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## ORIGINAL STUDY

# Long-term resveratrol supplementation improves pain perception, menopausal symptoms, and overall well-being in postmenopausal women: findings from a 24-month randomized, controlled, crossover trial

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**Abstract**

***Objective:*** Following concerns about hormone therapy, postmenopausal women need alternative options to manage menopause-related symptoms and improve their well-being. A 14-week pilot study has shown that supplementation with resveratrol, a phytoestrogen with circulatory benefits, can improve aspects of well-being including chronic pain, which is a common complaint in postmenopausal women. We aimed to confirm these benefits in a larger, long-term study.

***Methods:*** The Resveratrol for Healthy Ageing in Women study, a 24-month randomized, double-blind, placebo-controlled, two-period crossover intervention trial of resveratrol supplementation (75 mg BID) was conducted in 125 healthy postmenopausal women to evaluate effects on cognitive performance (results published elsewhere). Aspects of well-being including pain perception, mood and depressive symptoms, menopausal symptoms, sleep quality, and quality of life were assessed with questionnaires as secondary outcomes of the study. Cerebrovascular responsiveness to hypercapnia was measured as a surrogate marker of cerebrovascular function.

***Results:*** Resveratrol supplementation reduced composite pain score ($P < 0.001$), especially in overweight individuals; this was associated with improvements in cerebrovascular responsiveness to hypercapnia ($R = -0.329$, $P = 0.014$). Somatic menopausal symptoms ($P = 0.024$) and general well-being ($P = 0.010$) were also improved after resveratrol supplementation.

***Conclusions:*** These results confirm the pilot study finding that resveratrol supplementation can reduce chronic pain in age-related osteoarthritis and improve menopause-related quality of life in postmenopausal women. These improvements are sustained by supplementation for at least 12 months and are associated with enhancement of circulatory function.

***Clinical Trial Registration:*** ACTRN12616000679482p

***Key Words:*** Cerebrovascular function – Hot flushes – Menopause – Pain – Resveratrol – Well-being.

***Video Summary:*** http://links.lww.com/MENO/A638.

As life expectancy increases worldwide, many millions of women will be spending a third or more of their lives postmenopausally. After menopause, about 70% of women experience vasomotor symptoms due to the loss of endogenous estrogen.[1] Chronic aches and pain, particularly musculoskeletal, are the second most common symptoms reported by menopausal women[2] and can negatively affect sleep quality as well as perceived mood and stress.[3] Depressed mood can in turn reduce mental efficiency and motivation for everyday activities, which in the long term can lead to social deprivation and physical inactivity, resulting in a sedentary lifestyle that increases the prevalence of

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obesity and metabolic syndrome.[4-6] Influenced by all of these factors, the quality of life for women decreases postmenopausally.[7,8]

Loss of estrogen also impacts the vascular endothelium, evidenced by reduction of brachial artery flow-mediated dilatation (a measure of endothelium-dependent vasodilator function) that becomes worse with time after menopause.[9] This also extends to the microcirculation, including in the brain; cerebrovascular responsiveness (CVR) to hypercapnia, a measure of cerebral endothelial function, is reduced in postmenopausal women compared to premenopausal women and age-matched men.[10] Impaired CVR is in turn associated with major depression[11] and cognitive impairments,[12] affecting general well-being and independence of women. There is evidence of an association between the severity of hot flushes and impaired endothelial function in early postmenopausal women within 3 years of menopause.[13] Estrogen decline also influences pain perception; postmenopausal women reported significantly higher pain perception than premenopausal women[14] and those suffering from chronic pain were shown to be more susceptible to coronary disease.[15] Taken together, menopause-related symptoms may compromise endothelial function and accelerate the occurrence of chronic diseases. Interventions to reverse or delay this dysfunction may be beneficial for postmenopausal women's health and well-being.

Resveratrol is a phytoestrogen, which has weak estrogenic properties with selective binding to estrogen receptors and promote endothelial function due to increased nitric oxide bioavailability.[16] Evidence for circulatory benefits of resveratrol is extensive; it improves both systemic[17] and cerebral endothelial vasodilator function in humans.[18,19] In addition, there is in vitro evidence that resveratrol can also inhibit the degradation of mitochondria and apoptosis in human chondrocytes through anti-inflammatory and chondro-protective mechanisms.[20] There is also limited clinical evidence that resveratrol can improve joint pain, menopausal symptoms, and the general perception of well-being in postmenopausal women. Wong et al[21] were the first to report that resveratrol supplementation (150 mg/d for 14-wk) can reduce generalized pain perception and improve overall well-being in postmenopausal women; the improvements were associated with enhancements in circulatory function. To establish recommendations for resveratrol supplementation, the reported short-term benefits now need to be confirmed in a larger study demonstrating sustained long-term benefits.

We recently reported initial outcomes of a 24-month crossover intervention trial: Resveratrol for Healthy Ageing in Women (RESHAW). A parallel comparison after 12 months of supplementation showed sustained benefits of resveratrol (150 mg/d) versus placebo for cognitive performance and cerebrovascular function.[22] Benefits of resveratrol on cognitive performance (primary outcome), cerebrovascular function, and insulin sensitivity in 125 postmenopausal women after completion of the 24-month crossover has subsequently been reported (Thaung Zaw 2020, under review). We now report (1) effects of resveratrol on aspects of overall well-being such as pain perception, menopausal symptoms, mood and depressive symptoms, sleep quality, and perceived quality of life; (2) associations between improvements in well-being and cerebrovascular function; (3) differences between normal and overweight women on the effects of resveratrol on perceived well-being; and (4) the influence of concomitant discretionary use of fish oil supplements (not administered as part of the trial protocol) on the effects of resveratrol on pain perception, since fish oil, an alternative bioactive nutrient that can improve endothelial function, is commonly consumed by older Australians to alleviate joint stiffness and improve vitality.[23]

## METHODS

### Study design

A $2 \times 12$-month randomized, double-blind, placebo-controlled, crossover dietary intervention trial with resveratrol (RESHAW) was conducted at the Clinical Nutrition Research Centre of the University of Newcastle in Australia. For 90% power to detect a statistically significant ($P < 0.05$) medium effect size (Cohen $d = 0.5$) improvement in the primary outcome (overall cognitive performance), 87 completers were required for a crossover comparison. To allow for 45% attrition due to a long-term study and to account for the difficulty in acquiring feasible data for cerebrovascular function assessments, especially in older women, we aimed to recruit 170 women.

From November 2016 to May 2017, we recruited community dwelling women residing in the Hunter region of New South Wales through approved newspaper and radio campaigns and from a database of previous participants of the Clinical Nutrition Research Centre and from the Hunter Medical Research Volunteers Registry. Eligible participants were aged 45-85 years, more than 12 months of cessation of menses and not taking hormone therapy. We excluded participants who took insulin or warfarin or had a history of breast or cervical cancer, major heart, kidney or liver disease, a neurological disorder, clinical depression, or suspected dementia.

The study was conducted in accordance with the Declaration of Helsinki and the Principles of Good Clinical Practice as outlined by the International Conference on Harmonization. This study was approved by the University of Newcastle's Human Research Ethics Committee (H-2016-0091) and registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12616000679482p).

### Intervention

Resveratrol (Veri-te$^{TM}$ resveratrol) capsules (containing 75 mg of $>98\%$ of resveratrol) and placebo (comprised of several inert excipients) were identical in shape and color supplied by Evolva SA, Reinach, Switzerland. The capsule containers were only identifiable by code numbers. An independent investigator, who was not involved in recruitment or data collection, held the code and allocated volunteers to resveratrol or placebo capsules using the Altman randomization by minimization procedure[24] balancing the treatment

groups based on age, menopausal years, and clinic blood pressure at screening visit. All other investigators and participants were blinded to the supplement allocation throughout data collection and analysis.

Participants were instructed to take two capsules of their allocated treatment each day (one in the morning and one in the evening) for 12 months, after which they crossed over to the alternate treatment for a further 12 months. There was no washout period.

**Study procedures**

Volunteers refrained from medications, food, and beverages other than water for 2 hours before attending the screening visit. A written informed consent was obtained before any assessment. Volunteers with clinic blood pressure above 160/100 mm Hg were excluded.

As reported previously,[22] after routine anthropometric and cardiovascular measurements, participants underwent cerebrovascular function assessments including CVR to a hypercapnic challenge using transcranial Doppler ultrasound. Cognitive performance was then assessed using a battery of neuropsychological tests, whereas the transcranial Doppler ultrasound continuously assessed CVR to cognitive stimuli.

**Well-being measures**

Participants completed six paper-based questionnaires that assessed their perceptions on general living, that is, pain, mood and depressive symptoms, menopausal symptoms, sleep quality, and quality of life at baseline (month-0), at the end of first supplementation phase (month-12), and at the end of second supplementation phase (month-24).

*Pain*

Participants' pain symptomatology was assessed using Short-form McGill Pain questionnaire,[25] composed of three subscales: descriptive pain score, pain visual analog scale (VAS), and present pain intensity. For the descriptive pain score, participants were asked to rate the severity of chronic musculoskeletal pain with 15 descriptions of sensory pain, for example, throbbing, shooting, or aching, using the Likert scale of ''none = 0, mild = 1, moderate= 2, and severe= 3'', where a maximum score of 45 represents the most pain experienced. Participants also marked on a 10-cm VAS, where pain VAS represents 0 to 4 mm (no pain), 5 to 44 mm (mild pain), 45 to 74 mm (moderate pain), and more than 75 mm (severe pain).[26] Participants quantified their present pain intensity on a 5-point scale ranging from ''no pain'' to ''excruciating''. Each component of the subscale was expressed as a percentage and the average of the three was taken as a composite pain score. Participants also specified all the sources and locations of chronic pain on diagrams of both front and back of the body.

*Mood and depressive symptoms*

We assessed participants' mood states and depressive symptoms by Profile of Mood States and the Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaires. Profile of Mood States has proven to be an excellent measure of mood states and their fluctuations in postmenopausal women.[27] It is a validated questionnaire containing 65 expressions assessing various mood subscales, such as tension, depression, anger, fatigue, confusion, and vigor over the last 7 days before the scheduled visit and on the day of the visit. The participants rated on a 5-point scale for each mood statement, where ''1'' being ''not at all'' and ''5'' being ''extremely''. Each subscale score was expressed as a percentage with higher subscale scores indicated more negative mood except for the vigor subscale. Total mood disturbance was calculated by averaging the percentages of the negative mood subscales (tension, depression, anger, fatigue, and confusion) then subtracting the percentage of vigor.

The CES-D is a 20-item measure widely used to characterize depressive symptoms in the general population.[28] It measures major depressive symptomatology including depressive mood, feelings of guilt, and worthlessness. Participants rated the frequency of symptoms experienced during the last week. A numerical score of up to three for ''most days (5-7 d)'' was assigned to each question. A maximum score of 60 indicated the most depressive symptoms experienced, where a score of 16 is the cut-off point that has been typically recommended for depression.[29] CES-D score was expressed as a percentage; above 25% indicates major depression.

*Menopausal symptoms*

Menopausal symptoms, categorized as somatic, psychological, and urogenital symptoms, were assessed by the Menopause Rating Scale comprised of 11 questions, where the participants were asked to indicate their present menopausal symptoms from none, mild, moderate, severe, or very severe.[30] A value was assigned to each symptom severity, beginning from 'zero' for no symptoms through 'four' for very severe symptoms. A total score of 44 represents the worst menopausal symptoms and the severity of menopausal symptoms was expressed as a percentage. A score above 16 (36%) represents severe menopausal symptoms, a score of 9 to 15 (20%-34%) represents moderate symptoms, a score of 5 to 8 (11%-18%) represents mild symptoms and little or no symptoms for a score of 0 to 4 (0%-9%).[31]

*Sleep quality*

Pittsburgh Sleep Quality Index was used to assess the participant's sleep quality and disturbances over the last month.[32] Participants rated their sleep duration, quality, disturbances, latency, habitual sleep efficiency, and daytime dysfunction. These items were summed to yield a global score with a range from 0 to 21; higher scores indicate more sleep disturbance. A global score more than five (24%) represents poor sleep quality.

*Quality of life*

Participants rated their own perceptions of physical and mental health referring to the past 4 weeks using the short-

 

form 36 (SF-36) Health Survey. This tool has been validated for use in menopausal women.[33] It captures physical functioning, general health perceptions, vitality, bodily pain, mental health and physical role, emotional role, and social role functioning. Overall SF-36 quality of life was presented as a percentage where higher score represents positive health.

Pain, mood and depressive symptoms, menopausal symptoms, sleep disturbance, and quality of life percentage scores were averaged to obtain a composite score for overall well-being.

### Statistical analysis

The data distribution was normal and, therefore, the outcome measures were analyzed using parametric tests.

Within-individual treatment effects at the end of each supplementation period were compared in the crossover comparison using repeated measures analysis of variance. Outcomes evaluated were treatment differences (resveratrol-placebo) in pain perception, mood and depressive symptoms, menopausal symptoms, sleep quality, quality of life, and overall well-being.

A parallel comparison between placebo and resveratrol arms of differences in outcome measures after the first 12-month supplementation phase was also undertaken using one-way analysis of variance.

Pearson correlational analysis was applied to examine associations between treatment differences in CVR and well-being measures. The Benjamini-Hochberg procedure was used to correct *P* values for secondary outcomes (excluding subgroup analyses) to minimize type I errors[34]; the false discovery rate was set at 0.15. All statistical analyses were performed using SPSS version 25.0 (SPSS by IBM Inc. Chicago, IL). Data are presented as means ± standard error of the mean (SEM) unless otherwise stated.

#### *Subgroup analyses in the crossover comparison*

We categorized the cohort into normal body mass index (BMI) ($<25\ kg/m^2$) and overweight or obese BMI ($\geq 25\ kg/m^2$) to test whether BMI influenced the magnitude of response to resveratrol.

We also tested whether concomitant fish oil consumption influenced any effect of resveratrol on pain. We compared participants not taking fish oil supplements with a group who had reported taking fish oil before the study and continued to take the same dose throughout the study.

## RESULTS

Although we formerly aimed to recruit 170 women, due to logistical limitations, we enrolled 146 participants between November 2016 and May 2017, of which 129 completed the first 12 months (June 2018) and 125 completed the full 24-month crossover (June 2019). The final attrition rate was only 14%. Details of participant disposition, Consolidated Standards of Reporting Trials flowchart, adverse events and reasons for leaving the study were previously published[22] (Thaung Zaw 2020, under review). Treatment compliance averaged 95% in both groups.

For the parallel comparison, eight participants were excluded from the pain analysis due to recent knee replacement ($n=2$), laminectomy and shoulder surgery ($n=2$), injuries acquired at least a week before their clinic visit resulting in ongoing pain ($n=3$) and a recent diagnosis of sciatica ($n=1$), leaving 121 participants for analysis. One participant was excluded from the analysis of mood and depressive symptoms, sleep quality, and quality of life due to significant personal problems.

For the crossover comparison, 15 participants were excluded from the pain analysis due to recent hip or knee replacement ($n=6$), other surgeries ($n=3$) for fasciotomy on the leg, ear surgery, and hysterectomy due to prolapse, injuries acquired at least a week before their clinic visit resulting in ongoing pain ($n=3$), disc herniation ($n=1$), recent steroid injection to relieve pain ($n=1$) and a diagnosis of spinal stenosis ($n=1$), leaving 110 participants for pain analysis. Fourteen participants were excluded from the analysis of mood and depressive symptoms, sleep quality and quality of life as they reported critical life events, that is, death or significant concerns over the health of a family member ($n=10$), high carer burden ($n=3$), and worsening of sleep apnea ($n=1$), leaving 111 participants for analysis.

### Baseline characteristics

Table 1 describes baseline characteristics of the 125 completers. Participants averaged 65 ± 1 years of age and 15 ± 1 years postmenopausal. The cohort was overall slightly overweight but normotensive. At baseline, 59 (47%) participants were within normal BMI range (mean $22.2 \pm 0.3\ kg/m^2$) and 66 (53%) were overweight or obese (mean BMI $28.9 \pm 0.4\ kg/m^2$).

**TABLE 1.** *Baseline characteristics of participants who completed the 24-month study*

| Demographics ($N=125$) | Mean ± standard error of mean [95% confidence interval] |
|---|---|
| Age (y) | 65 ± 0.7 [64 to 67] |
| Menopausal years | 15 ± 0.8 [14 to 17] |
| Body mass index ($kg/m^2$) | 25.6 ± 0.3 [24.9 to 26.5] |
| Systolic blood pressure (mm Hg) | 126 ± 1.6 [123 to 129] |
| Diastolic blood pressure (mm Hg) | 69 ± 0.89 [67 to 71] |
| Pain perception | |
| Descriptive pain score (%) | 10.3 ± 1.2 [8.0 to 12.6] |
| Pain VAS (%) | 22.8 ± 2.0 [18.8 to 26.9] |
| Present pain intensity | 22.7 ± 1.8 [19.1 to 26.4] |
| Composite pain score (%) | 18.6 ± 1.6 [15.5 to 21.7] |
| Menopausal symptoms | |
| Psychological symptoms (%) | 14.7 ± 1.3 [12.1 to 17.2] |
| Somatic symptoms (%) | 21.5 ± 1.4 [18.7 to 24.3] |
| Urogenital symptoms (%) | 17.2 ± 1.5 [14.2 to 20.2] |
| Overall menopausal symptoms (%) | 17.7 ± 1.1 [15.6 to 19.8] |
| Mood disturbance (%) | 42.4 ± 1.7 [39.1 to 45.7] |
| Depressive symptoms (%) | 12.3 ± 0.93 [10.5 to 14.2] |
| Sleep disturbance (%) | 31.1 ± 1.6 [28.0 to 34.1] |
| SF-36 quality of life (%) | 77.3 ± 1.1 [75.2 to 79.4] |
| Overall well-being (%) | 8.8 ± 0.96 [6.9 to 10.8] |

For well-being measures, with the exception of quality of life, lower values indicate less disturbance at baseline.
SF-36, short-form 36; VAS, visual analog scale.

Thirty percent of participants ($n = 37$) reported regular fish oil consumption before study enrolment. There were no significant differences in baseline characteristics between placebo and resveratrol groups after randomization.

At baseline, participants' pain perception was mild, indicated by a VAS score of 22 mm.[26] The most common pain descriptor at baseline was ''aching'' (67%), followed by ''tender'' (37%). The common locations of reported chronic pain were in the lower back (30%), wrists and fingers (25%) followed by knees (23%) and hips (21%); and 20% of the cohort did not report any type of chronic musculoskeletal pain. The somatic menopausal symptoms were moderate, but the urogenital and psychological menopausal symptoms were reported as mild. Despite poor sleep quality, their self-reported mood disturbance and depressive symptoms were mild.

### Resveratrol improves pain perception, menopausal symptoms, and overall well-being

The parallel comparison after the first 12 months showed that regular resveratrol supplementation ($n = 56$) significantly reduced composite pain score by 38% compared with placebo ($n = 65$), with significant reductions in present pain intensity (38%) and pain VAS (43%) but not descriptive pain score (Fig. 1). We did not observe changes in other well-being measures in this comparison.

Table 2 describes results of the crossover comparison of well-being measures. Compared to placebo, resveratrol supplementation for 12 months significantly reduced the descriptive pain score (Cohen $d = 0.167$, $P = 0.028$) and present pain intensity (Cohen $d = 0.362$, $P < 0.001$), leading to an 18% reduction of composite pain score (Cohen $d = 0.264$, $P = 0.002$) without a significant reduction in pain VAS. Present pain intensity was the only parameter in which there was an order effect; resveratrol supplementation appeared less effective in those who took it first than in those who progressed from placebo to resveratrol. There was no indication in any of the pain parameters of a carryover effect of resveratrol 12 months after reverting to placebo. Menopausal symptoms were also affected; however, only the reduction of somatic menopausal symptoms by resveratrol was significant (Cohen $d = 0.160$, $P = 0.024$). Depressive symptoms and sleep disturbance tended to be lowered, and quality of life improved by resveratrol but these were not significant. However, overall well-being was improved by resveratrol (Cohen $d = 0.134$, $P = 0.010$).

### Correlations between improvements in pain and improvements in other well-being measures

No significant correlations were observed between treatment changes in pain and other well-being measures in the parallel comparison.

Crossover comparisons showed that reductions in pain VAS were associated with reductions in sleep disturbance ($R = 0.207$, $P = 0.030$) and mood disturbance ($R = 0.219$, $P = 0.029$). Reductions in descriptive pain score ($R = -0.269$, $P = 0.006$), pain VAS ($R = -0.239$, $P = 0.015$), present pain intensity ($R = -0.249$, $P = 0.011$), and composite pain score ($R = -0.275$, $P = 0.005$) were associated with improved SF-36 quality of life. Reductions in sleep disturbance ($R = -0.284$, $P = 0.002$) and mood disturbance ($R = -0.386$, $P < 0.001$) were also associated with improved SF-36 quality of life.

### Correlations between improvement in CVR to hypercapnia and improvements in well-being measures

No significant correlations were observed between treatment changes in well-being measures and in CVR to hypercapnia in the parallel comparison.

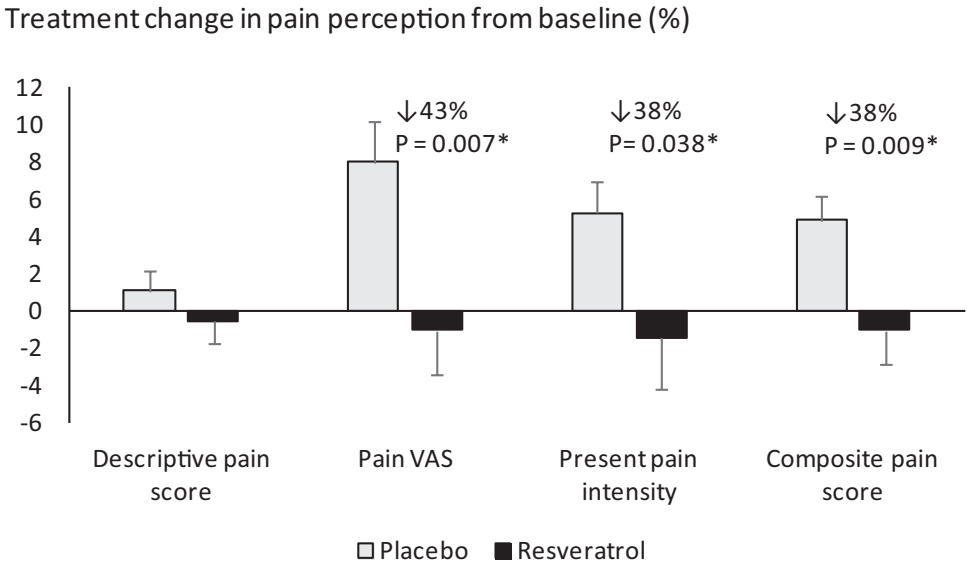


**FIG. 1.** Changes from baseline in descriptive pain score, pain VAS, pain intensity, and composite pain score after placebo and resveratrol supplementation for 12 months. ∗ indicates significance after Benjamini-Hochberg procedure to control false discovery rate. VAS, visual analog scale.

**TABLE 2.** *Within-individual crossover comparison of well-being measures after 12 months of placebo and resveratrol supplementation*

| Well-being measures, expressed as percentages | Placebo | Resveratrol | Resveratrol-Placebo | *P* (unadjusted) | *P* (B-H) |
|---|---|---|---|---|---|
| Pain perception | $N = 110$ | $N = 110$ | | | |
| Descriptive pain score | 12.8 ± 1.5 [10.0 to 15.7] | 10.5 ± 1.2 [8.2 to 12.8] | −2.3 ± 1.0 [−4.4 to −0.26] | **0.028**[a] | 0.073 |
| Pain VAS | 31.2 ± 2.6 [26.0 to 36.4] | 27.1 ± 2.4 [22.4 to 31.8] | −4.0 ± 2.3 [−8.7 to 0.51] | 0.081 | - |
| Present pain intensity | 30.0 ± 1.9 [25.5 to 34.5] | 22.0 ± 1.8 [18.4 to 25.6] | −7.9 ± 1.9 [−11.8 to −4.2] | **<0.001**[a] | 0.000 |
| Composite pain score | 23.5 ± 1.8 [19.9 to 27.2] | 18.9 ± 1.5 [16.0 to 21.9] | −4.6 ± 1.4 [−7.5 to −1.8] | **0.002**[a] | 0.013 |
| Menopausal symptoms | $N = 125$ | $N = 125$ | | | |
| Psychological symptoms | 13.4 ± 1.2 [11.0 to 15.9] | 12.8 ± 1.2 [10.5 to 15.2] | −0.60 ± 1.02 [−2.6 to 1.4] | 0.556 | - |
| Somatic symptoms | 23.4 ± 1.3 [20.7 to 26.0] | 20.9 ± 1.3 [18.4 to 23.4] | −2.5 ± 0.97 [−4.4 to −0.53] | **0.013**[a] | 0.040 |
| Urogenitial symptoms | 12.6 ± 1.2 [10.2 to 15.0] | 14.1 ± 1.4 [11.4 to 16.8] | 1.5 ± 0.90 [−0.25 to 3.3] | 0.091 | - |
| Overall menopausal symptoms | 16.7 ± 0.9 [14.9 to 18.6] | 16.2 ± 1.0 [14.3 to 18.1] | −0.57 ± 0.64 [−1.8 to 0.70] | 0.378 | - |
| Mood | $N = 111$ | $N = 111$ | | | |
| Mood disturbance | 41.8 ± 1.6 [38.8 to 44.9] | 42.5 ± 1.6 [39.2 to 45.8] | 0.66 ± 1.4 [−2.04 to 3.4] | 0.629 | - |
| Depressive symptoms | 10.9 ± 0.9 [9.2 to 12.7] | 10.4 ± 0.8 [8.7 to 12.0] | −0.60 ± 0.65 [−1.9 to 0.69] | 0.359 | - |
| Sleep | $N = 111$ | $N = 111$ | | | |
| Sleep disturbance | 29.1 ± 1.7 [25.7 to 32.5] | 27.8 ± 1.6 [24.5 to 31.0] | −1.4 ± 1.1 [−3.6 to 0.87] | 0.227 | - |
| Quality of life | $N = 111$ | $N = 111$ | | | |
| SF-36 quality-of-life | 77.7 ± 1.03 [75.7 to 79.8] | 78.1 ± 1.05 [76.0 to 80.1] | 0.32 ± 0.74 [−1.2 to 1.8] | 0.671 | - |
| Overall well-being | $N = 125$ | $N = 125$ | | | |
| | 9.9 ± 1.06 [7.8 to 12.0] | 11.5 ± 0.81 [9.9 to 13.1] | 1.52 ± 0.58 [0.37 to 2.7] | **0.010**[a] | 0.040 |

Data presented as mean ± standard error of mean [95% confidence interval].
Except for quality of life and overall well-being measures, the more negative treatment difference (resveratrol-placebo) means a reduction in the symptoms experienced with resveratrol.
B-H, Benjamini-Hochberg procedure for false discovery rate correction; SF-36, short-form 36; VAS, visual analogue scale.
[a]Significant after Benjamini-Hochberg procedure for false discovery rate.

The crossover comparison showed that resveratrol-induced reductions in composite pain score correlated with improvements in CVR to hypercapnia ($R = -0.329$, $P = 0.014$); stronger associations were observed in overweight individuals ($R = -0.579$, $P < 0.001$). Improvements in CVR to hypercapnia tended to be associated with improvements in overall well-being ($R = 0.206$, $P = 0.069$).

### Sub-analysis: responsiveness of resveratrol in the normal and overweight BMI groups

In all 125 completers, BMI correlated with descriptive pain score ($R = 0.326$, $P = 0.001$), pain VAS ($R = 0.470$, $P < 0.001$), present pain intensity ($R = 0.440$, $P < 0.001$), and composite pain score ($R = 0.463$, $P < 0.001$) at baseline.

Table 3 describes differences between normal and overweight/obese BMI groups in the crossover comparison of treatment effects on pain perception. The overweight and obese group reported significantly higher pain across all subscales at baseline compared to the normal weight individuals. Resveratrol reduced all pain subscales – significantly for pain VAS ($P = 0.012$) and composite pain score ($P = 0.022$) – in overweight and obese individuals compared to normal weight individuals.

There were no other significant differences in other well-being measures between BMI groups

### Sub-analysis: responsiveness of pain perception to resveratrol in participants who take fish oil supplements regularly

In our exploratory analysis of the 24-month crossover data, those women who reported taking fish oil throughout the study tended to have lower descriptive pain score (−4.8 ± 2.5%,

**TABLE 3.** *Within-individual crossover comparison of pain perception by body mass index (BMI) groups after 12 months of placebo and resveratrol supplementation*

| | Normal BMI ($N = 51$) Average BMI: 22.1 ± 0.3 kg/m$^2$ | | | | Overweight/obese BMI ($N = 59$) Average BMI: 28.9 ± 0.4 kg/m$^2$ | | | |
|---|---|---|---|---|---|---|---|---|
| Pain perception (%) | Baseline | Placebo | Resveratrol | Treatment difference | Baseline | Placebo | Resveratrol | Treatment difference |
| Descriptive pain score | 7.3 ± 1.7 [4.0 to 10.6] | 8.1 ± 1.3 [4.0 to 12.1] | 7.9 ± 1.2 [4.6 to 11.3] | −0.13 ± 1.5 [−3.1 to 2.9] | 12.9 ± 1.6[a] [9.8 to 16.0] | 16.9 ± 1.8 [13.2 to 20.7] | 12.7 ± 1.5 [9.6 to 15.8] | −4.3 ± 1.4 [−7.1 to −1.5] |
| Pain VAS | 15.3 ± 2.9 [9.6 to 20.9] | 19.4 ± 2.6 [12.3 to 26.4] | 21.5 ± 2.6 [14.6 to 28.3] | 2.1 ± 2.8 [−4.5 to 8.7] | 29.4 ± 2.7[a] [24.2 to 34.7] | 41.4 ± 2.9 [34.9 to 47.9] | 32.0 ± 3.2 [25.6 to 38.3] | −9.4 ± 3.4[a] [−15.5 to −3.3] |
| Present pain intensity | 16.5 ± 2.6 [11.4 to 21.6] | 22.7 ± 2.5 [16.4 to 29.1] | 18.0 ± 2.6 [12.8 to 23.3] | −4.6 ± 2.4 [−10.3 to 0.9] | 28.1 ± 2.4[a] [23.4 to 32.9] | 36.3 ± 2.5 [30.3 to 42.2] | 25.4 ± 2.1 [20.6 to 30.3] | −10.8 ± 2.9 [−16.0 to −5.6] |
| Composite pain score | 13.0 ± 2.2 [8.6 to 17.4] | 16.2 ± 1.9 [11.1 to 21.3] | 15.1 ± 1.7 [10.9 to 19.3] | −1.1 ± 1.8 [−5.2 to 3.0] | 23.5 ± 2.1[a] [19.4 to 27.5] | 29.9 ± 1.9 [25.1 to 34.6] | 22.2 ± 1.8 [18.3 to 26.2] | −7.7 ± 2.1[a] [−11.5 to −3.8] |

Data presented as mean ± standard error of mean [95% confidence interval]. VAS, visual analogue scale.
[a]Significant difference ($P < 0.05$) between normal and overweight/obese BMI groups.

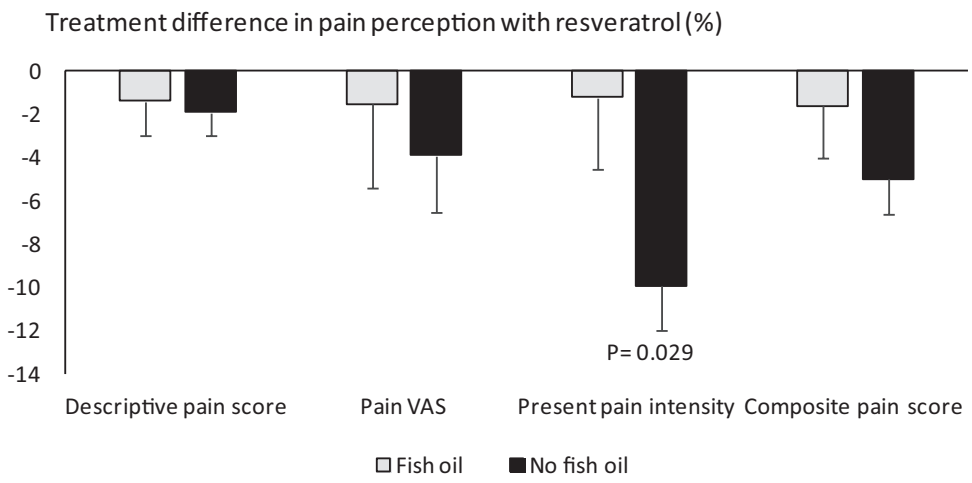


**FIG. 2.** Influence of regular fish-oil supplementation on effects of resveratrol on descriptive pain score, pain VAS, present pain intensity, and composite pain score in the within-individual crossover comparison. VAS, visual analog scale.

$P = 0.058$), pain VAS ($-3.9 \pm 4.5\%$, $P = 0.391$), present pain intensity ($-3.9 \pm 4.0\%$, $P = 0.333$), and composite pain score ($-4.2 \pm 3.4\%$, $P = 0.224$) at baseline compared with those not taking fish oil. Reductions in all subscales of pain perception by resveratrol tended to be blunted in the fish oil group, significantly in the case of present pain intensity (Cohen $d = 0.465$) (Fig. 2).

## DISCUSSION

In this 24-month crossover trial with 125 postmenopausal women, we found benefits of resveratrol in reducing pain experience and somatic menopausal symptoms. Resveratrol also tended to reduce depressive symptoms and sleep disturbance and improve quality of life. Taken together, these outcomes represent a significant improvement in overall well-being in older women supplemented with resveratrol. The improvements were associated with enhancement of cerebrovascular function by the low dose of resveratrol.

### Resveratrol improves pain perception

After resveratrol supplementation, there were modest reductions in measures of pain score and present pain intensity such that the composite pain score was 18% lower than when the women were taking the placebo supplement. The current results confirm our pilot findings in 80 postmenopausal women where we found similar benefits of resveratrol on general pain perception after supplementation for 14 weeks.[21] One limitation of our pilot study was that the participants had not been asked to identify the source and nature of their pain. However, in the present study, we asked participants to report any chronic musculoskeletal pain (not related to injury) and its location, to identify age-related osteoarthritis, the most common degenerative joint disease. In accordance, ''aching'' was the most common type of pain reported and the lower back, wrists and fingers, hips, and knees were the most prevalent pain areas.

Age-related osteoarthritis is a disease of the entire synovial joint, which usually involves destruction of articular cartilage, increased subchondral bone density, eburnation of bone that exposes nerves, and inflammation of synovium, all of which can lead to pain.[35,36] In addition, a critical etiology in osteoarthritis is the loss of blood supply to previously well-perfused structures; resulting in ischemic pain mediated by loss of oxygen and nutrients to the nerves.[35] Thus, standard anti-inflammatory drugs may not be effective or sufficient for management of pain in osteoarthritis due to its complex pathophysiology.[37] In the recent years, vasoactive nutrients such as curcumin, green tea, and resveratrol have been evaluated for their potential efficacy in osteoarthritis management due to their ability to improve blood flow, reduce proinflammatory mediators, and suppress inflammation.[38]

Resveratrol has been shown in vitro to reduce interleukin (IL) 1β in human primary articular chondrocytes by downregulating nuclear factor kappa beta pathways.[39] In rabbit models of arthritis, resveratrol injections protected articular cartilage degradation, reduced synovial inflammation and proteoglycan loss, which was mediated possibly via the suppression of inflammatory pathways.[40,41] Since fish oil supplements are often consumed for chronic joint pain, we undertook an exploratory analysis to see whether there was a synergistic benefit with resveratrol for reducing chronic pain. However, we did not find any additive benefit with fish oil supplementation. This contrasts with an in vitro study in which combined administration of omega-3 fatty acids and resveratrol exerted combined effects on reduction of inflammatory markers (IL-6 and IL-8) in a human chondrocyte model of chronic inflammation.[42] In our study, the ability of resveratrol to reduce chronic pain appears to become redundant in the presence of fish oil, which suggests that both fish oil and resveratrol might be acting through similar mechanisms to reduce joint inflammation. However, it is important to note that participants perceived mild pain in our study cohort. Hence, the combined effects of fish oil and resveratrol for those with moderate to severe pain are yet to be established. Resveratrol has been shown to act through multiple pathways to exert anti-inflammatory effects, for example via sirtuins that lower nuclear

 

factor kappa beta activity as well as inhibit cyclooxygenase and prostaglandin activity to limit the production of pro-inflammatory mediators. Hence, evaluation of joint-specific pro-inflammatory cytokines such as tumor necrosis factor-α, IL-6, and IL-8, which are known to be involved in articular cartilage inflammation and degradation,[38] should be considered in future studies of resveratrol's effects on joint pain, with or without fish oil.

Our observation that reductions in pain correlated with improvements in CVR to hypercapnia after resveratrol treatment suggests that the pain reduction might be due to increased perfusion of the affected subchondral bone. This association was more apparent in overweight individuals, who are more susceptible to circulatory dysfunction[43] as well as being at a greater risk of osteoarthritic pain due to mechanical overload on the joints.[44] Weight loss strategies have been shown to decrease pain and improve physical function in overweight individuals with osteoarthritis.[45] In this study, we observed reduction in pain perception without apparent changes in body weight after resveratrol supplementation in the overweight individuals. It is important to consider that a scenario in osteoarthritis pathology is the ischemic pain mediated by loss of oxygen and nutrients due to loss of blood supply to the previously perfused structures.[35] A review by Hancock and Riegger-Krugh[46] concluded that interventions improving blood flow by increased production of nitric oxide perhaps via the endothelial nitric oxide synthase action, could potentially decrease the pain associated with osteoarthritis. Physical activity, which increases nitric oxide production during the increased flow of blood through the muscle beds, has demonstrated clear benefits on both pain relief and functional improvement in knee osteoarthritis.[47] With the ability to increase nitric oxide bioavailability through multiple pathways,[16] resveratrol may have increased vasodilatation and blood flow in the affected tissues, which may have in turn reversed the hypoxia, improved nutrient exchange and relieved pain in the affected joint. One limitation of our study is that we did not measure specific joint perfusion, which may provide a clear explanation of possible mechanism of action in future studies.

To our knowledge, RESHAW is the longest clinical trial to report benefits of resveratrol in reducing age-related musculoskeletal pain in humans. In a shorter term study in patients with mild to moderate knee osteoarthritis (age 45-75 y old), Marouf et al[48] found that resveratrol (500 mg) as an adjunct therapy with meloxicam (15 mg) reduced pain severity and inflammatory markers (tumor necrosis factor-α, IL-1β, IL-6, and C-reactive protein) compared to placebo plus meloxicam after 90 days of supplementation. The oral resveratrol in knee osteoarthritis trial in France is currently evaluating the effects of 40 mg resveratrol BID for a week followed by 20 mg BID or a matching placebo for a total of 6 months on knee pain reduction in osteoarthritis patients.[49] Their findings will add the existing body of knowledge on the potential of resveratrol to alleviate pain and may provide further recommendations in osteoarthritis management.

We found that reductions in pain perception, mood, and sleep disturbances were associated with better quality of life. Although we did not find associations between mood or sleep outcomes and circulatory enhancements, it is plausible that improvements in cerebrovascular perfusion with resveratrol may have alleviated mood and sleep problems, which could reduce pain perception and thus lead to improved quality of life in older women.

**Resveratrol improves menopausal symptoms and overall well-being**

We observed reductions in vasomotor symptoms (hot flushes, night sweats) and other somatic symptoms (heart discomfort, sleep problems, muscle, and joint discomfort) with resveratrol supplementation. The somatic symptoms were more likely to show improvement than urogenital and psychological symptoms, as they were more bothersome at baseline. This is the first study to report benefits of long-term resveratrol supplementation for persistent menopausal symptoms in older postmenopausal women. One other study has shown that supplementation with 200 mg of fermented soy, 10 mg equol, and 25 mg resveratrol for 12 weeks improved menopausal symptoms and health-related quality of life in healthy menopausal women (50-55 y old) suffering from hot flushes.[50]

Although the cause of vasomotor symptoms is not completely understood, it is postulated that declining estrogen levels may alter the brain's temperature regulatory center, causing an individual to sweat or and shiver inappropriately. Moreover, hypoestrogenic women were shown to have poorer cerebral blood flow that was further compromised during hot flush episodes, indicating that vascular dysfunction may be linked to the severity of hot flushes.[51] Although hormone therapy is the most efficacious treatment for vasomotor symptoms, it is only recommended for women younger than 60 years or within 10 years of menopause due to concerns of coronary heart disease, thromboembolism, and invasive breast cancer.[52] Having weak estrogenic as well as potent vasoactive properties, resveratrol may have alleviated vasomotor symptoms through its actions on the vascular system, without causing unwanted estrogenic effects in other body systems. Nevertheless, the long-term efficacy and safety of resveratrol in the management of menopausal symptoms need to be confirmed in future studies in early postmenopausal women who are most commonly affected by menopausal symptoms.

We observed small, non-significant improvements in other well-being measures including depressive symptoms, sleep disturbance, and quality of life with resveratrol. Consistent with our pilot study results,[21] these small improvements amounted to better overall well-being, which was associated with increased CVR to hypercapnia, suggesting that enhanced circulatory function also has indirect benefits on self-reported physical and mental well-being. Since evidence has shown that improving cerebral perfusion could reverse depression,[53] it is possible that improved cerebral microcirculatory function in the older women after resveratrol supplementation may have reversed depressive symptoms and pain perception (as aforementioned), thereby improving mental efficiency and

functional capacity which in turn improved their perceived well-being. We acknowledge that the observed association between improvements in cerebrovascular function and overall well-being does not indicate causality; however, it calls for further investigation of potential cerebrovascular mechanisms by which resveratrol may enhance perceived well-being. Moreover, since our study was powered to observe the improvements in cognitive performance as a primary outcome, further adequately powered studies are warranted to confirm the additional long-term benefits of resveratrol on well-being measures.

## CONCLUSIONS

In this 24-month crossover study, we confirmed our pilot study finding that a low dose of resveratrol (75 mg BID) can reduce pain perception and improve total well-being in postmenopausal women, benefits that are associated with improvements in circulatory function. Importantly, we have shown that these benefits can be sustained for at least 12 months with regular supplementation. We also observed a reduction in menopausal symptoms, even in older women who were long-term postmenopausal. The finding that resveratrol was effective in reducing age-related osteoarthritis pain in women (especially in overweight or obese individuals) warrants future studies in men to see whether they will similarly benefit. Overall, low-dose resveratrol supplementation is a viable nonpharmacological intervention to alleviate menopause-related symptoms and improve quality of life in postmenopausal women.

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## REFERENCES


1. Buckler H. The menopause transition: endocrine changes and clinical symptoms. *J Br Menopause Soc* 2005;11:61-65.
2. Freeman EW, Sammel MD, Lin H, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol* 2007;110 (2 part 1):230-240.
3. Jones G, Sutton A. Quality of life in obese postmenopausal women. *Menopause Int* 2008;14:26-32.
4. Hartz AJ, Fischer ME, Bril G, et al. The association of obesity with joint pain and osteoarthritis in the HANES data. *J Chronic Dis* 1986;39:311-319.
5. Teede H, Lombard C, Deeks A. Obesity, metabolic complications and the menopause: an opportunity for prevention. *Climacteric* 2010;13:203-209.
6. Davis SR, Castelo-Branco C, Chedraui P, et al. Understanding weight gain at menopause. *Climacteric* 2012;15:419-429.
7. Blumel JE, Castelo-Branco C, Binfa L, et al. Quality of life after the menopause: a population study. *Maturitas* 2000;34:17-23.
8. Matthews KA, Bromberger JT. Does the menopausal transition affect health-related quality of life? *Am J Med* 2005;118:25-36.
9. Moreau KL, Hildreth KL, Meditz AL, Deane KD, Kohrt WM. Endothelial function is impaired across the stages of the menopause transition in healthy women. *J Clin Endocrinol Metab* 2012;97:4692-4700.
10. Matteis M, Troisi E, Monaldo BC, Caltagirone C, Silvestrini M. Age and sex differences in cerebral hemodynamics: a transcranial Doppler study. *Stroke* 1998;29:963-967.
11. Neu P, Schlattmann P, Schilling A, Hartmann A. Cerebrovascular reactivity in major depression: a pilot study. *Psychosom Med* 2004;66:6-8.
12. Wong RH, Evans HM, Howe PR. Poor cerebrovascular function is an early marker of cognitive decline in healthy postmenopausal women. *Alzheimerss Dement* 2016;2:162-168.
13. Bechlioulis A, Kalantaridou SN, Naka KK, et al. Endothelial function, but not carotid intima-media thickness, is affected early in menopause and is associated with severity of hot flushes. *J Clin Endocrinol Metab* 2010; 95:1199-1206.
14. Dugan SA, Powell LH, Kravitz HM, Everson Rose SA, Karavolos K, Luborsky J. Musculoskeletal pain and menopausal status. *Clin J Pain* 2006;22:325-331.
15. Berger A, Dukes EM, Oster G. Clinical characteristics and economic costs of patients with painful neuropathic disorders. *J Pain* 2004;5:143-149.
16. Xia N, Förstermann U, Li H. Resveratrol and endothelial nitric oxide. *Molecules* 2014;19:16102-16121.
17. Wong R, Howe P, Buckley J, Coates A, Kunz I, Berry N. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. *Nutr Metab Cardiovasc Dis* 2011;21:851-856.
18. Evans H, Howe P, Wong R. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomized placebo-controlled intervention trial. *Nutrients* 2017;9:27.
19. Wong R, Nealon R, Scholey A, Howe P. Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2016;26:393-399.
20. Csaki C, Keshishzadeh N, Fischer K, Shakibaei M. Regulation of inflammation signalling by resveratrol in human chondrocytes in vitro. *Biochem Pharmacol* 2008;75:677-687.
21. Wong RH, Evans HM, Howe PR. Resveratrol supplementation reduces pain experience by postmenopausal women. *Menopause* 2017;24:916-922.
22. Thaung Zaw JJ, Howe PR, Wong RH. Sustained cerebrovascular and cognitive benefits of resveratrol in postmenopausal women. *Nutrients* 2020;12:828.
23. Australian Institute of Health Welfare. *Medication use for arthritis and osteoporosis*. Canberra: AIHW; 2010.
24. Altman DG, Bland JM. Treatment allocation by minimisation. *BMJ* 2005;330:843.
25. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975;1:277-299.
26. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain* 2003;4:407-414.
27. Wyrwich KW, Yu H. Validation of POMS questionnaire in postmenopausal women. *Qual Life Re* 2011;20:1111-1121.
28. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measure* 1977;1:385-401.
29. Weissman MM, Sholomskas D, Pottenger M, Prusoff BA, Locke BZ. Assessing depressive symptoms in five psychiatric populations: a validation study. *Am J Epidemiol* 1977;106:203-214.
30. Schneider H, Heinemann L, Rosemeier H-P, Potthoff P, Behre H. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric* 2000;3:59-64.
31. Heinemann LAJ, DoMinh T, Strelow F, Gerbsch S, Schnitker J, Schneider HPG. The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. *Health Qual Life Outcomes* 2004;2:67.
32. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193-213.
33. Mishra G, Schofield M. Norms for the physical and mental health component summary scores of the SF-36 for young, middle-aged and older Australian women. *Qual Life Res* 1998;7:215-220.
34. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J Royal stat Soc* 1995;57:289-300.
35. Bonnet C, Walsh D. Osteoarthritis, angiogenesis and inflammation. *Rheumatology* 2005;44:7-16.
36. Creamer P. Osteoarthritis pain and its treatment. *Curr Opin Rheumatol* 2000;12:450-455.
37. Wang A, Leong DJ, Cardoso L, Sun HB. Nutraceuticals and osteoarthritis pain. *Pharmacol Ther* 2018;187:167-179.
38. Wang Z-M, Chen Y-C, Wang D-P. Resveratrol, a natural antioxidant, protects monosodium iodoacetate-induced osteoarthritic pain in rats. *Biomed Pharmacother* 2016;83:763-770.


 

39. Shakibaei M, Csaki C, Nebrich S, Mobasheri A. Resveratrol suppresses interleukin-1 (-induced inflammatory signaling and apoptosis in human articular chondrocytes: potential for use as a novel nutraceutical for the treatment of osteoarthritis. *Biochem Pharmacol* 2008;76:1426-1439.
40. Elmali N, Baysal O, Harma A, Esenkaya I, Mizrak B. Effects of resveratrol in inflammatory arthritis. *Inflammation* 2007;30:1-6.
41. Elmali N, Esenkaya I, Harma A, Ertem K, Turkoz Y, Mizrak B. Effect of resveratrol in experimental osteoarthritis in rabbits. *Inflamm Res* 2005; 54:158-162.
42. Schwager J, Richard N, Riegger C, Salem N. ω-3 PUFAs and resveratrol differently modulate acute and chronic inflammatory processes. *BioMed Res Int* 2015;2015:535189.
43. Steinberg HO, Chaker H, Leaming R, Johnson A, Brechtel G, Baron AD. Obesity/insulin resistance is associated with endothelial dysfunction. Implications for the syndrome of insulin resistance. *J Clin Invest* 1996;97:2601-2610.
44. Felson DT. Weight and osteoarthritis. *Am J Clin Nutr* 1996;63:430S-432S.
45. Vincent HK, Heywood K, Connelly J, Hurley RW. Obesity and weight loss in the treatment and prevention of osteoarthritis. *PM R* 2012;4 (suppl 5):S59-S67.
46. Hancock CM, Riegger-Krugh C. Modulation of pain in osteoarthritis: the role of nitric oxide. *Clin J Pain* 2008;24:353-365.
47. Sharma L. Examination of exercise effects on knee osteoarthritis outcomes: why should the local mechanical environment be considered? *Arthritis Rheum* 2003;49:255-260.
48. Marouf BH, Hussain SA, Ali ZS, Ahmmad RS. Resveratrol supplementation reduces pain and inflammation in knee osteoarthritis patients treated with meloxicam: a randomized placebo-controlled study. *J Med Food* 2018;21:1253-1259.
49. Nguyen C, Boutron I, Baron G, et al. Evolution of pain at 3 months by oral resveratrol in knee osteoarthritis (ARTHROL): protocol for a multicentre randomized double-blind placebo-controlled trial. *BMJ Open* 2017;7: e017652.
50. Davinelli S, Scapagnini G, Marzatico F, Nobile V, Ferrara N, Corbi G. Influence of equol and resveratrol supplementation on health-related quality of life in menopausal women: a randomized, placebo-controlled study. *Maturitas* 2017;96:77-83.
51. Greene RA. Estrogen and cerebral blood flow: a mechanism to explain the impact of estrogen on the incidence and treatment of Alzheimer's disease. *Int J Fertil Womens Med* 2000;45:253-257.
52. The NAMS 2017 Hormone Therapy Position Statement Advisory Panel. The 2017 hormone therapy position statement of The North American Menopause Society. *Menopause* 2017;24:728-753.
53. Bench C, Frackowiak R, Dolan RJ. Changes in regional cerebral blood flow on recovery from depression. *Psychol Med* 1995;25:247-261.