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Effects of Soy Bread on Cardiovascular Risk Factor, Inflammation and Oxidative Stress in Women With Active Rheumatoid Arthritis: A Randomized Double-Blind Controlled Trial

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ABSTRACT

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder with widespread synovitis. Isoflavones, the main active component of soy, have been reported to have potent anti-inflammatory effects; the previous RA animal models showed the promising effect of soy supplementation. We aimed to evaluate the effect of soy bread on inflammatory markers and lipid profiles in RA patients. The present study was designed as a randomized controlled trial. RA patients were randomly allocated to obtain soy bread (n = 22) or placebo bread (n = 22) for 8 weeks. Fasting serum levels of lipid profile, total antioxidant capacity (TAC), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and DAS28 were checked. Findings showed that there were no significant differences between the two groups in physical activity and dietary intake at the beginning of the study and the end of the study. There were no significant differences between the two groups in measured lipid profile markers, including high-density lipoprotein, low-density lipoprotein, total cholesterol, triglyceride, and very low-density lipoprotein, at the end of the trial. In addition, TAC and CRP also were not significant at the end of the trial between the 2 groups (0.66 and 0.12, respectively). However, the serum levels of TNF-α reduced significantly in the soy bread group at the end of the intervention ($p < 0.000$) and compared with the control group ($p < 0.019$). Soy bread consumption only decreased circulating TNF-α serum concentration. Other outcome measures were not changed following supplementation. Future long-term, well-designed studies are needed to confirm these findings.

Trial Registration: Iranian Registry of Clinical Trials Identifier: IRCT20181021041396N1

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Ghaedi E, Helli B; Data curation: Ahmadi-engali K, Sayyaf A; Formal analysis: Ghaedi E, Ahmadi-engali K; Funding acquisition: Helli B; Investigation: Helli B, Rajaei E; Methodology: Haidari F, Rajaei E; Project administration: Helli B, Haidari F, Ghaedi E; Resources: Helli B; Software: Ghaedi E, Ahmadi-engali K; Supervision: Helli B, Rajaei E; Validation: Haidari F, Helli B, Rajaei E; Visualization: Ghaedi E, Helli B; Writing - original draft: Ghaedi E, Sayyaf A; Writing - review & editing: Sayyaf A, Ghaedi E, Haidari F, Rajaei E, Ahmadi-engali K, Helli B.

Keywords: Arthritis, rheumatoid; Soy foods; Functional food; Inflammation; Oxidative stress; Randomized controlled trial

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disorder without a well-known etiology that affects approximately 1% of the world's population [1,2]. It is mostly characterized by widespread synovitis that leads to articular cartilage and marginal bone erosions and, eventually, different extents of joint destruction and deformity [3]. Apart from restricting pain and swollen joints, which could lead to joint destruction [4], RA is known as a systemic disease with different extra-articular signs like vasculitis, cardiovascular diseases (CVDs), lung damage, anemia, and neuropathy [5]. While the pathophysiology of RA is not fully understood, inflammation is implicated as one of the main characteristics [6]. Although inflammation against infection is a positive response of an immune system, in autoimmune diseases, inflammation can worsen the condition [7]. Different inflammatory factors like tumor necrosis factor-α (TNF-α), interleukin (IL)-6, and IL-1β generated by monocytes, macrophages, and synovial fibroblasts have fundamental roles in the development and pathogenesis of RA [2,8]. TNF-α plays its role at several stages in B-cell proliferation, antibody production, and secretion and increases the effects of other cytokines on B-cell function [9]. Furthermore, it can disrupt the oxidant/antioxidant balance in favor of lipid peroxidation through increased production of reactive oxygen species [10]. In addition, it can induce endothelial cell and leukocyte activation, angiogenesis, synovial fibroblast proliferation and activation of matrix metalloproteinase [8].

Several anti-inflammatory drugs are reported to be useful against RA, like anti-inflammatory agents like nonsteroidal anti-inflammatory drugs (NSAIDs), but their use is complicated due to their side effects and also high cost [11]. Several side effects are reported for anti-inflammatory drugs like nephropathy, hepatopathy, and gastrointestinal side effects [12]. Different drugs are used to induce permanent remission, reduce pain and swelling, and prevent disability. Due to lots of problems associated with all of these drugs, complementary medicine has gained high interest among RA patients [13].

Soy is a good source of plant protein, which contain several other healthful compounds like isoflavones [14]. The 2 most well-known isoflavones are genistein and daidzein, whose beneficial effects have been reported in several diseases like cancer, osteoporosis, diabetes and CVD [15]. Isoflavones are reported to have potent anti-inflammatory effects; for instance, Equol, a metabolite of daidzein in the gut following the action of the gut microbiome, possesses high antioxidant and anti-inflammatory properties [16]. However, the synthetic potency of soybean recipients is different. Some polymorphisms alter the individuals' responses to isoflavones, worsening inflammatory status while decreasing inflammation in others [17].

Previous animal studies showed anti-arthritogenic, antioxidant, and hypolipemic actions of isoflavones and soy products in RA animal models [18]. In that case, genistein suppresses the secretion of IL-1β, IL-6 TNF-α, IL-4, interferon-gamma, and matrix-metalloproteinases [19-23]. Other active compounds of soy, like lunasin, showed a similar suppressing effect on the above-mentioned inflammatory factors [24]. Soy products also improved the antioxidant-oxidant balance in the RA animal model; in essence, soy decreases malondialdehyde as an indicator of lipid peroxidation; the activity of antioxidant enzymes like paraoxonase and arylesterase activity restored after soy supplementation in the RA model [25].

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On the whole, most studies that evaluated the effect of soy in RA are limited to animal models. Furthermore, as mentioned earlier, the most specific component of soy products is investigated in the majority of them. Whole soy products with different ingredients like macronutrients and different micronutrients could lead to better health outcomes rather than soy isoflavones or soy protein alone [26,27]. Previously, soy milk was investigated in RA patients as one of the whole soy products [28]. However, there is a lack of well-designed clinical trials in RA patients so far. To our knowledge, for the first time, we aimed to evaluate the effect of soy bread, as a new product, on inflammatory markers and CVD risk factors in RA patients.

MATERIALS AND METHODS

Participants

All participants were patients with established arthritis rheumatoid who were available for sampling from the Rheumatology Department at Dr. Rajaei's clinic, affiliated with Ahvaz Jundishapour University of Medical Sciences (AJUMS), Ahvaz, Iran. During preliminary screening, 60 patients were checked, and finally, 50 enrolled between November 2019 and January 2020. All participants were aged between 25 and 75 years old; the present study enrolled patients with different rural and urban inhabitants in Khuzestan province. All patients have to meet the following inclusion criteria before they can be enrolled in the present study: 1) RA affliction of at least six months before participation in the present trial; 2) body mass index (BMI) < 35 kg/m^2; and 3) informed consent before participation. Patients were not included in present trial if they: 1) had a history of myocardial infarction or other CVDs-related comorbidities; 2) being pregnant or lactating; 3) had a history of abnormal hepatic function, renal, digestive diseases or cancer; 4) consumed nutritional supplements in the last 3 months; 5) used following drugs in the last month prior to randomization; contraceptives; and 6) consumed alcohol or smoked in the last month. During the study, also subjects were excluded if: 1) were unwilling to remain in the study; 2) the dose(s) and type of medication changed; 3) compliance of lower than 80%; 4) any sensitivity or side-effects after supplementation; and 5) changes in diet or physical activity during the study. If any of the participants received a supplement that may interfere with the present study, he/she was not included.

Study design

The present study was a randomized, placebo-controlled, double-blind, parallel clinical trial. The present trial was in keeping with the Declaration of Helsinki. Prior to randomization, all the subjects completed written informed consent; the AJUMS research ethical committee approved the study protocol. The trial was registered in the Iranian Registry of Clinical Trials (www.irct.ir); IRCT20181021041396N1. All patients were randomly allocated to one intervention group (IG) (n = 22) or control group (CG) (n = 22) through computer-generated randomization. Before entrance to any of the groups, patients were matched based on age, gender, and energy intake. IG received soy bread, while CG received placebo bread for 6 weeks. Due to the lack of an evidence-based appropriate dose of soy bread in RA patients, we have to use a similar dose in postmenopausal women with abdominal obesity patients based on a previously published study. All participants and health staff were unaware of the allocation until the final analysis. All patients were checked every week to monitor the exact compliance of aligned supplements in both groups. To restrict any undesirable effect of confounding factors, all patients were advised not to change their regular habits and lifestyle, specifically their diet and physical activity.

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Table 1. Characteristics of the intervention and placebo groups at the baseline and the end of study

Characteristics	Baseline			After 6 weeks of supplementation		
	Soy bread	Placebo bread	p value	Soy bread	Placebo bread	p value
No. of patients (female/male)	22 (female)	22 (female)		-	-	
Age (yr)	30–60	30–60		-	-	
Physical activity				-	-	
Severe (Q1)	30.00 ± 51.63	25.22 ± 44.73	0.364	-	-	
Mild (Q2)	60.22 ± 50.53	27.27 ± 23.07	0.468	-	-	
Medium (Q3)	76.81 ± 61.96	39.31 ± 39.79	0.200	-	-	
Low (Q4)	4.90 ± 2.06	3.40 ± 2.06	0.764	-	-	
Proteins intake (g/d)	77.47 ± 18.78	73.91 ± 6.12	0.326	103.68 ± 18.78	6.23 ± 70.20	0.624
Carbohydrates intake (g/d)	196.73 ± 107.67	171.74 ± 15.49	0.388	171.74 ± 15.49	211 ± 15.76	0.083
Fat intake (g/d)	38.64 ± 7.28	40.69 ± 3.0	0.432	46.82 ± 7.28	44.38 ± 3.00	0.392
Total energy intake (kcal)	1,436.8 ± 488.6	1,355.3 ± 82.8	0.355	2,078.8 ± 488.7	1,559.0 ± 84.3	0.087
Dietary fiber intake (g/1,000 kcal)	42.95 ± 2.42	10.17 ± 4.2	0.213	47.28 ± 2.42	15.91 ± 4.32	0.353
Insoluble fiber	1.03 ± 0.21	0.49 ± 0.16	0.552	1.21 ± 0.21	0.86 ± 0.16	0.118
Soluble fiber	0.18 ± 0.03	0.10 ± 0.04	0.847	0.18 ± 0.03	0.18 ± 0.42	0.212
Cholesterol	307.30 ± 47.54	336.40 ± 42.57	0.180	215.60 ± 47.54	349.50 ± 43.50	0.830

Data are shown as mean ± standard deviation or number (%). Statistical analysis was performed using an independent t-test.

Supplementation

In order to supply 30 g of isolated soy protein, the IG consumed 90 g of soy bread, as every 100 g of soy bread provides 40 g of isolated soy protein. They have been recommended to eat them before their lunch and dinner for 2 months, whilst CG of placebo bread similarly 2 times a day and just before lunch and dinner as IG. Participants have been recommended to use breads in crushed form if they have problems with chewing. Both soy bread and placebo bread are prepared by Sarina company, commercially named Dr. Soy. Every 6 weeks, all participants were supplied with their needed bread. The chemical composition of both 2 breads is outlined in **Table 1**. All chemical analytical procedures were conducted in Sepid laboratory according to approved guidelines of the Association of Analytical Communities. Both soy and placebo bread were the same in shape, color, size, packaging, and coding. Finally, the compliance of supplementation was judged by counting the number of boxes and also checking through phone calls every week.

Questionnaires, physical activity, anthropometrical and nutritional assessments

All subjects completed a general questionnaire containing demographic variables (age, sex), duration of diseases, drug history, and daily life habits at the beginning and the end of the study. Furthermore, systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean blood pressure also were recorded for all patients. Body weight and height were measured in minimum clothes by the use of a digital scale and stadiometer to the nearest 0.1 kg and 0.1 cm, respectively (Seca, Hamburg, Germany). BMI was calculated based on the approved formula.

Dietary intakes of nutrients were checked using a 24-hour diet recall questionnaire for 2 days, including 1 working day and 1 weekend day. Finally, dietary recalls were analyzed using Nutritionist IV software (First Databank, San Bruno, CA, USA) adjusted for Iranian foods.

Physical activity levels were assessed by all subjects based on the International Physical Activity Questionnaire (IPAQ short form) at the beginning and end of the trial [29].

Biochemical measurements

Fasting blood samples (10 mL) (overnight fast for 10–12 hours) were obtained from the antecubital vein before and after the trial. The sample was then centrifuged at 3,000 rpm

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for 10 minutes at 4°C. Serum was separated and stored at −80°C until final analysis. Serum levels of lipid profile were checked by commercial kits (Pars Azmoon, Tehran, Iran). Serum levels of total antioxidant capacity (TAC) and TNF-α were measured by the enzyme-linked immunosorbent assay method according to the manufacturer's instruction (IBL, International GmBH, Hamburg, Germany). Coefficients of variation for both intra and inter-assay were < 5%.

Statistical analyses

The normal distribution of all variables was tested by the Kolmogorov-Smirnov test. All categorical variables between the 2 groups are checked by the Pearson χ^2 test. In addition, a t-test, including paired and independent, was conducted to compare the intra-group and inter-group results. The value of $p < 0.05$ was considered as statistically significant. All statistical analyses were performed by the Statistical Package for Social Science version 17 (SPSS Inc., Chicago, IL, USA).

RESULTS

At first, among screened patients, 65 subjects were included in the last allocation. Finally, 44 women with RA (age range of 30–60 years and BMI range of 24–27 kg/m^2) were entered for the last analysis. Eventually, 22 patients were allocated to each group, including soy bread and placebo bread. All selected patients completed the trial; all participants tolerated the intervention well for 8 weeks except for some minor side effects. Mild bloating was reported in three enrolled subjects. Three subjects did not continue the trial due to problems with chewing soy bread; although compensating methods like crushing were recommended, they were not included in the last analysis.

At baseline, there were no significant differences between the 2 groups in physical activity and dietary intake at the beginning of the study. In essence, protein, carbohydrate, fat, and fiber intake, as well as medication dose (data not shown), were not significantly different between the two groups at the end of the trial, as shown in **Table 1**.

Table 2 represents the effect of soy bread consumption on lipid profile, inflammatory markers, and TAC. There were no significant differences between the two groups in measured lipid profile markers, including high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol (TC), triglyceride (TG), and very low-density lipoprotein (VLDL), at the end of the trial between the two groups of patients. In addition, TAC and C-reactive protein (CRP) also were not significant at the end of the trial between the 2 groups (0.66 and 0.12, respectively). However, the serum levels of TNF-α were reduced significantly in the soy bread group at the end of the intervention ($p < 0.000$) and compared with the control group ($p < 0.019$).

DISCUSSION

Different types of soy products are consumed around the world. Asians consume fermented soy foods, while Americans use the more processed form of it. Whilst different types of soy-based products and isoflavones were investigated in several studies, whole soy products were reported to have more beneficial effects [26,27]. Whole soy products like soy flour and

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Table 2. The effect of soy bread intake on lipid profile, antioxidant, and inflammatory markers among women with rheumatoid arthritis

Variable	Soy bread (n = 22)	Placebo bread (n = 22)	p*
	mean ± SD	mean ± SD	
HDL (mg/dL)			
Baseline	51.50 ± 13.65	52.45 ± 10.07	0.79
End of trial	51.77 ± 15.08	51.95 ± 11.63	0.96
p†	0.922	0.764	
LDL (mg/dL)			
Baseline	101.50 ± 37.15	101.81 ± 29.41	0.97
End of trial	77.27 ± 29.13	83.68 ± 30.16	0.47
p†	0.008	0.015	
TC (mg/dL)			
Baseline	172.00 ± 46.89	169.31 ± 48.36	0.85
End of trial	144.59 ± 38.79	146.18 ± 44.72	0.13
p†	0.002	0.038	
TG (mg/dL)			
Baseline	100.09 ± 32.62	145.40 ± 70.29	0.01
End of trial	86.68 ± 22.61	112.54 ± 49.13	0.20
p†	0.005	0.027	
VLDL (mg/dL)			
Baseline	19.88 ± 5.66	24.77 ± 10.72	0.06
End of trial	17.24 ± 4.56	22.45 ± 9.87	0.11
p†	0.001	0.027	
TNF-α (pg/mL)			
Baseline	39.75 ± 25.36	26.85 ± 18.97	0.06
End of trial	11.00 ± 2.80	18.06 ± 13.33	0.02
p†	< 0.000	0.07	
TAC (mM)			
Baseline	0.31 ± 0.20	0.31 ± 0.17	0.98
End of trial	0.57 ± 0.53	0.50 ± 0.42	0.66
p†	0.035	0.052	
CRP (mg/L)			
Baseline	0.59 ± 0.95	1.13 ± 1.12	0.09
End of trial	0.50 ± 0.80	0.95 ± 1.09	0.12
p†	0.68	0.21	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; VLDL, very low-density lipoprotein; TNF-α, tumor necrosis factor-α; TAC, total antioxidant capacity; CRP, C-reactive protein. mM: millimolar.
*Obtained from independent sample t-test; †Obtained from paired t-test.

bread, soy milk, and soy nut contain different compounds like fibers, helpful fatty acids, oligosaccharides, different active agents like lunasin, glycitein isoflavones, phytoestrogens and inositol-based substances like pinitol [26,30]. Therefore, all of these compounds may have superior value than exclusive compounds. Bread is the staple food in the Iranian diet [31]; in the present trial, whole soy bread was used, which contains all beneficial compounds.

Fortification of bread with soy flour can increase the quality of protein and improve its effects on human health [32]. There is a very limited number of studies with soy-bread supplementation [31-34]; soy-bread supplementation leads to improvement of anthropometric indices and blood pressure [31-34]. Different anti-arthritogenic, antioxidant, anti-inflammatory, and hypolipemic actions of soy-based products and soy components were reported in animal models of RA [6,23,25,35-38]. Suppressed IL-1β, IL-6 TNF-α, IL-4, interferon-gamma and matrix-metalloproteinases and malondialdehyde (MDA) and increased activity of antioxidant enzymes like paraoxonase and arylesterase following soy-based products has been indicated [19-23,28]. Treatment with soy-based products resulted in significant histological improvements like time to onset of arthritis, clinical arthritis severity

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score, histopathological arthritis severity score, and cell-mediated immunity to collagen [6,36,38]. Radiological results showed that bone degradation was inhibited by the treatment [23]. A previous clinical trial assessed the effect of puerarin on carotid intima-media thickness (CIMT) and other CVD risk factors in RA [19]. In that study, treatment with 400 mg of puerarin exerted a significant effect against CIMT progression in patients with active RA, which may be associated with the improvement of insulin resistance [19]. Other clinical trials evaluated the effects of soy milk consumption on inflammatory and oxidative stress markers among RA patients. Soy milk consumption for one month resulted in a significant reduction in TNF-α and high-sensitivity C-reactive protein (hs-CRP); however, adiponectin, leptin, IL-1, IL-6, and MDA were not changed significantly [28].

The effect of soy supplementation on inflammatory factors has been studied in different diseases. However, significant controversy was reported in all of those studies; some clinical trials reported that soy supplementation improved inflammatory biomarkers such as CRP, hs-CRP, IL-6 and TNF-α [39-42], while others suggested no helpful effect on inflammation [43-48]. Previous meta-analysis revealed no beneficial effect on blood hs-CRP concentration; however, authors claimed that in different groups, natural soy products may decrease hs-CRP plasma levels compared to the other origin of isoflavones [49]; other meta-analysis in post-menopausal subjects showed same results however they also reported that soy isoflavones may make a significant reduction in CRP levels only among women with raised levels of it [50]. Similar to our findings, daily oral consumption of soy isoflavones extract, which consists of 60.8 mg of genistein, 16 mg of daidzein, and 3.2 mg of glicitein had a favorable effect on serum TNF-α levels which did not affect CRP levels [51]. Other than decreased circulating TNF-α, other inflammatory biomarkers, CRP, and TAC did not change following supplementation with soy bread in women with RA.

Genistein and daidzein hinder the generation of pro-inflammatory cytokines by blocking the nuclear factor kappa B transcriptional system (inhibition of IκB phosphorylation) [52], which is the main controller of downstream inflammatory factors [53]. Furthermore, soy isoflavones have been reported to prevent the overproduction of nitric oxide and prostaglandin (PG) E_2 in macrophages, which are the main cells releasing pro-inflammatory contributors [54]. Metabolites of arachidonic acid (AA), including PG, leukotrienes, thromboxanes, and nitric oxide (NO), are essential mediators of inflammation; soy isoflavones prevent the overproduction of NO and PGE_2 in macrophages that are the main cells releasing pro-inflammatory contributors [54]. In fact, isoflavones regulate AA metabolism by preventing the protein levels and activities of pro-inflammatory enzymes such as phospholipase A2, lipoxygenase, cyclooxygenase-2, and inducible nitric oxide synthase [55]. One of the studied anti-inflammatory mechanisms of isoflavones is through the inhibition of cell adhesion molecule expression [56]. Macrophage-like and fibroblast-like synoviocytes of synovium tissue are positive for estrogen receptors, both α and β [57]. Due to the similarity of isoflavones to 17β-oestradiol, they can affect through binding to both the classical estrogen receptor [58]. Whole soy products reported to be more potent in activating estrogen receptor; this activation in situ could produce immune [58].

Dyslipidemia is also frequently reported in RA, maybe due to a secondary impact of the chronic inflammatory state. This status could not be neglected, and preventive and corrective actions must be taken to decrease CVD risk factors in RA patients [59]. Previous meta-analysis investigating soy products and serum lipids showed that intake of soy products resulted in a significant reduction in serum LDL-cholesterol TG and TC concentrations whilst

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it increased HDL concentration significantly [60]. Interestingly, again, in this study, whole soy products appeared to be more beneficial than soy supplementation, whereas isoflavone supplementation had no effects on the lipid profile [60]. Here in the present study, soy bread supplementation did not lead to any significant change in lipid profile components.

Different reactions were reported in different subjects after taking soy-based products. For instance, the dissimilar ability of people in metabolizing daidzein, one of the most plentiful soy isoflavones, to equol. It should be noted that Asians have more capacity to produce equol [49]. In addition, the synthetic potency of soybean recipients is different. Some polymorphisms alter the individual's response to isoflavones, worsening inflammatory status, but in some polymorphisms, soy intake decreases inflammation. Therefore, soy-based products may lead to different effects in different patients [17].

Some mild gastrointestinal side effects were reported following soy-based products, like constipation, bloating, and nausea. It can also cause allergic reactions involving rash, itching, and anaphylaxis in some people [61,62].

CONCLUSION

Soy bread consumption did not lead to any change in measured CVD risk factors, including a lipid profile, oxidative stress, and inflammatory markers, except decreased circulating TNF-α serum concentration. Future long-term, well-designed studies are needed to confirm these findings.

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