) criteria, were included.The patients were randomized in two groups, receiving 6 g/day Chamomile tea as 2 teabags twice a day for 42 days or placebo teabags, containing as similar. DAS-28 as an identified variable was calculated. For this, erythrocyte sedimentation rate (ESR) was measured before and after the study. Also all the patients were clinically examined, in order to determine the tender joints and swollen joints number. They reported the pain by Visual Analogue Scale (VAS). Nutrition intake was measured at both times in order to minimize the cofounders. *Results:* Groups were matched at the beginning in demographic characteristics, such weight height, age and BMI. During the intervention BMI didn't change, but tender joints number and ESR changed significantly (P=0.000 and P=0.018, respectively). *Conclusion:* This study showed that Chamomile could decrease the inflammation similar to cell studies before. It can be a complementary treatment for RA patients.

Key words: rheumatoid arthritis, chamomile, inflammation, appetite, omega-3 fatty acids, obesity

Introduction

Rheumatoid arthritis (RA) is an inflammatory chronic disorder with an unknown etiology which occurs in about 1% of the population worldwide (1). The prevalence rate of RA among Iranian people is high and estimated about 0.32% (2). According to two studies in Iran, RA is growing from 0.3 to 0.37 during 15 years in last decade (2, 3).Disease commonly is incidentally reported to be between ages 30 and 50 years old, with a 3 times more susceptibility in women (4). However, the etiology of disease is not clearly known but the main physiopathology reason is the imbalance in the levels of inflammatory and anti inflammatory mediators (4, 5)

Non-steroidal anti-inflammatory drugs (NSAIDs) and disease modifying anti-rheumatic drugs (DMARDs) are widely used medicines for relieving and controlling RA development and symptoms (6).However, these existing pharmaceutical protocols usually come up with undesired side effects; therefore, finding an alternative treatment, like medicinal plants in RA treatment have

gained recently a noticeable consideration in clinical and experimental studies (7, 8)[7].

Chamomile (Matricaria chamomilla L.) is one of the most well-known herbal plants. The dried flower part of plant is used traditionally for wide spectrum of medicinal purposes including rheumatic pain and inflammation. Evidence-based information regarding the bioactivity of this herb is presented (7, 8). *Chamomile* consist several phenolic compounds like apigenin, quercetin, patuletin, luteolin and their glucosides (8). Some cellular and animal models showed anti inflammatory effect for flavonoids on pro-inflammatory effects and levels of cytokines, which play a crucial role in induction and progression of RA (8-11).

Although some experimental studies had shown the effect of *chamomile* reducing the inflammation in cell culture (9), the possible modulation on rheumatoid arthritis inflammation has not been investigated so far. Therefore we conducted a randomized clinical trial to study the possible beneficial effects of *chamomile* tea consumption on ESR, DAS-28 and VAS signs and symptoms in RA patients.

Materials and Methods

Study subject

This study was conducted between December 2014 and March 2015 involving 44 female patients with RA who fulfilled the American college of rheumatology (ACR) criteria 2010, and who had been referred to clinics at the Tabriz University of Medical Sciences. Patients were ageing between 20 to 65 years old with a body mass index (BMI) lower than 30. All patients with RA enrolled (n=65) in this study and among them, 44 who had selected eligible based on inclusion criteria were involved in intervention. Inclusion criteria were as follow: 1) Subjects diagnosed with rheumatoid arthritis, based on American College of Rheumatology (ACR-2010) criteria; 2) Patients with moderate and less rheumatoid arthritis score (DAS-28<5.1); 3) Stable medication for at least 3 weeks prior to the intervention and during that; 5) Willing to participate in the study; 6) Ages between 20 and 65 and 7) Have a body mass index (BMI) less than 30 and more than 18.5. Exclusion criteria were as follow: 1) Pregnant and lactating women; 2) Patients with cardiovascular, lung, hepatic, kidney and haematic diseases 3) Having chronic inflammatory diseases such as Sjogern, Sicca, MS, Lupus Erythematosus and Hashimoto's disease; 4) Patients with gastro duodenal ulcer; 5) Patients with a high sensibility to the experimental drugs; 6) Patients participating in another study just 3 weeks before the intervention and 7) Taking any vitamin, mineral or omega 3 supplement 3 months before the intervention. In the first visit, a rheumatologist examined the patients and filled a medical records, including age, age at disease onset, morning stiffness duration, disease duration and number of swollen and tender joints. The self reported pain degree was asked from patients and scored with Visual Analog Scale (VAS). The duration of study follow-up was 6 weeks. None of these 44 patients were relatives, in order to prevent statistical bias.

This study was a double blinded randomized, controlled clinical trial with treatment and control groups running in parallel for a period of 6 weeks (Figure 1). The Ethical committee of Tabriz University of Medical Sciences approved the study protocol and was registered on the Iranian registry of clinical trials website (available at: http://www.irct.ir, identifier: IRCT: IRCT2015010111335N4).

All subjects gave written informed consent before clinical trial enrollment. The sample size was de-

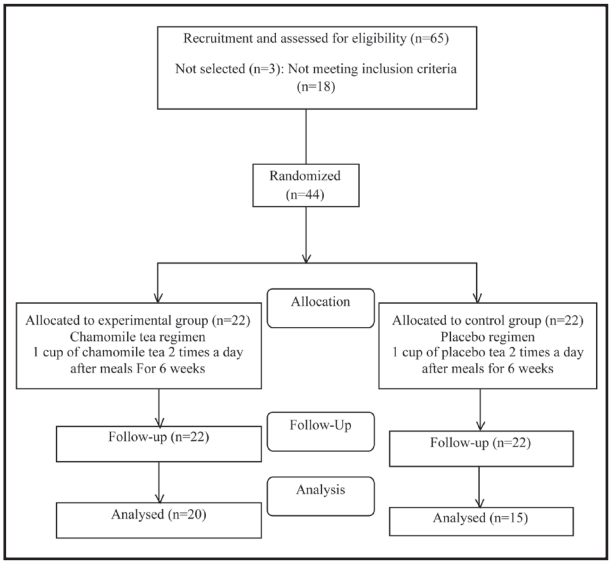

Figure 1. Flow diagram showing participants enrollment and study design

termined based on the primary information obtained from the study by Sang-Cheol et al (12). A general questionnaire was completed for each patient. Body weight was measured using a scale (Seca, Germany), without shoes and wearing light clothing.

Anthropometric and dietary measurements

Height was measured using a mounted tape without shoes. BMI was calculated as the weight in kilogram divided by the height in meters squared. Information about daily energy and macronutrient intakes was obtained by 24-h recall method for 3 days, including 2 week day and 1 weekend. Three day average of energy and macronutrient intakes of all subjects was analyzed by Nutritionist IV software (First Databank Inc., Hearst corp., San Bruno, ca, USA).

Intervention group

Drying of *chamomile* flowers was done with a similar condition for all of flowers, in room temperature away from light. First the species of *Chamomile* were determined in herbarium and then dried in a dark place in instant time period. The tea bags were containing approximately 3 g of *chamomile* dried flower and wheat bran as placebo, which was identical in appearance, color and herbal odor. They all packed in tea factory at a certain time (Jam, Lahijan). The patients received the supplements on the onset of the study, and were monitored for consumption continuation and any possible adverse effects by telephone interviews. The intervention group (n = 22) consumed one cup of *chamomile* tea bag, infused in 150 ml hot water for 10 min, two times a day immediately after lunch and dinner for 6 weeks. The control group (n = 22) consumed an equivalent wheat bran tea bags, packed exactly like the *chamomile* tea bags, with a similar color without any nutritional effect infused in hot water, twice a day for 6 week period. Subjects were asked to maintain their usual dietary intake, physical activity and to avoid any changes in their medication. The compliance of the volunteers with the study protocol was monitored by telephone interviews once a week and counting returned tea bags in person every 2 weeks. In addition consumption check lists were collected every 3 weeks during the study. In study onset a seven day run in period was planned for flavonoid rich foods such as black tea (more than 2 glasses with 240 ml volume), onion, and green leafy vegetables to be consumed at least during the study. Investigator and patients were blinded about which subject belongs to which group.

Biochemical assessment

Teabags were handed in to participants with similar packing which were coded by Jam tea manufacturer. Blood sampling was collected from venous blood (10 ml) from each subject between 7:00 and 9:00 a.m. after an overnight fasting. Erythrocyte sedimentation rate (ESR) after 1 h was measured using Ves-Matic 200 cube Erythrocyte Sedimentation Rate (ESR) measuring instrument (Diesse Ves-Matic, Italy). Lost to follow-up occurred for two patients in intervention group because of intra-articular corticosteroid injection and disease deterioration. Subjects in placebo group stop continuing the intervention because of surgery, travelling and unwillingness for continuing. All anthropometric, dietary intakes, blood sampling, clinical examinations and biochemical measurements were assessed again at the end of intervention period in both groups.

Disease Activity Score-28 (DAS-28)

The DAS is a combined index that has been developed in Nijmegen in the eighties to measure the disease activity in patients with rheumatoid arthritis. It has been extensively validated for its use in *clinical trials* in combination with the EULAR response criteria.

DAS-28 data were taken out as disease severity by the following formula:

$$DAS\text{-}28 = 0.56*\ddot{O}(t28) + 0.28*\ddot{O}(sw28) + 0.70*Ln(ESR) + 0.014*VAS$$

In this formula (t) is the tender joints (0-28), (sw) is the swollen joints (0-28), ESR is erythrocyte sedimentation rate and VAS is visual analoge scale of pain(0-10). Evaluation of response to a treatment can be made much easier and more objective using the DAS28, by assessing the number of swollen and tender joints and measuring the ESR. VAS was asked from the patients. The DAS-28 ranges between 0 and 10, indicating how active the RA is at this moment (13).

Statistical analysis

All the results are expressed as Mean ± SEM. A repeated measure model was used for two group comparison in both times. All analyses were performed using statistical software Minitab15 and Spss16 for Windows and *P* value of less than 0.05 was considered statistically significant.

Results

All of the patients (22 patients in *chamomile* tea group and 22 patients in placebo group) didn't complete the study. Compliance estimated more than 95% in average. Participants did not report any adverse effects or symptoms with the *chamomile* tea consumption during the study.

Table 1 showed demographic and base line characteristics (weight, height, age, BMI and wrist) have no any significant differences between the study groups. In another words, groups were matched in all of this items at beginning and during the intervention.

Table 2 presents the daily dietary intake details of participants throughout the study. There were no significant differences in energy and macronutrients intakes between two groups at baseline. Total energy, protein and carbohydrate intakes also did not change significantly in any of the groups during the study but fat intake changed after adjustment for base line examinations.

Table 3 shows the groups were matched in the beginning for disease duration and DAS-28 and its constituents covering tender joints and swollen joints number, ESR value and VAS number. Significant changes were seen in ESR and tender joints number in treatment group, but DAS-28 and swollen joints number and Visual Analogue Scale did not change.

Discussion

This study is the first clinical trial, conducted to evaluate the effect of *Chamomile* supplementation on inflammation and disease treatment in Rheumatoid

Table 1. Demographic characteristic of study participants

Treatment	Chamomile		Placebo		Pv	Pv	Pv
Time	Before	After	Before	After	Matching	Treatment	Time
Statistic	Mean±SE	Mean ± SE	Mean±SE	Mean±SE			
Weight (kg)	71.23±2.57	70.9±2.55	70.2±3.14	70.07±3.06	.800	0.207	0.992
Height (cm)	161.95±1.8	-	162.62±1.63	-	.793	-	-
Age	48.9±1.86	-	46.13±3.23	-	.465	-	-
BMI	27.03±0.66	26.91±0.65	26.46±0.96	26.42±0.94	.617	0.542	0.983
Wrist	89.7±2.33	89.7±2.33	89.53±2.23	89.53±2.23	.960	0.068	1.000

Data are presented as Mean± Standard error, p< 0.05 is statistically significant

Table 2. Participants diet analysis.

Treatment	Chamomile		Placebo		Pv	Pv	Pv
Time	Before	After	Before	After	Matching	Treatment	Time
Statistic	Mean±SE	Mean±SE	Mean±SE	Mean±SE			
Protein	79.17±4.26	75.13±4.68	77.19±4.27	79.43±5.49	0.527	0.657	0.750
Fat	53.42±2.58	57.19±2.31	64.32±3.81	59.7±3.54	0.282	0.039	0.353
Kilocalories	2043±75.43	2089.92±63.14	2085±103.95	2091.47±105.51	0.636	0.902	0.879
Carbohydrate	318.12±13.66	319.23±9.98	304.66±18.99	323.95±12.04	0.948	0.517	0.560

$P^{matching}$: P<0.05 significantly difference between two groups for statics; $P^{treatment}$: P<0.05 significantly difference for intervention; P^{time}: P<0.05 significantly difference between two times before and after. All data are expressed as Mean± Standard error.

Table 1. Disease related characteristics

Treatment	Chamomile		Placebo		Pv	Pv	Pv
Time	Before	After	Before	After	Matching	Treatment	Time
Statistic	Mean±SE	Mean±SE	Mean±SE	Mean±SE			
Disease duration	11.3±1.71	11.3±1.71	8.83±1.83	8.83±1.83	.337	0.099	1.000
DAS-28	3.36±0.17	3.06±0.19	3.37±0.28	3.43±0.26	.964	0.108	0.540
ESR	21.8±2.42	19.4±2.23	25±4.57	27.33±4.89	.513	0.018	0.600
Tender joints	2.51±0.33	1.96±0.3	4.27±0.84	4.47±0.88	.067	0.000	0.690
Swollen joints	1.27±0.2	1.21±0.36	1.08±0.33	1.21±0.37	.610	0.208	0.931
VAS	3.35±0.35	2.65±0.24	3.07±0.3	2.93±0.33	.560	0.916	0.241

SE: Standard Error; p< 0.05 is statistically significant; DAS-28: Disease Activity Score, ESR: erythrocyte sedimentation rate, VAS: Visual Analoge Scale of disease activity.

Arthritis. Both groups were matched before the intervention in order to minimize the confounders. This study showed that 6 g/day *chamomile* tea consumption for 42 days caused significant decreases in ESR levels and tender joints number in intervention group, while there was not any significant change in DAS-28, Visual Analogue Scale and swollen joints number in intervention group. *Chamomile* tea did not lead to any harmful changes in the treatment group. Furthermore, no significant changes were seen between and within groups in weight and BMI of subjects after 6 weeks of intervention, which is parallel to Zemestani et al study (14). In Weidner et al study, *Chamomile* alcoholic extract prescription for 6 weeks didn't change the weight in diet obsessed rats, significantly (15). Although any mechanism in probable effect in weight reduction, have not been seen in rats for *chamomile*. Totally *Chamomile* tea consumption has not any effect in participant's food receiving, so that BMI would not be a confounder in biochemical interpretation.

Chamomile consists of high level of phenols such as Coumarin and Flavonoids, which they have, free radical scavenging effects (16). So that *Chamomile* as a rich source for antioxidant components, modulated the oxidative stress in diabetic patients in Zemestani et al study (14).

NF-κB regulates the expression of pro-inflammatory cytokines (17, 18) . Imbalanced activation of NF-κB is involved in pathogenesis of inflammatory diseases. Suppression of NF-κB activation by certain inhibitors could down-regulate the gene expression of pro-inflammatory cytokines, and then block the development of inflammatory diseases (19). *Chamomile* is a rich source of apigenin, which been shown to down regulate NF-κB through the inhibition of Akt (11). It's a potent antioxidant, cyclooxygenase (COX) inhibitor, cell cycle inhibitor, protein kinas C inhibitor, and apoptosis inducer (20).

Oxidative protective effect of *Chamomile* via nitric oxide reduction was revealed in a study (16) which was not detected in ours. Shipochliev et al concluded that anti-inflammatory effect of *Chamomile* is due to prostaglandin E1 production inhibition (21). In another study Janmejai et al show that *Chamomile* has the same mechanism to non steroid drugs in COX-2 inhibition (22). For example, Chamazulene as a main constituents of *Chamomile*, has the same structure to ibuprofen and has key role in prostaglandin production inhibition (23).

According to this findings and inflammation mechanism in Rheumatoid Arthritis; and because of that which the key treatment is suppression of inflammatory cascade, it's concluded that any supplement or drug which can improve the disease activity and decrease the ESR as potent marker for inflammation, can alleviate the symptoms and pain. In this study *Chamomile* supplementation could improve the disease degree, by decreasing the ESR value, which means inflammation improvement. Cyclooxygenase-2 (COX-2) regulates proliferation, angiogenesis, inflammation, and tumor genesis. COX expression is elevated in the

synovial lining layer, the subsynovial, synoviocytes, the vascular endothelial cells, and mononuclear inflammatory cells in patients with rheumatoid arthritis (RA) or osteoarthritis (OA) (24). Abnormal breakdown of connective tissue contributes to pathological conditions such as RA and atherosclerosis. In another cellular study apigenin could inhibit the collagenase activity by 85.3% at 500 p.m. (20).

Apigenin in another study showed greater inhibition of COX-2 induction than celecoxib (20). These results are consistent with a report that apigenin decreased NO production by down- regulating COX-2 expression in the same cells (25). Reactive Oxygen Spices (ROS) plays an important role in cartilage degradation (26). Cellular ROS generation stimulates the expression of COX-2 (27). Nevertheless, apigenin suppressed LPS-induced COX-2 expression in RAW 264.7 cells .This suppression could be caused by inhibition of Akt activation, or by inhibition of Arashidonic acid release causing suppression of Prostaglandin synthesis (10). As a whole, our results suggest that this effect of *chamomile* in RA patients is resulted from apigenin which may retard inflammatory processes in rheumatoid synovial by suppressing NO production and COX- 2 expression. Inhibition of COX-2 expression and cellular adhesion molecules (9) have been seen in cell studies which be suggested as a probable mechanisms that *chamomile* induces its anti-inflammatory and anti-Oxidant effects and ESR as an inflammatory sign were reduced. So that according to this study *chamomile* show the same effect of cellular study in human, in RA patients which was due to down regulation of the inflammation and disease severity improvement.

Otherwise, the inhibition of the collagenase reaction occurred at 500 ~M apigenin, which is cytotoxic to RAW 264.7 cells and HUVECs. Direct injection of apigenin (500 pM) to inflammatory joints might allow inhibition of collagenase without toxicity to other cell types. The inhibitory activities if apigenin on the inflammatory responses suggests that it may be useful as a functional food component or an alternative medicine to help treat inflammatory symptoms (20).

The goal of RA treatment is remission. Definition of remission, however, remains controversial. DAS-28 is a tool which can be used to assess the disease activity during a period .(13). In another word in patients if any constituents of DAS-28 such as ESR and tender and swollen joints decreases in treatment procedure, it means that disease have been suppressed.

Author's contributions

Authors' Contributions: This manuscript was extracted from the thesis written by Mahzad Sanayei, MSc student of Nutrition. Soltanali Mahboob: study design and supervision; Mahzad Sanayei: study design, Data collection, manuscript drafting; Saeed Pirouzpanah: consultation during study design and implementation, manuscript edition; Mehrzad Hajaliloo: consultation during study design and implementation; Abdolrasoul Safaiyan: statistical data analysis.

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Correspondence:
Mahzad Sanayei
MSc of Nutrition. Department of Biochemistry and Nutrition, Faculty of Health and Nutrition,
Tabriz University of Medical Science, Tabriz, Iran.
Email: mahzad.sanayei@gmail.com