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ORIGINAL ARTICLE

Resveratrol as an effective adjuvant therapy in the management of rheumatoid arthritis: a clinical study

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Abstract
Resveratrol (RSV), a naturally occurring polyphenol, has been found to have potent antioxidant, anti-inflammatory, and anti-cancer effects. Recently, RSV was reported as a new potential agent to suppress inflammation of collagen-induced arthritis in a mouse model. Nevertheless, the clinical benefits of RSV in the management of rheumatoid arthritis (RA) were not studied. This randomized controlled clinical trial aims to shed some light on the therapeutic benefits of RSV in the treatment of RA in patients with different stages of the disease activity. In this randomized controlled clinical trial, 100 RA patients (68 female, 32 male) were enrolled randomly and divided into two groups, each of 50 patients: an RSV-treated group that received a daily RSV capsule of 1 g with the conventional treatment for 3 months and a control group that just received the regular treatment. The clinical and biochemical markers of RA in both groups were assessed. It was found that the clinical markers (i.e., the 28-joint count for swelling and tenderness) and the disease activity score assessment for 28 joints were significantly lowered in the RSV-treated group. Moreover, serum levels of certain biochemical markers (i.e., C-reactive protein, erythrocyte sedimentation rate, undercarboxylated osteocalcin, matrix metalloproteinase-3, tumor necrosis factor alpha, and interleukin-6) were also significantly decreased in RSV-treated patients. The current study suggests the addition of RSV as an adjuvant to the conventional antirheumatic drugs.

Keywords DAS28-ESR · Resveratrol · Rheumatoid arthritis · TNF-α · ucOC

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease that usually manifests as chronic multiple-joint inflammation with distortion of joint cartilage [1]. Although the etiology of the disease involves different mechanisms, the inflammatory cytokines such as the tumor necrosis factor alpha (TNF-α) and the interleukins (IL-1, IL-6, and IL-17) play a major role [2]. High concentrations of TNF-α and IL-1 can be recovered from the plasma and the synovial fluid of RA patients, where they are responsible for the induction of hyperplasia of the synovial cells at joints, hence precipitating RA [3]. The cytokines also induce matrix metalloproteinases and/or activate osteoclasts, causing irreversible damage of soft tissues and bones. Unfortunately, the side effect profiles of several tested drugs, with claimed suppressive effects on cytokines, have limited their usefulness, necessitating the search for an ideal, safer agent [4].

Resveratrol (RSV) is a natural polyphenolic compound with a chemical formula of 3,5,4′-trihydroxystilbene that occurs in peanuts and in the skin of red grapes in addition to several other natural sources [5]. Research studies have shown that it exerts a variety of favorable actions. It prolonged life span in mice as well as in certain organisms and was found to have antioxidant and anti-inflammatory effects in addition to a protective effect against diabetes mellitus [6, 7]. Resveratrol was also found of benefit in preventing brain plaque deposition in neurodegenerative diseases such as Alzheimer's [8]. It was also reported that

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it possesses a potent and specific inhibitory effect on the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), which is induced by TNF-α or IL-1β [9, 10]. And with regard to RA, resveratrol was found effective in preventing hyperplasia of synovial cells in animal models as well as in isolated human cells [9, 10].

More recently, RSV was found to decrease serum and joint tissue levels of TNF-α, IL-1β, IL-6, and monocyte chemoattractant protein 1, as well as the soluble receptor activator of NF-κB ligand. Expression of NF-κB was decreased in resveratrol-fed mice, so it was concluded that dietary supplementation with RSV may alleviate inflammation and bone destruction in collagen-induced arthritis in the mice model [11]. Moreover, RSV was capable of inducing apoptosis of fibroblast-like synoviocytes (FLS) derived from RA patients through the activation of caspase-8-a process that modulates apoptotic machinery of the mitochondria. This indicates that RSV induces extensive apoptotic cell death, along with a caspase-dependent or caspase-independent pathway, by converging on mitochondrial signaling in RA FLS. Accordingly, RSV is considered as a potential treatment for RA [10, 12]. Resveratrol also modulated inflammatory arthritis in rodents through selective suppression of the cellular and humoral responses responsible for RA disease development. Although such findings may explain the protective effects of red wine (which is rich in RSV) against RA, they more importantly offer a potential effective and safe agent for the treatment of RA [13]. It is worth mentioning that the safety of different doses of RSV in humans, as a complementary nutritional substance, was reported in several studies [14, 15].

Finally, since the therapeutic value of RSV in RA has never been tested so far on humans, the present prospective cohort study was designed to explore the influence of RSV oral capsules, added to conventional RA therapy, on the biochemical and clinical markers in RA patients through a randomized controlled clinical trial. Changes in these markers between pre- and post-treatment with RSV will be determined.

Material and methods

This study was conducted between July 2016 and June 2017. The protocol was approved by the Institutional Review Board of the Faculty of Medicine at Assiut University, Assiut, Egypt, (Approval Number 2542/2015) and all selected subjects have signed informed consents as volunteers. The research was conducted in compliance with the Helsinki Agreement as well as with the research ethics standards of Egypt.

Study population

All selected subjects were Egyptian RA patients followed up by the outpatient clinics of the Rheumatology and Rehabilitation Department of Assiut University Hospital, Assiut, Egypt. They were diagnosed in accordance with the revised criteria of the American College of Rheumatology (ACR) [16]. A total of 100 patients, who fulfilled the inclusion criteria, were enrolled in a sequential manner throughout the timeframe of the study so that one patient is randomly assigned to either a test group or a control group and the following patient is assigned to the remaining group that is left after assigning the first patient. So eventually, both groups had an equal number of 50 patients.

In order to avoid direct or indirect effects on the pharmacokinetics and/or pharmacodynamics of resveratrol on RA patients, patients with any of the following conditions were excluded: infections, diabetes mellitus, peripheral vascular disease, coronary artery disease, thyroid dysfunction, liver or kidney disease, Parkinson's disease, and other chronic disorders. Exclusion criteria also included smokers, excessive alcoholics, and patients whose diets included ingredients with claimed antioxidant and antirheumatic effects such as grape seed extract, ginkgo biloba, quercetin, large amounts of red grapes, and vitamin C during the last 3 months before the enrollment. In addition, patients receiving biologic therapy, such as anti-TNF-α drugs, were also excluded because of the possible additive effects of RSV on TNF-α.

Each member of the test group received one daily oral soft gel capsule containing 1 g of resveratrol (Life Smart Labs, MA, USA) for 3 months in addition to the disease-modifying antirheumatic drugs (DMARDs) he/she was receiving, while members of the control group received just their regular treatment. This RSV dose was found to fall within the safety dosage limits discussed in the aforementioned studies for the treatment of diseases such as Alzheimer's, cancer, and diabetes [17–19] in addition to the effective dosages used in animal models [13].

The antirheumatic drugs used were leflunomide, hydroxychloroquine, sulfasalazine, methotrexate, prednisolone, and various nonsteroidal anti-inflammatory drugs. Although the selected drugs and their dosages varied between the patients, they were stable for each patient in either group for 6 months prior to and throughout the individual study period of 3 months. The patients were followed up regularly during the study period to monitor possible side effects or complaints from RSV.

Resveratrol authenticity

The RSV capsules used in this study were analyzed for authenticity and content using HPLC with diode array detector according to Singh et al. [20] and the RSV reference standard was obtained from Sigma Aldrich (Seelze, Geramny). The mean content was found to be 97.8 ± 1.45%.

Clinical and biochemical monitoring

The clinical and biochemical markers for RA activity and bone health were obtained before and after the individual study period (3 months) for each patient in both study groups. These measures were tender joint count-28 (TJC-28), swollen joint count-28 (SJC-28), rheumatoid factor (RF), matrix metalloproteinase-3 (MMP-3), undercarboxylated osteocalcin (ucOC), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

Blood samples were collected under aseptic safety measures by venipuncture and were on-site centrifuged at 2500×*g* for 10 min at 4 °C, and were then stored at − 30 °C until analysis time. Serum ucOC levels were analyzed by electro-chemiluminescence immunoassay (ECLIA) kits (Sanko Junyaku Co Ltd, Tokyo, Japan) according to Sokoll et al. [21]. Serum MMP-3 was measured by Stromelysin-1-Kit (Fuji chemical Industries LTD, Japan) using an enzyme immunoassay (EIA) technique reported by Obata et al. [22]. Serum levels of TNF-α and IL-6 were determined by enzyme-linked immune-sorbent assay (ELISA, Abcam plc, Cambridge, UK) as described by Tas et al. [23]

The disease activity score assessing 28 joints (DAS28) was also calculated for each patient, pre- and post-study, using erythrocyte sedimentation rate (DAS28-ESR) as a good indicator recommended by selected specific studies [24, 25]. Moreover, for the sake of deeper investigation, we further subdivided the RSV-treated subjects into two subgroups after the study period: moderate-to-good responders and non-responders. This subdivision was based on the response criteria of the European League Against Rheumatism (EULAR) [26]. According to these criteria, good responders must show low DAS28-ESR (≤ 3.2) with a decrease of > 1.2 from the baseline, moderate responders must show moderate disease activity score ($3.2 <$ DAS28-ESR ≤ 5.1) with a decrease of > 0.6 and ≤ 1.2 from the baseline, and non-responders are whose DAS28-ESR is high (> 5.1) with a decrease of ≤ 0.6 from the baseline.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 19.0, SPSS Inc. Chicago, IL, USA). The results were presented as the mean ± standard error of the mean (SEM). Comparisons between the test group and the control group, as well as between moderate-to-good responders and non-responders among the test group, were performed using one-way analysis of variance (ANOVA) with Tukey's honest significant difference (HSD) for post hoc analysis. Significance was defined by the p value, where $p \leq 0.001$ was considered highly significant, $0.001 < p \leq 0.05$ was considered significant, and $p > 0.05$ was considered non-significant.

Results

All the 100 selected patients have completed the study without any dropout or complaint from the addition of resveratrol to their antirheumatic drug regimens. As shown in Table 1, there was no significant difference between the RSV-treated group and the control group regarding the demography (i.e., age, duration of the disease, weight, height, and body mass index) and the clinical and biochemical indices (i.e., RF positivity, SJC-28, TJC-28, CRP, ESR, ucOC, MMP-3, TNF-α, IL-6, and DAS28-ESR) measured just before the conduction of the study. The highest and lowest DAS28-ESR for the test group was 7.02 and 1.85, respectively, while the highest and lowest values for the control group were 6.52 and 3.24, respectively. So, the enrolled patients presented with variable disease activity as depicted in Fig. 1.

Interestingly, the differences in clinical and biochemical indices have changed dramatically, in favor of the RSV-treated group, after the treatment period. Except for RF positivity, which has non-significantly decreased in the RSV-treated group, CRP has significantly decreased ($p \leq 0.05$) and the other biochemical markers (i.e., ESR, ucOC, MMP-3, TNF-α, IL-6) have highly significantly decreased ($p < 0.001$), as shown in Table 2. Similarly, the clinical markers (i.e., SJC-28 and TJC-28) and DAS28-ESR have highly significantly decreased in the RSV-treated group as shown in Fig. 1. The highest and lowest DAS28-ESR for the test group was 4.89 and 1.74, respectively, while the highest and lowest values for the control group were 6.31 and 3.17, respectively.

Within the RSV-treated group, it was found that 9 patients were non-responders while 41 patients were moderate-to-good responders according to the EULAR response criteria. As presented in Table 3, the differences in the clinical indices (i.e., SJC-28 and TJC-28) between responders and non-responders, before the addition of resveratrol (RSV) to the antirheumatic drugs, were significant ($p < 0.05$) in favor of the responders, and the significance level became higher ($p < 0.001$) after the RSV treatment period (3 months). Regarding the biochemical features prior to the commencement of the study, there was no significant difference ($p > 0.05$) between both subgroups for RF positivity, CRP, ucOC, and TNF-α while the difference was significant in favor of the responders for the other indices. However, all the biochemical indices were found to be significantly lower in the responder subgroup after the study period. On the other hand, the DAS28-ESR was significantly lowered pre- and post-RSV addition in the responder subgroup as depicted in Fig. 1.

Discussion

The present study investigated the effect of a daily single oral dose of 1000 mg of RSV co-administered with conventional

Table 1 Demographic, clinical, and biochemical characteristics of the control and the test groups prior to the conduction of the study

Features	Control group[a] ($n = 50$)	RSV-treated group[a] ($n = 50$)	p value
Demographic features			
Sex (male:female)	18:32	14:36	–
Age (years)	44.2 ± 16.4	46.5 ± 12.3	> 0.05 (NS)
Duration of disease (years)	9.8 ± 5.5	9.4 ± 5.8	> 0.05 (NS)
Weight (kg)	71.4 ± 13.5	70.9 ± 12.9	> 0.05 (NS)
Height (m)	1.64 ± 0.16	1.61 ± 0.12	> 0.05 (NS)
BMI (kg/m^2)	26.5 ± 1.9	27.3 ± 1.5	> 0.05 (NS)
Clinical and biochemical features			
SJC-28	4.3 ± 1.4	4.1 ± 1.3	> 0.05 (NS)
TJC-28	5.9 ± 2.0	5.7 ± 1.8	> 0.05 (NS)
RF positivity (% of patients)	90	92	–
CRP (mg/dL)	2.9 ± 0.8	2.7 ± 0.7	> 0.05 (NS)
ESR (mm/h)	43.8 ± 14.8	39.4 ± 11.5	> 0.05 (NS)
ucOC (ng/mL)	4.5 ± 0.7	4.1 ± 0.6	> 0.05 (NS)
MMP-3 (ng/mL)	198.6 ± 27.9	188.6 ± 21.2	> 0.05 (NS)
TNF-α (pg/mL)	31.5 ± 12.3	32.0 ± 8.1	> 0.05 (NS)
IL-6 (pg/mL)	54.0 ± 25.4	50.5 ± 17.2	> 0.05 (NS)
DAS28-ESR	4.91 ± 0.92	4.62 ± 0.99	> 0.05 (NS)

BMI, body mass index; *CRP*, C-reactive protein; *DAS28-ESR*, disease activity score assessing 28 joints calculated with ESR; *ESR*, erythrocyte sedimentation rate; *IL-6*; interleukin-6; *MMP-3*, matrix metalloproteinase; *NS*, non-significant; *RF*, rheumatoid factor; *RSV*, resveratrol; *SJC-28*, swollen joint count assessing 28 joints; *TJC-28*, tender joint count assessing 28 joints; *TNF-α*, tumor necrosis factor alpha; *ucOC*, undercarboxylated osteocalcin

[a] Mean ± SEM

antirheumatic drugs to RA patients over a period of 3 months. Compared with the control group, the RSV-treated group has shown significant drop in the major clinical and biochemical markers involved in the mechanism of disease activity. These indices remained almost unchanged in the control group throughout the study period. However, nine patients (18%) from the RSV-treated group were considered non-responders to the addition of RSV to their regular antirheumatics. This subgroup has already shown considerable lower baseline values of the biochemical and clinical indices compared with the responder group, as shown in Table 3 and Fig. 1, indicating a good response to their standard antirheumatic drugs and ruling out potential refractoriness to the disease or nonadherence to the RSV added to their therapeutic regimens.

Resveratrol has been studied in a variety of clinical trials for a variety of disorders such as cardiovascular diseases, diabetes, obesity, and cancer [27, 28]. The results in such trials have shown contrasting outcomes from the use of this agent. For example, RSV has exhibited some benefits in the management of hypertension, diabetes mellitus, and lipid profile, and it enhanced the efficacy of oral amoxicillin in certain infections [29–32]. On the other hand, RSV has lacked evident advantages in the management of pain in endometriosis, nonalcoholic fatty

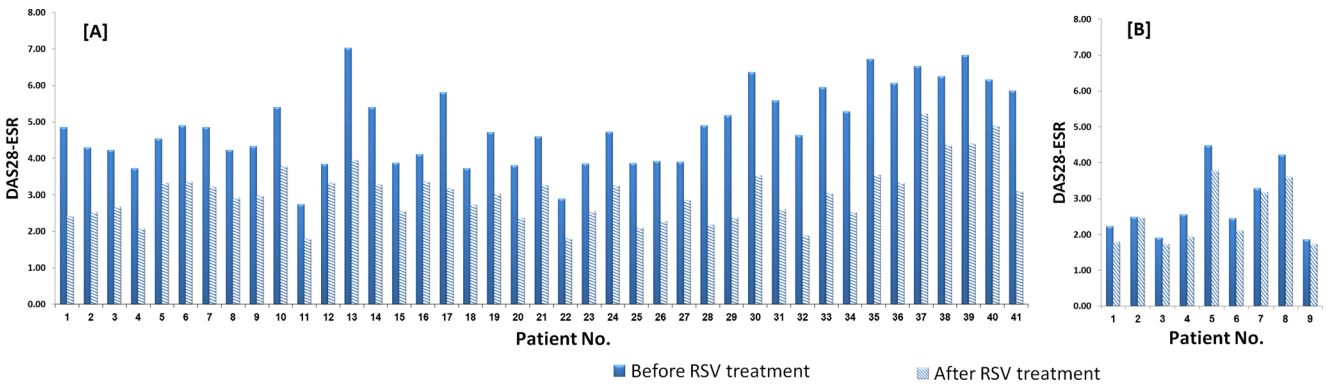

Fig. 1 DAS28-ESR for RA patients before and 3-months after the addition of resveratrol to the antirheumatic drugs. **a** Moderate-to-good responders ($n = 41$). **b** Non-responders ($n = 9$)

Table 2 Clinical and biochemical characteristics of the control and the test groups after the study period

Features	Control group[a] ($n = 50$)	RSV-treated group[a] ($n = 50$)	p value
SJC-28	4.1 ± 1.5	2.5 ± 1.1	< 0.001 (HS)
TJC-28	5.7 ± 2.1	3.1 ± 1.7	< 0.001 (HS)
RF positivity (% of patients)	90	86	–
CRP (mg/dL)	2.6 ± 0.7	2.1 ± 0.4	< 0.01 (S)
ESR (mm/h)	41.7 ± 20.4	23.5 ± 9.7	< 0.001 (HS)
ucOC (ng/mL)	4.2 ± 0.6	2.5 ± 0.5	< 0.001 (HS)
MMP-3 (ng/mL)	195.2 ± 32.4	127.4 ± 18.6	< 0.001 (HS)
TNF-α (pg/mL)	29.7 ± 11.8	18.3 ± 6.2	< 0.001 (HS)
IL-6 (pg/mL)	51.2 ± 22.1	23.5 ± 7.1	< 0.001 (HS)
DAS28-ESR	4.78 ± 0.87	3.12 ± 0.80	< 0.001 (HS)

CRP, C-reactive protein; *DAS28-ESR*, disease activity score assessing 28 joints calculated with ESR; *ESR*, erythrocyte sedimentation rate; *HS*, highly significant; *IL-6*, interleukin-6; *MMP-3*, matrix metalloproteinase; *RF*, rheumatoid factor; *RSV*, resveratrol; *S*, significant; *SJC-28*, swollen joint count assessing 28 joints; *TJC-28*, tender joint count assessing 28 joints; *TNF-α*, tumor necrosis factor alpha; *ucOC*, undercarboxylated osteocalcin

[a] Mean ± SEM

liver, and walking problems in patients with peripheral artery disease [33–35]. Although sample sizes and treatment protocols in these studies may have played a role in the conflicting outcomes, this may also indicate that the mechanism of certain illnesses may not be the potential target for RSV. It is worth mentioning that the average reduction in the DAS28, which is attributable to the addition of RSV in our study, was − 1.66 which was found to be superior to the reduction of the same score by − 0.59 using atorvastatin in a previous study [36].

Table 3 Comparison between pre- and post-treatment clinical and biochemical indices of moderate-to-good responders and non-responders to resveratrol

Index	Time of measure	Moderate-to-good responders[a] ($n = 41$; 12 M, 29 F)	Non-responders[a] ($n = 9$; 2 M, 7 F)	p value
SJC-28	Pre-treatment	3.8 ± 1.0	4.5 ± 1.4	< 0.05 (S)
	Post-treatment	1.5 ± 0.8	3.9 ± 1.3	< 0.001 (HS)
TJC-28	Pre-treatment	5.3 ± 1.8	6.2 ± 2.5	< 0.05 (S)
	Post-treatment	2.2 ± 1.4	4.3 ± 1.9	< 0.001 (HS)
RF positivity (% of patients)	Pre-treatment	92.7	88.9	–
	Post-treatment	85.4	88.9	–
CRP (mg/dL)	Pre-treatment	2.9 ± 0.9	2.6 ± 0.5	> 0.05 (NS)
	Post-treatment	1.8 ± 0.5	2.3 ± 0.4	< 0.01 (S)
ESR (mm/h)	Pre-treatment	44.2 ± 15.4	32.8 ± 12.1	< 0.01 (S)
	Post-treatment	23.7 ± 9.1	28.6 ± 10.9	< 0.01 (S)
ucOC (ng/mL)	Pre-treatment	4.2 ± 0.9	3.6 ± 0.8	> 0.05 (NS)
	Post-treatment	2.5 ± 0.6	3.1 ± 0.7	< 0.01 (S)
MMP-3 (ng/mL)	Pre-treatment	184.0 ± 17.4	155.1 ± 15.9	< 0.01 (S)
	Post-treatment	124.3 ± 18.2	138.9 ± 12.7	< 0.01 (S)
TNF-α (pg/mL)	Pre-treatment	34.1 ± 9.2	30.5 ± 7.6	> 0.05 (NS)
	Post-treatment	17.9 ± 7.0	24.1 ± 6.0	< 0.01 (S)
IL-6 (pg/mL)	Pre-treatment	55.7 ± 18.5	45.2 ± 16.4	< 0.01 (S)
	Post-treatment	23.6 ± 7.4	36.7 ± 9.8	< 0.01 (S)
DAS28-ESR	Pre-treatment	4.98 ± 1.07	4.02 ± 0.96	< 0.01 (S)
	Post-treatment	3.02 ± 0.77	3.79 ± 0.82	< 0.01 (S)

CRP, C-reactive protein; *DAS28-ESR*, disease activity score assessing 28 joints calculated with ESR; *ESR*, erythrocyte sedimentation rate; *F*, female; *IL-6*, interleukin-6; *M*, male; *MMP-3*, matrix metalloproteinase; *NS*, non-significant; *RF*, rheumatoid factor; *S*, significant; *SJC-28*, swollen joint count assessing 28 joints; *TJC-28*, tender joint count assessing 28 joints; *TNF-α*, tumor necrosis factor alpha; *ucOC*, undercarboxylated osteocalcin

[a] Mean ± SEM

Up to the time of this clinical trial, there was no other similar study to compare our results with. However, our findings may confirm the beneficial effect of wine, which is rich in RSV, on the disease activity of RA [37]. Our findings have also shown a significant effect of RSV in lowering the serum levels of TNF-α and IL-6 (Fig. 2), which was reported to be significantly higher in the RA population than in healthy subjects [38]. And while some minor gastrointestinal side effects of RSV were reported in some other studies [17, 39], our enrolled patients have safely tolerated the RSV dose administered without reported adverse events. However, one of the precautions that must be taken into consideration is that the RSV metabolite trans-resveratrol sulfate is a possible inhibitor of certain cytochrome P450 enzymes in humans and may interact with medications that are mainly metabolized by CYP2C9, which is not the case for the antirheumatic drugs used in this study [18].

Finally, despite the promising outcomes of this study regarding the use of RSV in the management of RA, we believe that it is still early to be considered as a primary treatment for the disease because of some limitations. The relatively small sample size and the fact that all study subjects were selected from a single geographic region make generalizability of the outcomes questionable. Also, we did not perform radiographic investigations to support the positive outcomes of the clinical and biochemical markers of the disease used in our study. This was due to the short term of the study period which may not reveal significant radiographic changes provided that the patients were also receiving disease-modifying agents that are supposed to reduce joint damage. So, the role of RSV in the treatment of RA is better described as an adjuvant until more is explored about its efficacy through more comprehensive and larger scale, multicenter clinical studies. We cannot confirm which base DMARD therapy was ideal for the combination with RSV at this point because these agents and their doses have largely varied between patients. Future studies should, however, be designed to test RSV activity in a strictly defined DMARD therapy. The possible clinical effect of RSV, as an antioxidant, in lowering the oxidative and nitrative stress in RA will be considered.

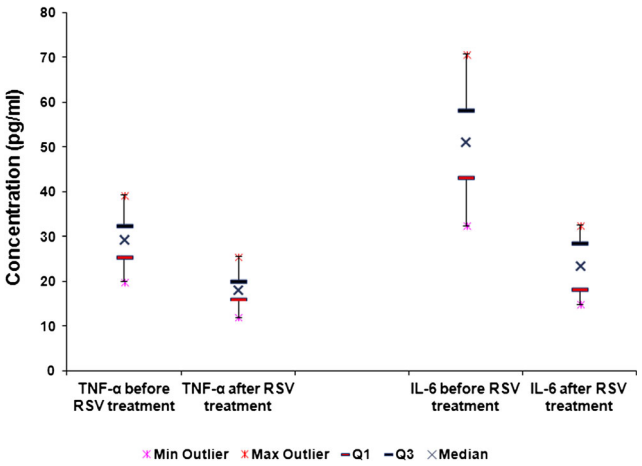

Fig. 2 Box and whisker plot of serum levels of inflammatory cytokines (TNF-α and IL-6) before and after the addition of resveratrol to the antirheumatic agents

Conclusion

In conclusion, this study has shown that the co-administration of oral resveratrol to RA patients has improved the disease management by reducing its activity as well as some of its clinical and biochemical markers. The improvement in the disease activity may be a result of changes in bone mineral metabolism and the actions of cytokines involved in etiopathogenesis of RA, supported by the antioxidant effect of RSV through the reduction of the oxidative and nitrative stress. Accordingly, and until more comprehensive studies are conducted, we can suggest the use of resveratrol as an adjuvant to conventional antirheumatic agents.

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Role of the authors The authors had design for this study, followed-up RA patients, analyzed data, wrote the manuscript and had full authority to submit the final manuscript. Toxicological Research & Studies Center at Taibah University had only supervised the safety data for this study, with no participation on this study.

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Compliance with ethical standards

Disclosures None.

Ethics approval and consent to participate All RA patients participated in the study gave informed consent and ethical approval for the study was obtained by Institutional Review Board of the Faculty of Medicine at Assiut University.

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