

Resveratrol supplementation reduces pain experience by postmenopausal women

Rachel H.X. Wong, PhD, Hamish M. Evans, BioMed Sci, Hons, and Peter R.C. Howe, PhD

Abstract

Objective: Pain is a common complaint among postmenopausal women. It has been postulated that vascular dysfunction caused by estrogen decline at menopause plays a key role in the initiation and progression of degradative joint disease, namely age-related osteoarthritis. We evaluated whether supplementation with resveratrol, a phytoestrogen, could improve aspects of well-being such as chronic pain that is commonly experienced by postmenopausal women.

Methods: A 14-week randomized, double-blind, placebo-controlled intervention with trans-resveratrol (75 mg, twice daily) was conducted in 80 healthy postmenopausal women. Aspects of well-being, including pain, menopausal symptoms, sleep quality, depressive symptoms, mood states, and quality of life were assessed by Short form-36 at baseline and at the end of treatment. Rating scales were averaged to provide a composite score representing overall well-being. Cerebral vasodilator responsiveness to hypercapnia was also assessed as a surrogate marker for cerebrovascular function.

Results: Compared with placebo treatment, there was a significant reduction in pain and an improvement in total well-being after resveratrol supplementation. Both benefits, including measures of quality of life, correlated with improvements in cerebrovascular function.

Conclusions: Our preliminary findings indicate potential for resveratrol treatment to reduce chronic pain in age-related osteoarthritis. Resveratrol consumption may also boost perceptions of well-being in postmenopausal women. Further investigation to elucidate underlying mechanisms is warranted.

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

Pain particularly from musculoskeletal sources, is often chronic and can cause severe distress that interferes with sleep quality, functional activities, mood, and cognitive performance, all of which have implications for quality of life (QoL) and physical disability. Epidemiological studies including the women in the Penn Ovarian Aging Study¹⁻³ demonstrated that half of postmenopausal women complained of joint pain or stiffness second to hot flashes (a somatic symptom of menopause); yet the generalized pain experienced by postmenopausal women is underaddressed in current management practice compared with other vasomotor symptoms such as hot flashes or urogenital discomfort. This is important because those reporting more pain tend to be less physically active, thereby fostering a sedentary lifestyle that negatively impacts cardiovascular and metabolic health.³

It is postulated that vascular pathology plays a role in the initiation and progression of joint diseases, attributable to the influx of proinflammatory mediators entering the circulation, creating a systemic inflammatory milieu that is in proportion to pain severity.⁴ As a result, pain may be associated with endothelial dysfunction. Additionally, loss of estrogen at menopause not only alters the physiology of muscles, tendons, ligaments, and bones, making them less resistant to daily mechanical stressors,⁵⁻⁷ but also impairs endothelial function, thereby contributing to the pathogenesis of many chronic diseases.⁸ Coupled with aging, the impact of estrogen deficiency further impairs cerebral vasodilator function in postmenopausal women compared with men, thereby negatively impacting cognitive performance and contributing to hot flashes.^{9,10}

Phytoestrogens such as isoflavones exhibit estrogenic effects, though less potent, by selective binding to estrogen receptors; they elicit positive effects on bone, brain, and cardiovascular tissues without affecting the uterus or breast.¹¹ However, the benefits of phytoestrogen for the management of menopausal symptoms are mixed.^{12,13} A systematic review found that soy isoflavones were effective in reducing hot flush intensity and episodes, but failed to reduce pain or mood or cognitive disturbances.¹³ In contrast, a recent meta-analysis found no improvements of hot flashes with phytoestrogen supplementation compared with placebo.¹² So far, only a

Received October 18, 2016; revised and accepted January 9, 2017.
From the University of Newcastle, School of Biomedical Sciences and Pharmacy, Callaghan, New South Wales, Australia.
Funding/support: Hunter Medical Research Institute 3D Healing Grant 2014, DSM Nutritional Products Ltd.
Financial disclosure/conflicts of interest: None reported.
Address correspondence to: Rachel H.X. Wong, PhD, University of Newcastle, School of Biomedical Sciences and Pharmacy, Callaghan, New South Wales 2308, Australia. E-mail: Rachel.wong@newcastle.edu.au

handful of studies has found that phytoestrogens reduce pain in postmenopausal women. Supplementation of 80 mg isoflavones from Red Clover extract was shown to reduce vasomotor symptoms, joint/muscle pain, and headaches.¹⁴ Daily consumption of 90 mg isoflavones in soy protein powder for 16 weeks was equally effective as pharmaceutical hormone therapy (HT) in reducing joint pain symptoms by 40% compared with the placebo.¹⁵ However, pain experience and intensity were measured with one question in the Menopausal Rating Scale (MRS) in these studies.¹⁶ Such measures of pain may be insufficient or insensitive for capturing generalized pain. Furthermore, the maximal clinical response to soy protein diet or supplements is observed in people who are equol-producers. Equol is the end product of the biotransformation of daidzein (a major isoflavone in soy) and is responsible for the purported health benefits.¹⁷ This may explain the variance in the outcomes of soy isoflavone trials.

Resveratrol is a polyphenolic stilbene that occurs naturally in grapes. It has been characterized as a phytoestrogen on the basis of its ability to bind to estrogen receptors to enhance endothelial function by increasing nitric oxide bioavailability.¹⁸ Additionally, preclinical evidence shows that resveratrol can stimulate bone cell proliferation and differentiation, and inhibit apoptosis of chondrocytes through anti-inflammatory mechanisms.¹⁹ Unlike isoflavones, its metabolism is not dependent on gut microflora; thus, its benefits are not limited to a phenotype.²⁰ So far, no studies have explored the potential of resveratrol for managing conditions such as pain, vasomotor symptoms, poor mood, and cognitive performance associated with menopause. We recently reported the effects of a 14-week resveratrol supplementation trial on cognitive performance, cerebrovascular function, and mood states in postmenopausal women.²¹ In the same study, we also evaluated aspects of overall well-being such as pain perception, menopausal symptoms, sleep quality, perceived QoL, and depressive symptoms, and tested whether these improvements were related to enhancements of cerebrovascular function. We now report these secondary outcomes.

METHODS

A 14-week randomized, double-blind, placebo-controlled intervention was undertaken at the University of Newcastle's Clinical Nutrition Research Centre. Eighty community-dwelling women residing in the Hunter region of New South Wales aged between 45 and 85 years, who were postmenopausal (self-reported amenorrhea for more than 6 months) and not taking HT were recruited to participate. Participants were excluded if they were smokers or were taking insulin, warfarin, or HT within the past 6 months, had suspected dementia, had been diagnosed with depression, had a history of breast or cervical cancer, or had cardiovascular disease, kidney, liver disease, or neurological disorders. The study was approved by the University of Newcastle Human Research Ethics Committee, registered with the Australia and New Zealand Clinical Trials Registry (ACTRN12615000291583), and conducted according to

International Conference on Harmonization Guidelines for Good Clinical Practice. Written informed consent was obtained before commencement.

Study procedures

Details of the study protocol and outcome assessments have been published.²² Volunteers attended the research facility having refrained from medication, food, and beverages other than water for at least an hour. To rule out suspected dementia (score of <78/100), the Australian version of the Modified Mini-Mental State Examination was administered.²³

After assessments of cerebrovascular responsiveness (CVR) to a hypercapnic challenge, participants concluded the visit by completing six paper-based questionnaires pertaining to overall well-being (ie, pain, sleep, mood, perception of physical and psychological well-being, and menopausal symptoms) that were designed to assess varying aspects of one's general living. CVR to hypercapnia is a measure of global vasodilatation capacity of the cerebral vessels and therefore used as a surrogate for health of circulatory function in this study. CVR to hypercapnia in the middle cerebral artery was assessed using transcranial Doppler ultrasound (DopplerBox X; Compumedics DWL, Singen, Germany). The hypercapnic challenge involved inhaling a carbogen gas mixture (5% CO₂, 95% O₂) for 180 s. Participants without a measurable temporal window were excluded from this assessment.

Participants' pain symptomatology was assessed through the Short-form McGill Pain questionnaire, containing 15 descriptors of sensory pain, where the women had to assign an intensity of either none, mild, moderate, or severe to each descriptor.²⁴ A numerical value was assigned to each intensity scale, with a maximum score of 45, indicating most pain experienced. Participants were also told to mark on the 10-cm visual analog scale (VAS) and quantify their present pain intensity (range from "0" for no pain to "5" for excruciating) for an estimate of their overall pain intensity. Each subscale score was expressed as a percentage (ie, a 3-cm mark on the VAS would be 30%) and averaged to give a composite score for pain.

Sleep was assessed through the Pittsburgh Sleep Quality Index where the maximal score of 21 indicated worst quality.²⁵ Menopausal symptoms were assessed using the MRS as this has been shown to be effective in measuring treatment effects on QoL across the full range of severity of complaints in aging women.¹⁶ The MRS has 11 questions with an option to check one of five ratings of the severity of symptoms (range from "none" = 0 to "very severe" = 4). Subscales pertaining to somatic, psychological, and urogenital symptoms were also examined. A composite for the severity of menopausal symptoms was expressed as a percentage of the sum of scores from a maximum score of 44.

The participants' own perceptions of their physical and mental health were also recorded using the Short form-36 (SF-36) Health Survey, a validated questionnaire in menopausal women. It consists of eight subscales of physical

functioning, general health perceptions, vitality, bodily pain, mental health and physical role, emotional role, and social role functioning. A maximum score of 100, equivalent to no disability, was assigned to each scale.²⁶ Overall perception of QoL was calculated by averaging the scores on the eight subscales.

Mood states and depressive symptoms were assessed by Profile of Mood States (POMS) and Centre for Epidemiologic Studies Depression Scale (CES-D) questionnaires, respectively. Six subscales of tension, depression, anger, fatigue, confusion, and vigor in the POMS were expressed as percentages of their maximum score for each subscale. Overall mood was then calculated by summing the percentages for all subscales (except vigor) and subtracting the percentage obtained for vigor. The CES-D composed of 20 questions which participants rated the frequency of their experience during the last week for each question. A numerical score of up to three for “most days (5-7 days)” was assigned to each question. A maximum score of 60 indicated most depressive symptoms experienced.

Measures of QoL, pain, sleep quality, menopausal symptoms, mood states, and depressive symptoms were averaged to give a composite score for total well-being, as the combination and severity of symptoms were likely to differ between individuals.

During the 14-week intervention, participants were instructed to consume one capsule containing 75 mg of 99% pure synthetic trans-resveratrol (resVida, DSM Nutritional Products Ltd, Switzerland) or matching placebo twice daily. They were also told to maintain their habitual dietary and medication regime. Participants were allocated to each treatment group using the allocation by minimization method based on years since cessation of menses.²⁷ The first participant was randomly allocated by a coin toss. The placebo comprised several inert excipients (calcium hydrogen phosphate, microcrystalline cellulose, prosolv 50, and hydrated magnesium silicate). Compliance was facilitated by a follow-up phone call at mid-intervention to enquire about the participants' well-being, and participants were told to record the time of capsule consumption in their supplement diary each day. At the end of the trial, all remaining capsules were counted and tallied with the corresponding diary records to calculate overall compliance. The participants returned at the end of the 14-week intervention for reassessment of outcome measures. Blinding was maintained until all data analysis had been completed.

Statistical analysis

Using a per protocol (PP) analysis, treatment differences by time effects were determined by generalized linear modeling, if the assumption of equal variances was met (Levene's test of homogeneity) (SPSS version 21.0, IBM Inc, Chicago, IL). An intention-to-treat (ITT) analysis was also performed on the outcomes by multiple imputation for missing values. Treatment differences for all measures except QoL were reversed to reflect improvements after 14 weeks of supplementation. Pearson's correlation analysis was used to determine whether the improvements in each measure of well-being and total well-being were related to enhancements of CVR to hypercapnia, hereby used as a surrogate marker of circulatory function. The adjusted level of significance was set at *P* less than 0.017 to account for multiple comparisons in the secondary outcomes. Data are presented as mean \pm SEM.

RESULTS

Participant characteristics are described in Table 1. Their average age was 61.5 ± 0.9 years and they were 11.6 ± 1.0 years postmenopausal. While the cohort was overweight (average body mass index [BMI] 26.7 ± 0.6 kg/m²), they were normotensive. No significant differences in participant characteristics between groups were evident after randomization.

Of the 80 women enrolled in the study, 8 withdrew before the end of the intervention; 6 of them had been assigned to the placebo group. Two participant assigned to the resveratrol group who dropped out had carer duties and therefore was unable to attend the second visit. No adverse effects were reported. An average compliance of 92% with capsule counts was achieved for both groups.

After 14 weeks of supplementation, CVR to hypercapnia was significantly enhanced in the resveratrol group compared with that in the placebo group (end of intervention values in the placebo group: $52.4 \pm 2.3\%$; resveratrol group: $58.1 \pm 2.4\%$; *P* = 0.011).

As shown in Table 2, 60% of participants from both resveratrol and placebo groups reported “aching” pain as the most common pain complaint at baseline.

Table 3 depicts the individual measures and their subscale percentages of outcome measures, and overall well-being at baseline and at the end of the intervention. Both ITT and PP analyses showed that regular resveratrol supplementation

TABLE 1. Participant characteristics at baseline by treatment groups

	Placebo (n = 35)	Resveratrol (n = 37)	<i>P</i> (Levene's test)	<i>P</i> (between groups)
Age, y	61.5 \pm 1.4	61.3 \pm 1.1	0.042	0.905
Years since onset of menopause	11.0 \pm 1.3	11.9 \pm 1.6	0.383	0.685
BMI, kg/m ²	26.4 \pm 0.9	26.7 \pm 0.8	0.589	0.802
Waist circumference, cm	86.2 \pm 2.2	87.4 \pm 1.7	0.241	0.676
Clinic systolic blood pressure, mm Hg	125.1 \pm 2.1	125.1 \pm 2.3	0.520	0.990
Clinic diastolic blood pressure, mm Hg	69.6 \pm 1.5	72.5 \pm 1.4	0.729	0.164
Cerebrovascular responsiveness to hypercapnia, %	51.9 \pm 2.9	50.7 \pm 2.2	0.111	0.483

BMI, body mass index.

TABLE 2. Percentages of participants who experienced each pain descriptor at week 0 and week 14 and the changes in percentages after treatment

	Week 0		Week 14		Δ (week 14 to week 0)	
	Placebo	Resveratrol	Placebo	Resveratrol	Placebo	Resveratrol
Throbbing	14	31	20	12	6	-19
Shooting	20	22	20	6	0	-17
Stabbing	14	14	11	9	-3	-6
Sharp	31	19	26	12	-6	-8
Cramping	37	33	37	21	0	-14
Gnawing	14	11	11	6	-3	-6
Hot burning	23	25	26	15	3	-11
Aching	57	58	71	53	14	-8
Heavy	11	11	11	12	0	0
Tender	6	28	37	41	-14	11
Splitting	29	3	9	3	3	0
Tiring	29	36	37	21	9	-17
Sickening	1	11	9	6	9	-6
Fearful	3	17	3	15	0	-3
Punishing	3	3	6	6	3	3

significantly reduced overall pain by 10% compared with placebo, with reductions in all three subscales of pain.

The change in pain intensity to the various types of pain did not differ significantly between the groups, although the resveratrol-treated group showed reductions in pain intensity to most pain descriptors (Fig. 1). Nonetheless, the treatment-induced improvement in overall pain correlated with the treatment change in CVR to hypercapnia (pain: $r = 0.405$, $P = 0.004$) (Fig. 2).

No significant improvements were observed for all other outcome measures, except for total well-being, where the effects of resveratrol more than doubled that of the placebo group; however, the significance was lost in the ITT analysis (Table 3).

Improvements in QoL and total well-being significantly correlated with treatment changes in CVR to hypercapnia ($r = 0.382$, $P = 0.007$; and $r = 0.453$, $P = 0.002$, respectively) (Fig. 2). No other significant correlations between treatment changes in CVR to hypercapnia and other outcomes of well-being were observed.

DISCUSSION

We evaluated whether regular resveratrol supplementation could improve cognitive performance, cerebrovascular function, mood, and aspects of well-being in relatively healthy postmenopausal women living in the community who were at least 10 years since onset of menopause.

TABLE 3. Individual outcome measures of well-being and total well-being expressed as percentages

	Week 0		Week 14		Δ (week 14 to week 0) ^a		Levene's sig.	P PP	P ITT
	Placebo	Resveratrol	Placebo	Resveratrol	Placebo	Resveratrol			
Overall pain	16.5 ± 2.4	15.9 ± 2.2	20.3 ± 2.5	10.1 ± 2.4	-3.8 ± 2.0	5.8 ± 1.5	0.785	<0.001 ^b	0.007^b
Pain score	8.2 ± 1.6	10.7 ± 1.5	9.6 ± 1.5	6.1 ± 1.5	-1.4 ± 1.1	4.6 ± 1.2	0.135	0.001 ^b	0.004^b
VAS	19.6 ± 3.1	17.4 ± 2.9	23.8 ± 3.1	11.2 ± 2.9	-4.2 ± 2.4	6.2 ± 1.7	0.159	<0.001 ^b	<0.001^b
PPI	20.6 ± 2.9	19.4 ± 2.8	23.0 ± 2.9	13.1 ± 2.8	-2.4 ± 2.8	6.3 ± 2.5	0.288	0.011^b	0.019
Total sleep index	35.9 ± 2.9	30.1 ± 2.9	30.7 ± 2.8	24.9 ± 2.8	5.2 ± 2.3	5.2 ± 1.8	0.145	0.230	0.484
Sleep duration	34.3 ± 5.7	19.0 ± 4.6	28.3 ± 5.3	14.3 ± 3.7	6.0 ± 3.4	4.8 ± 4.6	0.461	0.799	0.817
Sleep disturbances	59.6 ± 3.2	52.4 ± 3.7	50.5 ± 2.9	48.6 ± 3.4	9.1 ± 3.6	3.8 ± 3.8	0.419	0.302	0.990
Sleep latency	48.5 ± 5.4	41.0 ± 6.1	35.4 ± 5.4	32.4 ± 5.2	13.1 ± 5.6	8.6 ± 5.0	0.349	0.515	0.651
Daytime sleepiness	21.2 ± 3.5	27.6 ± 2.2	21.2 ± 4.1	17.1 ± 3.2	0.0 ± 4.6	10.5 ± 3.0	0.599	0.131	0.585
Sleep efficiency	43.4 ± 6.2	26.7 ± 5.1	41.4 ± 6.2	27.6 ± 5.2	2.0 ± 6.3	-1.0 ± 5.2	0.556	0.397	0.874
Medication use	15.2 ± 5.4	10.5 ± 4.3	11.1 ± 5.2	12.4 ± 4.5	4.0 ± 4.0	-1.9 ± 3.9	0.925	0.288	0.875
Sleep quality	49.5 ± 5.3	42.9 ± 3.8	35.4 ± 4.8	27.6 ± 3.5	14.1 ± 5.6	15.2 ± 3.7	0.047	0.644 ^c	0.710 ^c
Menopausal symptoms	23.9 ± 2.1	20.5 ± 2.1	18.0 ± 1.8	14.1 ± 1.8	5.9 ± 1.7	6.4 ± 1.6	0.504	0.547	0.580
Somatic	35.3 ± 2.6	25.4 ± 2.6	26.7 ± 2.4	17.7 ± 2.4	8.6 ± 2.2	7.7 ± 2.2	0.066	0.756	0.760
Psychological	16.5 ± 2.7	16.2 ± 2.6	13.5 ± 2.4	12.1 ± 2.4	3.0 ± 1.9	4.1 ± 1.8	0.856	0.701	0.688
Urogenital	19.2 ± 3.5	22.1 ± 3.4	12.6 ± 2.2	13.1 ± 2.1	6.6 ± 2.8	9.0 ± 2.7	0.851	0.315	0.808
QoL	77.3 ± 2.3	81.6 ± 2.3	79.7 ± 2.1	84.4 ± 2.1	2.4 ± 2.3	2.8 ± 2.3	0.233	0.804	0.761
Depressive symptoms	12.7 ± 2.9	14.1 ± 1.8	15.3 ± 2.3	12.8 ± 1.3	-2.6 ± 1.9	1.3 ± 1.9	0.238	0.099	0.103
Overall mood	-35.8 ± 14.0	-35.6 ± 13.8	-26.4 ± 13.5	-6.6 ± 13.3	9.4 ± 7.4	29.0 ± 7.2	0.465	0.079	0.434
Total well-being	35.3 ± 3.0	32.1 ± 3.0	31.8 ± 3.1	24.7 ± 3.1	3.5 ± 1.6	7.4 ± 1.6	0.179	0.008^b	0.046

With the exception of the quality of life (QoL) measure, a lower value at week 0 and week 14 means a reduction in the symptom experienced.

ITT, intention to treat; PPI, present pain intensity; PP, per protocol; VAS, visual analog scale.

^aTreatment differences have been reversed so that a positive value reflects improvement in a symptom after 14 weeks of intervention, except for QoL.

^bCompared with placebo ($P < 0.017$).

^cMann-Whitney U test.

Bold values indicates statistical significance ($P < 0.017$).

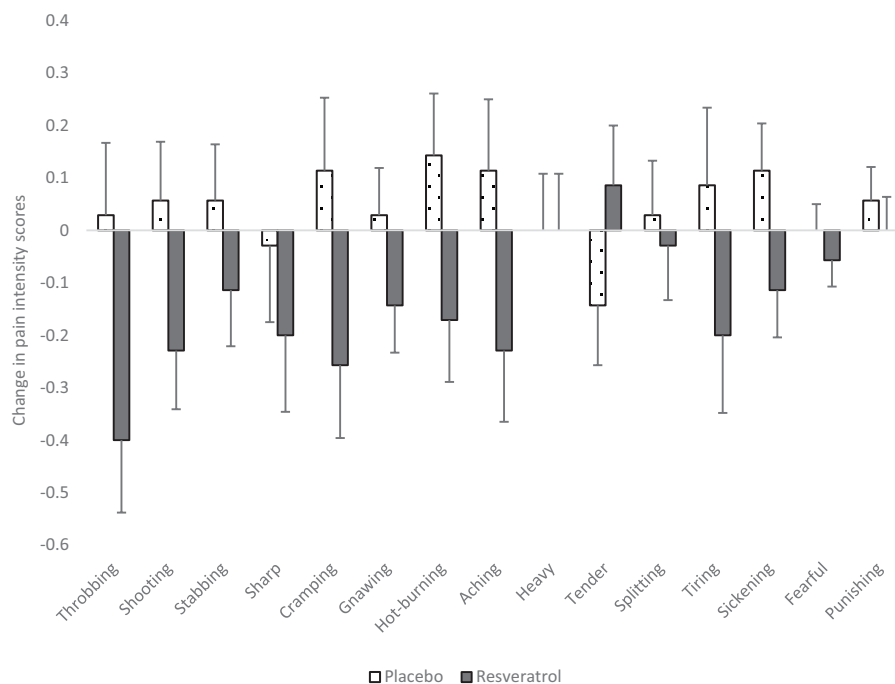


FIG. 1. Changes (week 14 to week 0; mean \pm SEM) in pain intensity scores for each pain descriptor in the McGill Pain Questionnaire in the placebo and resveratrol groups.

Consumption of resveratrol for 14 weeks not only improved cognitive performance and cerebrovascular function,²¹ but we now show for the first time that resveratrol also improved total well-being and reduced pain experienced by postmenopausal women.

Given the subjective nature of measurements for aspects of well-being it is not surprising that there were improvements of all symptoms in the placebo group, except for pain and depressive symptoms. Moreover, the responses may be expected to fluctuate in the course of menopause,²⁸ hence the importance of a placebo comparison. Indeed, we observed a significantly greater response in total well-being and QoL with resveratrol supplementation than with placebo. Interestingly, in all subscales pertaining to pain, the absence of a placebo response confirms the efficacy of resveratrol for reducing pain in postmenopausal women.

A limitation of this study was that the participants did not specify the source and nature of their pain. Reductions in pain were presumed to be age-related osteoarthritis as a large proportion of participants reported aching pain (Table 2). Age-related osteoarthritis is characterized by the breakdown of intra-articular structures and loss of blood supply (and thus nutrients) to previously perfused structures that result in ischemic pain.²⁹ A growing number of studies have been evaluating the potential efficacy of bioactive nutrients such as curcumin, epigallocatechin gallate, genistein, and resveratrol for the management of osteoarthritis. The proposed mechanism of action of these bioactive nutrients is primarily through the reduction of proinflammatory mediators such as interleukin (IL)-1 β and tumor necrosis factor (TNF)- α , thereby attenuating matrix degradation and apoptosis of human

chondrocytes. Resveratrol has been shown in vitro to reduce IL-1 β in human primary articular chondrocytes by down-regulating nuclear factor kappa beta pathways.³⁰ Furthermore, recent findings support the idea of a synergistic dose and time-dependent effect of resveratrol and curcumin to reduce IL-1 β -induced apoptosis of chondrocytes compared with treatment with the individual compounds.³¹ However, clinical evidence in humans, particularly in relation to pain in postmenopausal women, is lacking: curcumin supplementation (200 mg/d for 8 months) was found to reduce proinflammatory markers, which were accompanied by improved physical function and QoL in sufferers of mild to moderate knee osteoarthritis³²; 100 mg of resveratrol in combination with 75 mg of grape skin polyphenols attenuated the postprandial inflammatory response to consumption of a high-fat meal.³³ There are currently no studies linking the reduction in osteoarthritic or generalized pain to the reduction in proinflammatory markers. Thus, the potential for resveratrol to reduce systemic inflammation for the management of osteoarthritis warrants further investigation.

One of the aims of this study was to evaluate the benefits of resveratrol for enhancing cerebrovascular function, which deteriorates with ageing and is worsened by menopause-related estrogen deficits.⁹ While we did not explicitly assess blood flow to joints in this study, our assessment of CVR to hypercapnia in cerebral arteries may reflect changes in systemic circulatory function. We have previously shown that resveratrol can enhance vasodilator function in the brachial artery in humans³⁴ and in cerebral arteries,³⁵ indicating the efficacy of resveratrol for improving overall circulation, mediated by the up-regulation of nitric oxide bioavailability.³⁶ We speculate that our finding of

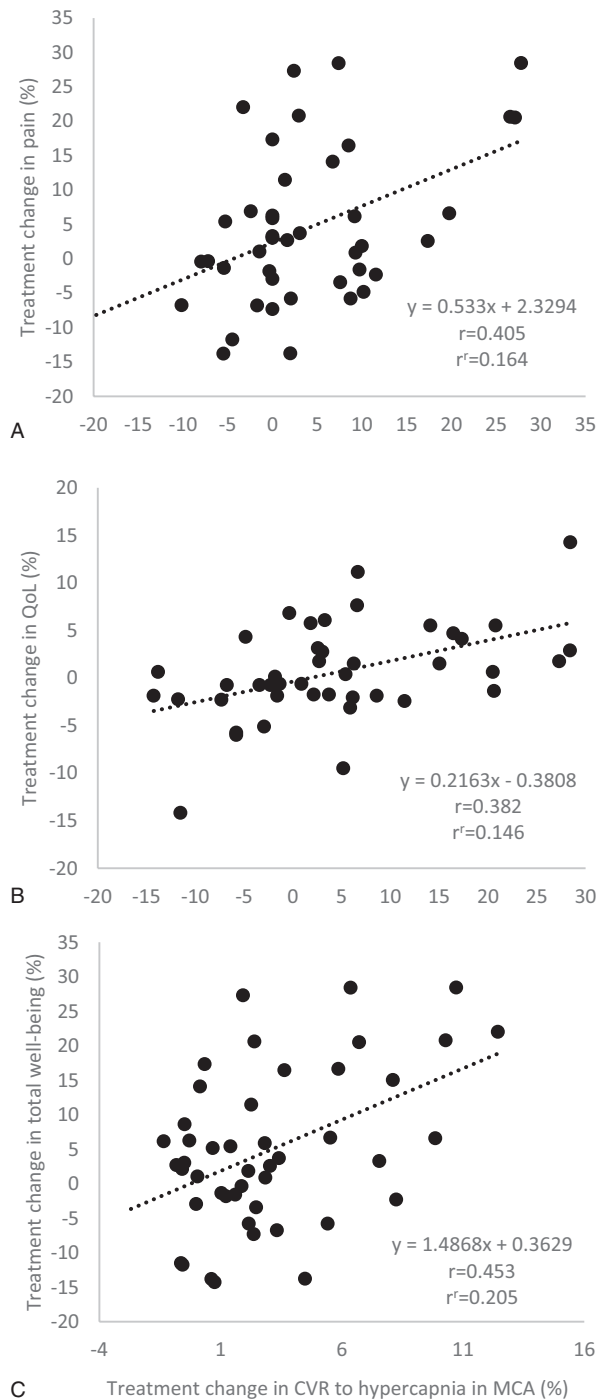


FIG. 2. Correlation between changes (week 14 to week 0) in (A) overall pain; (B) quality of life (QoL); and (C) total well-being and the change in cerebrovascular responsiveness (CVR) to hypercapnia. MCA, middle cerebral artery.

a correlation between treatment reduction in pain and improvement in CVR to hypercapnia suggests that pain reduction with resveratrol may be due to increased perfusion in the affected subchondral bone. It is hypothesized that the **increased production of nitric oxide by endothelial cells from surrounding tissues after resveratrol treatment may reverse the hypoxia in the affected tissues to improve vasodilatation**, thereby improving

nutrient exchange to the affected joint and to promote healing.³⁷ Furthermore, CVR to hypercapnia also correlated with QoL, suggesting that enhanced circulatory function has indirect benefits on self-reported physical and mental capacity. An alternative hypothesis is that the elevation of mood resulting from increased cerebrovascular perfusion has offset the perception of pain. However, no significant relationship between pain reduction and improved QoL was observed in our study ($r = 0.256$, $P = 0.045$).

Findings from this pilot investigation offer perspectives and considerations for the design of future interventions pertaining to the use of resveratrol for ameliorating pain in age-related osteoarthritis in both sexes. Studies should consider a more comprehensive assessment of pain that includes location and history of trauma, and also objective measures of joint stiffness and mobility. We did not expect to see improvements in menopausal symptoms with resveratrol as our cohort of women were at least a decade postmenopausal and they reported mild symptoms. A meta-analysis examining the effectiveness of phytoestrogens (isoflavone, genistein, and soy extract) reported no benefits for reducing vasomotor symptoms (ie, hot flashes) for perimenopausal and postmenopausal women experiencing symptoms compared with placebo.¹² However, the finding that women with lower estrogen levels have poorer cerebral perfusion, which is further compromised during a hot flush episode, suggests that vascular dysfunction may be linked to the severity of vasomotor symptoms.¹⁰ Therefore, the effects of resveratrol on menopausal symptoms should be assessed in perimenopausal and postmenopausal women with poor vascular function.

CONCLUSIONS

In conclusion, **results from this study suggest that resveratrol may be effective for reducing pain and improving total well-being in postmenopausal women through improvements in circulatory function. Given the systemic inflammation milieu of age-related osteoarthritis, the potential for resveratrol alone or in combination with other polyphenols such as curcumin to decrease proinflammatory mediators and reduce pain associated with age-related osteoarthritis should be further investigated in humans.**

REFERENCES

1. Brown WJ, Mishra GD, Dobson A. Changes in physical symptoms during the menopause transition. *Int J Behav Med* 2002;9:53-67.
2. 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.
3. Freeman EW, Sammel MD, Lin H, Gracia CR, Kapoor S. Symptoms in the menopausal transition: hormone and behavioral correlates. *Obstet Gynecol* 2008;111:127-136.
4. Laskarin G, Persic V, Kukic SR, et al. Can pain intensity in osteoarthritis joint be indicator of the impairment of endothelial function? *Med Hypotheses* 2016;94:15-19.
5. Greising SM, Baltgalvis KA, Lowe DA, Warren GL. Hormone therapy and skeletal muscle strength: a meta-analysis. *J Gerontol A Biol Sci Med Sci* 2009;64:1071-1081.
6. Nedergaard A, Henriksen K, Karsdal MA, Christiansen C. Menopause, estrogens and frailty. *Gynecol Endocrinol* 2013;29:418-423.

7. Kadi F, Karlsson C, Larsson B, et al. The effects of physical activity and estrogen treatment on rat fast and slow skeletal muscles following ovariectomy. *J Muscle Res Cell Motil* 2002;23:335-339.
8. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. *Pharmacol Rev* 2008;60:210-241.
9. Wong RHX, Evans HM, Howe PRC. Poor cerebrovascular function is an early marker of cognitive decline in healthy postmenopausal women. *Alzheimer Dementia Transl Res Clin Intervent* 2016;2:162-168.
10. 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 Women M* 2000;45:253-257.
11. Dornstauder E, Jisa E, Unterrieder I, Krenn L, Kubelka W, Jungbauer A. Estrogenic activity of two standardized red clover extracts (Menoflavon intended for large scale use in hormone replacement therapy. *J Steroid Biochem Molec Biol* 2001;78:67-75.
12. Chen MN, Lin CC, Liu CF. Efficacy of phytoestrogens for menopausal symptoms: a meta-analysis and systematic review. *Climacteric* 2015;18:260-269.
13. Thomas AJ, Ismail R, Taylor-Swanson L, et al. Effects of isoflavones and amino acid therapies for hot flashes and co-occurring symptoms during the menopausal transition and early postmenopause: a systematic review. *Maturitas* 2014;78:263-276.
14. Hidalgo LA, Chedraui PA, Morocho N, Ross S, San Miguel G. The effect of red clover isoflavones on menopausal symptoms, lipids and vaginal cytology in menopausal women: a randomized, double-blind, placebo-controlled study. *Gynecol Endocrinol* 2005;21:257-264.
15. Carmignani LO, Pedro AO, Costa-Paiva LH, Pinto-Neto AM. The effect of dietary soy supplementation compared to estrogen and placebo on menopausal symptoms: a randomized controlled trial. *Maturitas* 2010;67:262-269.
16. Heinemann LA, DoMinh T, Strelow F, Gerbsch S, Schnitker J, Schneider HP. The Menopause Rating Scale (MRS) as outcome measure for hormone treatment? A validation study. *Health Qual Life Outcomes* 2004;2:67.
17. Setchell KDR, Brown NM, Lydeking-Olsen E. The clinical importance of the metabolite equol: a clue to the effectiveness of soy and its isoflavones. *J Nutr* 2002;132:3577-3584.
18. Moutsatsou P. The spectrum of phytoestrogens in nature: our knowledge is expanding. *Hormones (Athens)* 2007;6:173-193.
19. Tou JC. Evaluating resveratrol as a therapeutic bone agent: preclinical evidence from rat models of osteoporosis. *Ann N Y Acad Sci* 2015;1348:75-85.
20. Wenzel E, Somoza V. Metabolism and bioavailability of trans-resveratrol. *Mol Nutr Food Res* 2005;49:472-481.
21. Evans H, Howe P, Wong R. Effects of resveratrol on cognitive performance, mood and cerebrovascular function in post-menopausal women; a 14-week randomised placebo-controlled intervention trial. *Nutrients* 2017;9:27.
22. Evans H, Howe P, Wong R. Clinical evaluation of effects of chronic resveratrol supplementation on cerebrovascular function, cognition, mood, physical function and general well-being in postmenopausal women: rationale and study design. *Nutrients* 2016;8:150.
23. Bravo G, Hebert R. Age- and education-specific reference values for the Mini-Mental and modified Mini-Mental State Examinations derived from a non-demented elderly population. *Int J Geriatr Psychiatry* 1997;12:1008-1018.
24. Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the Short-form McGill Pain Questionnaire (SF-MPQ-2). *Pain* 2009;144:35-42.
25. Buysse DJ, Reynolds CF 3rd, 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.
26. Mishra G, Schofield MJ. 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.
27. Altman DG, Bland JM. Treatment allocation by minimisation. *Brit Med J* 2005;330:843-.
28. Sonawalla SB, Rosenbaum JF. Placebo response in depression. *Dialogues Clin Neurosci* 2002;4:105-113.
29. Findlay DM. Vascular pathology and osteoarthritis. *Rheumatology* 2007;46:1763-1768.
30. Shen CL, Smith BJ, Lo DF, et al. Dietary polyphenols and mechanisms of osteoarthritis. *J Nutr Biochem* 2012;23:1367-1377.
31. Shakibaei M, Mobasheri A, Buhrmann C. Curcumin synergizes with resveratrol to stimulate the MAPK signaling pathway in human articular chondrocytes in vitro. *Genes Nutr* 2011;6:171-179.
32. Belcaro G, Cesarone MR, Dugall M, et al. Efficacy and safety of Meriva, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Altern Med Rev* 2010;15:337-344.
33. Ghanim H, Sia CL, Korzeniewski K, et al. A resveratrol and polyphenol preparation suppresses oxidative and inflammatory stress response to a high-fat, high-carbohydrate meal. *J Clin Endocrinol Metab* 2011;96:1409-1414.
34. Wong RHX, Howe PRC, Buckley JD, Coates AM, Kunz I, Berry NM. Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. *Nutr Metab Cardiovasc Dis* 2011;21:851-856.
35. Wong RHX, Nealon RS, Scholey A, Howe PRC. Low dose resveratrol improves cerebrovascular function in type 2 diabetes mellitus. *Nutr Metab Cardiovasc Dis* 2016;26:393-399.
36. Li H, Xia N, Förstermann U. Cardiovascular effects and molecular targets of resveratrol. *Nitric Oxide* 2012;26:102-110.
37. Hancock CM, Riegger-Krugh C. Modulation of pain in osteoarthritis: the role of nitric oxide. *Clin J Pain* 2008;24:353-365.