

The effect of boosting polyphenol intake for women's cancer survivors on arthralgia, mood and hot flushes - a pilot real World evaluation

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Abstract

Purpose: Late toxicities such as arthritis, common after breast and other cancers, impacts quality of life and restricts the ability to exercise. Epidemiology studies have linked higher intake of polyphenol-rich foods with less arthritis. Laboratory studies show these foods reduce intraarticular inflammation and oxidative stress, allowing greater mobility although clinical intervention studies are lacking.

Methods: This was an open label evaluation of a polyphenol-rich whole food supplement (Pomi-T) supplied to volunteer members of a Japanese Women's Cancer Support Group, Tokyo. 44 of 120 women responded to invitations. Joint discomfort, mobility, mood and hot flushes were recorded at baseline and after 2 months Pomi-T using validated questionnaires. 38 of 44 completed pre and post forms (average age of 48, range 26-62 years).

Results: The mean improvement in mood was 1.9 (19.96-18.06), with a paired T-test of $p=0.01$. Mean reduction in hot flush score was 6.68 (38.41-31.71), with a two tailed sign test of $p=0.016$. Mean reduction in joint pain, stiffness and immobility was 3.84 (25.21-21.37), with a two tailed sign test of $p=0.011$. Positive comments from individuals included an unexpected reduction in hay fever symptoms in 8 patients.

Conclusion: This open labelled study demonstrated that symptomatic women with breast and other cancers had a statistically significant reduction in arthralgia, hot flushes and improved mood after consuming a polyphenol-rich nutritional supplement. The reduction in hay fever symptoms requires separate exploration but this pilot has provided sufficient encouragement and justification to proceed to a more statistically robust double-blind, randomised control trial.

Keywords: Breast cancer; Polyphenols; Arthritis; Mood; Hot flushes

Introduction

Joint discomfort and stiffness are more common among women following cancer treatments, with studies consistently reporting an incidence of over 55%, adversely affecting mobility

and long-term quality of life [1-3]. There are several reasons for why the prevalence of these troublesome symptoms are greater in breast cancer patients as opposed to that of the general population. Chemotherapy drugs such as Taxotere and Oxaliplatin can cause arthralgia, which can chronically persist, especially in women who have been rendered prematurely post-menopausal or received additional Herceptin therapy. Women treated for breast cancer can experience ipsilateral shoulder stiffness related to axillary surgery

and radiotherapy, with one third of women taking Tamoxifen reporting symptoms of arthralgia [3]. Over the last 10 years, the standard care for postmenopausal women has increasingly focused on aromatase inhibitors (AI), which are associated with bothersome AI-associated Musculoskeletal Symptoms (AIMSS) in more than 50% of patients [4,5].

As well as causing discomfort, persistent arthralgia can also compromise the effectiveness of adjuvant therapies by reducing compliance to hormone treatment [5]. Discontinuation rates of aromatase inhibitors have been recognised in up to 30% of women suffering from arthralgia and stiffness [3,6]. Poor adherence to AI therapy has also been associated with worse disease-free and overall survival from breast cancer [7]. In addition, arthritis can significantly impact patient's ability to exercise, which can lead to an exacerbation of further symptoms and complications associated with cancer [8,9]. In particular, regular exercise can mitigate the risks of weight gain, hot flushes, fatigue, peripheral neuropathy, erectile function, arthritis itself and osteoporosis, as well as improve medication compliance, mood and sleep patterns [6,8,10,11]. Restricted mobility may have even more sinister consequences for patients, as cohort studies have consistently linked a reduced relapse rate and improved survival benefit amongst those able to be physically active after several different types of cancer, including breast cancer [8,12-16].

The goals of medical treatment for arthritis are largely to relieve pain but analgesia such as Nonsteroidal Anti-Inflammatory (NSAI) agents have significant long-term cardiovascular, renal and gastrointestinal risks [3,17]. Complementary therapies including acupuncture, yoga and Pilates help maintain or improve joint mobility, increase joint strength and minimise the disabling effects of arthritis [2,18]. Dietary measures also have a role over and above weight reduction. People who eat greater quantities of fruit, herbs and vegetables have a lower incidence of arthritis for many reasons, one of which is the phytochemical content of these foods [19,20]. Phytochemicals are chemical compounds which are found naturally in plants and are responsible for the colour, taste, and aroma of plant-based foods. Their regular intake is linked to a lower risk of cancer, improvement in cancer outcomes, reduction in the risk of arthritis, lower pain severity in patients with established arthritis, and improved exercise performance [20-22]. Boosting dietary intake is particularly relevant for cancer survivors as this could enhance exercise capacity and improve mobility, causing a reduction in arthralgia and arthritis progression [12,23-28]. Furthermore, a higher intake of phytochemicals is linked to a lower incidence of chronic degenerative disease, meaning their regular intake may help lessen the severity and incidence of the numerous conditions which are more common after cancer treatment [19,29]. The symptomatic benefits of phytochemicals are thought to be due to their influence on several biological pathways, which have been described and summarised in a recent review [20]. These

include improving gut health via their prebiotic properties, aiding weight reduction, downregulating excess articular inflammation and inhibiting cartilage degeneration [9,21,30]. Polyphenols, in particular, also possess direct, joint-protective properties by inhibiting overproduction of Matrix Metalloproteinase (MMPs) enzymes, which are responsible for extracellular matrix (cartilage - collagen and proteoglycan aggrecan) degeneration [30]. Polyphenols also exert anti-apoptotic effects on chondrocytes in joints exposed to oxidative stress or inflammation, further reducing cartilage degeneration [9].

Although the regular intake of phytochemical-rich whole foods including herbs, spices, tea, cruciferous vegetables and fruit is encouraged for the alleviation of arthralgia, Over The Counter (OTC) therapies are particularly popular amongst people with arthritis and musculoskeletal conditions. Reports from *Real World* surveys suggest that over 50% of arthralgia sufferers have used a variety of OTC products at one stage in their illness, with this figure going over 75% in patients living with cancer who have arthralgia [31-33]. The charity *Arthritis Research UK* has comprehensively reviewed 30 available OTC nutritional supplements, highlighting their potential benefits but emphasizing the significant gaps in research [9,32-36]. Commonly used OTC supplements include glucosamine, fish oils, chondroitin and a variety of concentrated polyphenol rich whole food capsules [37,38].

A whole food nutritional supplement can be a convenient way to boost intake of polyphenol-rich foods and ensure sustained intake throughout the day. Interventional studies of some polyphenol-rich supplements have demonstrated health benefits ranging from decreased arthralgia, improved digestion and reduced markers of cancer progression [1,39-43]. For this study the OTC supplement Pomi-T was selected given that it has demonstrated a high safety profile in a randomised trial in which participants also reported improvements in joint discomfort [1,43]. Pomi-T contains no phytoestrogenic polyphenols, which may be which may be a risk factor for breast cancer persistence/recurrence. The ingredients of Pomi-T also have joint protective properties (pomegranate, turmeric, green tea and broccoli), which will be briefly summarised along with the likely active phytochemicals and within them:

Pomegranate (*Punica granatum*): The whole fruit and particularly the ground seeds of pomegranate are particularly rich in anthocyanins, flavonoids, gallic acid, ellagic acid, quercetin, and ellagitannins. Laboratory studies have shown that pomegranate extract protected joints from toxic exposure by inhibited interleukin-1 beta (IL-1 β)-induced expression of matrix metalloproteinases MMP [44]. In human trials, consumption of pomegranate extract helped pain control and decreased serum oxidative stress and the expression of several inflammatory markers [45]. Pomegranate is also a good sources of plant nitrates which

in view of its additional citrus bioflavonoid and vitamin C content is converted into Nitric Oxide (NO). NO is one of the postulated reasons why pomegranate extract is reported to improve exercise performance and muscle recovery [46-51].

Turmeric (*Curcuma longa*): Turmeric contains curcuminoid polyphenols which are responsible for its vibrant yellow colour, and have the capability of interacting with numerous molecular targets involved in inflammation [19]. In one notable laboratory study, treatment with turmeric prior to the administration of arthritis-inducing toxins in rats was found to inhibit joint inflammation via de-activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kappa B), cyclooxygenase-2 (COX-2) and receptor activator of nuclear factor kappa B (RANK) [52]. This led to reduced peri-articular joint destruction and osteoclast formation. In humans, a Randomised Control Trial (RCT) studying the effects of three months of a turmeric food supplement demonstrated significant improvements in pain severity and disability scores versus placebo [41]. In another RCT study, 8 weeks of turmeric root extract improved joint pain severity and the ability to perform daily activities, along with reduced stiffness scores [40]. A further study identified that turmeric out-performed ibuprofen in analgesic and joint mobility properties in existing arthritis sufferers. Patients which received a turmeric food supplement expressed significantly lower pain levels when mobilising [41]. Finally, in terms of exercise performance, turmeric capsules downregulated biological inflammation during recovery after exercise-induced muscle damage, and increased functional capacity during subsequent exercise sessions [39].

Green tea (*Camellia sinensis*): Green tea, particularly the dried whole leaf extract, is rich in catechins, including epigallocatechin 3-gallate (EGCG) [20,53-55]. A number of in vitro studies, using bovine and human chondrocytes derived from Osteoarthritis (OA) and Rheumatoid Arthritis (RA) cartilage have demonstrated that pre-incubation with tea extract, or pure EGCG, reduced the expression of pro-inflammatory cytokines such as IL-1 β , tumour necrosis factor alpha (TNF α), IL-6, prostaglandin E2 and COX-2 when exposed to oxidative stress. Diminished levels of pro-inflammatory cytokines in turn dampen the activation of matrix-degrading MMPs [44,56-64]. Although prospective clinical RCTs are lacking with respect to the efficacy of green tea extracts in patients with arthritis, numerous studies have confirmed an association between moderate tea intake and a lower incidence of arthritis, along with a solid safety profile [55,65].

Broccoli: Broccoli is a cruciferous vegetable rich in phytochemicals such as isothiocyanate and its metabolite sulforaphane (SFN). These phytochemicals have been reported to have significant health benefits encompassing the prevention and treatment of cancer, atherosclerosis and numerous inflammatory disorders [20,66-68]. In several animal models of arthritis, diets supplemented with extra SFN-rich broccoli significantly reduced

cartilage destruction via profound effects on several biochemical pathways [69-71]. SFN directly enhances glutathione production and is a potent inducer of the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2). NRF2 promotes an adaptive antioxidant enzyme response in the presence of excessive oxidative stress which attenuates genetic damage within tissues, including joints [66,67,72-74]. In addition, NRF2 directly modulates MMP expression in chondrocytes via an epigenetic effect [75-77]. This blunts the production of IL and TNF inflammatory cytokines, and upregulates the production of Histone Deacetylase (HDAC) inhibitor, which has direct chondroprotective properties [71,77].

Links have been reported in large cohort trials between improved mood and higher dietary polyphenol content, often in combination with enhanced cognitive function [78-80]. There are a number of potential explanations for this. Firstly, improved joint health can lead to an improved ability to exercise, which will increase endorphin and serotonin levels [8,10,81-83]. Polyphenols also have prebiotic properties which can augment gut health and downregulate systemic inflammation, both of which are known to have a significant effect on reducing cognitive impairment and positively impacting mood [78,84,85]. Likewise, plant nitrates are converted to NO, in the presence of polyphenols and vitamin C, which act on arterial walls to increase brain and tissue oxygenation [86]. Finally, polyphenols such as EGCG, found in green tea, and curcumin, found in turmeric can have a direct positive effect on the brain by ameliorating excess oxidative stress, and engaging in signalling pathways which link molecules that act at the interface between cellular metabolism and synaptic plasticity [78-80].

Methodology

This was an open label evaluation of a polyphenol-rich whole food supplement which was supplied to voluntary members of the Japanese Women's Cancer Support Group, Tokyo. Invitations to volunteers were sent by internal email to 120 eligible members. From April to May 2020, 50 women responded and were supplied with a two-month supply of the whole food supplement (Pomi-T), and sent three validated questionnaires at baseline and 2 months. Of the 44 participants who completed the initial questionnaire, 38 completed both the pre and post forms. The 38 participants had histologically confirmed cancer, with an average age of 48 (range 26-62 years). No other demographic data was recorded.

Participants completed the questionnaires themselves then posted them back to the co-ordinating support group office. Severity of joint symptoms were recorded using the WOMAC questionnaire, which has been validated mainly for symptoms related to large joints, such as the knee and hip. The WOMAC questionnaire has 12 questions subdivided into pain, stiffness and difficulties in performing daily activities. Participants recorded the severity of their symptoms on a 5 point scale ranging from none (0) to extreme (5) [87]. A single total score was extracted from

the questionnaire by the Japanese co-ordinator of the study. Mood was recorded with the Mood Rating Scale (MRS), which is a self-reported measure of normal mood, consisting of six 150 mm visual analogue subscales with defined anchor points. The subscales are: tense-relaxed, sad-happy, tired-energetic, confused-clear headed, irritable-easy-going, unsure-confident [88,89]. The six subscales were summated to obtain a single total score. Hot flushes were recorded using the validated 7-day diary hot flushes questionnaire. Each hot flush was graded by the participant on a 4-point scale (mild to severe). The total score was determined by the summation of the grades of each flush for a 7-day period [90]. The anonymised results of the questionnaires were summarised in an excel spread sheet and sent to an independent statistician in the UK.

Women were also asked to record their personal observations in an open comments box at the end of the 2-month period. All these comments, translated into English by the Japanese supporter of the study and are recorded, in their own words, in Table 1.

1	The stiffness in my fingers in the morning seemed to be abated. Normally there is pain in my knee joints which makes climbing stairs a trial but this helped to the extent that I did not feel much pain and could get up the stairs easier. This supplement helped my hay fever symptoms, I did not need to take any associated medicine. I had a general uplift in my feelings and physical situation.
2	Tablet a little large; I had the feeling that my symptoms of hay fever were reduced.
3	The packaging is good and the capsule effective; Felt better in myself. I felt less dropping in my feelings and I did not get irritated as much. Felt less pain in my joints, felt a lightening of my allergy to house dust and a reduction in tendency to hot flushes. Felt less exhausted than normal. In general I was less irritable, and in certain joints I had less pain.
4	The size of the capsule is large. There was no change in my occurrence of hot flushes. There seemed to be no change in my general condition whilst taking the supplement.
5	The capsule is large and the smell of the capsule is strong.
6	Unfortunately, I did not notice any improvements in my hot flushes.
7	It seemed to help with my shortness of breath. I seemed to have a better general skin condition whilst taking the supplement. I do not see any advantage for me to continue with this supplement.
8	I had the feeling that hot flush severity was reduced but it was difficult to judge on an occurrence incident, it did not seem to help on an incident base.
9	I noticed on my morning run that the pain in my legs was reduced. The capsule is large, the size should be reduced.
10	The supplement capsule size is slightly large.
11	Whilst taking the supplement I noticed a reduction in the occurrence of hot flushes.
12	Over the two-month period I did not notice much change in my condition. I take good care with my diet, perhaps the food supplement would help a person whom has difficulty in consuming a balanced diet. At first as a side effect I had diarrhoea but perhaps that was not the supplement.
13	During the night I often get hot flushes and it is uncomfortable, I have the feeling that with taking the food supplement that the symptoms have become somewhat lighter; I had a reduction in feeling stress when I took the supplement and a general increase of feel in wellbeing.
14	There was a reduction in hot flushes; I also felt a reduction in joint pains; the supplement helped reduce my anxiety level and increased my feeling of wellbeing.
15	The size of the capsule is large, a smaller size would be better.

16	Whilst taking the food supplement I felt a decrease in intensity of my hot flushes; Taking the supplement, my toilet function became regular and good. I did get any relief from my joint pains and I found the capsule a bit large.
17	I noticed after taking pomi-t for a few days that I had an alleviation of the tendonitis in both my little fingers, now I they feel almost fully alleviated. I also had some discomfort in my elbow and knee joints but this also seems to have alleviated. I don't know if it was an effect of the supplement but also my hay fever/ house dust symptoms this season somewhat alleviated.
18	My hay fever symptoms seemed better and my mood was more stable when I took the supplement. There are only good things in the supplement so I feel surely in the product. A smaller size capsule would be better.
19	At first, I did not notice any benefits but after one month I noticed that the occurrence of hot flushes decreased. When I climb stairs I have pain in my right knee joint but this also seems to have somewhat reduced since taking the food supplement. It does not seem to have helped my headaches. It does seem to have helped with the sensation of coldness that I used to have in my ankles.
20	After a certain length of time taking the food supplement I noticed an alleviation in certain joint pains.
21	Two weeks after taking this I had an improvement in my hot flushes but this may have been due to other factors. I felt benefits from Pomi-T for my hot flushes.
22	I did not feel any effects /benefits from the supplement.
23	During the middle of April, my stomach swelled up and I had discomfort so I stopped taking the capsules. After stopping the capsules I did notice an increase in the frequency of my hot flushes.
24	I noticed a real decrease in the pain level in my thigh joints. In general, I noticed a decrease in pain in my joints, I was taking certain drugs but the pain lowering seemed significant. I will continue to take Pomi-T.
25	It seemed to help my back pain a little.
26	The capsule is a bit large but it seemed to help a little with my hay fever symptoms.
27	In the first month I did not notice any discernible effects but after a month or so I noticed some improvement in the lines and skin condition around my eyes.
28	It seems to help alleviating pain in my wrist and some hay fever symptoms. After stopping the food supplement I noticed that I had more pain in my joints again.
29	It seemed to alleviate my hot flushes severity.
30	It did not help with my hot flushes; I think a 2-month trial is not long enough to gauge effects
31	My hay fever this year did not seem so severe.
32	It seemed to help improve my constipation. It seemed to help me be less exhausted.
33	It seemed to help alleviate my hot flush syndrome and my hay fever symptoms.
34	I had an improvement in general feeling. My hot flushes seemed to be much lighter than previously; the numb feeling in my legs also seemed to improve.
35	I seemed to get an improvement in my skin tone.

36	I noticed increased flexibility in my joints, getting up in the morning and when getting up from a chair. I noticed a reduction in the number and severity of hot flushes and an upward swing in attitude and feeling of wellbeing.
37	I noticed during the course of taking Pomi-T that my normal weak joints did not happened. <div>stopped; all the others completed the 2month study.</div>

Discussion

Table 1: Self-reported comments from participants-in their own words.

The Pomi-T supplement: Each vegan capsule contains 150mg whole pomegranate fruit powder (*Punica granatum*); 30mg ground green tea leaf (*Camellia sinensis*) of 5:1 extract (equivalent to 150 mg of whole leaf); 150 mg whole ground turmeric; 150 mg whole ground broccoli florets (*Brassica oleracea*). The Swiss manufacturers (Helsinn Integrative) are adherent to good manufacturing practice guidelines and perform in-house analysis for authenticity and purity from heavy metals and pesticides on each batch. It was supplied free to the women volunteers by the Japanese distributor PT Plus (Higashi Kanamachi 5-48-28, Katsushika-ku, Tokyo 125-0041, Japan).

Results

Statistical analysis took place independently from the trial committee. The Social Statistics software was used for the analysis (<https://www.socscistatistics.com>). Total scores for each participant were obtained from each questionnaire via the validated published process [87,88,90]. Mood, hot flushes and arthralgia were analysed separately comparing before and after scores (baseline versus two months).

Mood: Data was normally distributed hence a paired t-test was used. The mean improvement in mood was 1.9 (19.96-18.06), the T-test value calculation was 2.55, p=0.01.

Hot flushes: The data was not normally distributed so a within patient comparison of scores a two tailed sign test was used. The mean reduction in hot flush score was 6.68 (38.41-31.71). The z-value was 2.41404, p=0.0157.

Joint pains: A two tails sign statistical test was used. Mean reduction in joint pain, stiffness and immobility score was 3.84 (25.21-21.37). The z-value was 2.556, p=0.011.

Open comments of the participants are listed in Table 1. No statistical analysis was performed on these comments. It can be seen from this table that 14 patients indicated their hot flushes improved. Thirteen patients experienced a reduction in joint pain, stiffness or mobility. Eight patients reported that their hay fever symptoms had improved and that they were less dependent on, or no longer required anti-allergy medication. Six patients exhibited better mood or vitality. One patient developed indigestion and

This unrandomised, small-scale pilot evaluation has a number of methodological weaknesses. However, what this study lacked in statistical strength it gained in novelty and potential importance in the management of arthritis, mood and hot flushes. This is the first study which has assessed the impact of a nutritional intervention on the treatment of symptomatic female patients with breast cancer. Arthralgia, hot flushes and mood changes are particularly troublesome symptoms which affect over half of women post breast cancer, especially in those taking hormonal therapies [1-5]. As many standard pharmacological treatments often fail to manage these symptoms and carry the risk of additional side effects, patients are increasingly turning to complementary self-help therapies. These therapies have varying degrees of benefit, but most lack evidence [35,91]. This study evaluated the influence of a widely available OTC nutritional supplement, which has previously been reported to be safe and well tolerated in an earlier double-blind RCT conducted in prostate cancer patients [1,43]. The Pomi-T supplement contains dried whole foods and whole food extracts as a method to boost overall intake of polyphenols, rather than patients receiving individual chemical isolates, which has raised concerns in previous studies [19,20]. In this evaluation only one participant discontinued Pomi-T before 2 months, with most women expressing their wish to continue taking the supplement after study completion.

The reduction in arthralgia and joint stiffness was statistically significant despite the small sample size, s and as 13 of the 38 participants also commented that their joint symptoms had improved, this finding is likely to be clinically relevant. The underlying mechanisms of how polyphenols reduce systemic and articular inflammation have been explained earlier. It would be useful to know in future studies whether articular symptoms also improved in the small joints, such as the hands and feet, in addition to large joints, which were addressed in the WOMAC questionnaire. Likewise, although the WOMAC questionnaire did include questions on mobility [87], it would be useful to have a more objective measure of exercise capacity with grip strength monitors, step counters, walking tests and more exercise-specific questionnaires.

A statistically significant improvement in mood was also seen following two months of treatment with Pomi-T. The MRS is a reliable and validated tool in this setting, and hence it will

be utilised in the next study. It is not known, however, whether mood increased via the direct biological influence of polyphenol rich foods, indirectly because of the greater sense of wellbeing stemming from reduced arthralgia and increased mobility, or simply because of a placebo effect. The next double-blind, placebo-controlled trial will shed more light on this, especially as a subgroup analysis is planned to allow evaluation of mood independently from arthralgia and exercise levels.

According to the Menopause Epidemiology Study, hot flushes are one of the main reasons for why menopausal women seek medical care and OTC treatments [92]. Various lifestyle interventions can help women cope with hot flushes [93], with weight reduction programs being the most successful [94]. Yet, it is not clear why hot flushes significantly improved in the participants of this evaluation, as the two-month intervention period was likely too short for a significant weight reduction effect to be seen. Reducing arthralgia can lead to enhanced exercise capacity, but studies have not definitively linked increased exercise with lower hot flushes [95]. Recent work suggests that foods rich in phytochemicals benefit women experiencing menopausal symptoms through tighter regulation of oxidative stress, although further research is required to assess this theory [95]. Women with a diet consisting of high levels of phytoestrogenic polyphenols tend to have less menopausal symptoms, although most robust trials of phytoestrogenic food supplements have not substantiated this claim. In addition, there are also justifiable oncogenic concerns with concentrated phytoestrogens in women with breast cancer [96]. Further biochemical evaluation is required to establish the potential underlying mechanisms of how phytochemicals work

This evaluation did not formally measure hay fever symptoms, and the comments from 8 of the participants were spontaneous. This was not completely unexpected, as polyphenols have previously been investigated for their anti-allergic effect in models and in human clinical trials [97]. Their anti-inflammatory profile is known to impact on the recruitment of mast cells and other immune cells to mucous membranes [98]. In addition, their endogenous anti-oxidant properties have been reported to limit the extent of cellular injury from free radicals during an allergic insult [99]. This evaluation took place in late spring in Japan, just before the "Cherry Blossom" season which is associated with a higher pollen count. No firm conclusions can be made regarding a beneficial effect of Pomi-T on hay fever symptoms, but it would be interesting to repeat this evaluation focusing specifically on the effect of Pomi-T in individuals who suffer from hay fever over a similar time period using designated formal measures of allergy symptom severity.

In conclusion, OTC supplements are relatively inexpensive, ubiquitously available self-help treatments commonly taken by women with breast cancer in an attempt to mitigate troublesome

chronic symptoms. However, despite their popularity most established OTC supplements lack formal evaluation, with their price and lack of intellectual property acting as discouraging factors which mean that sponsors are unlikely to recoup their investments. Nonetheless, there is a strong clinical need to confirm or refute the symptomatic benefits of polyphenol nutritional supplements, due to the potential clinical implications it may have for millions of women globally. Statistically significant results were ascertained from this small, open observational evaluation and the participant comments were interesting and insightful. This data is encouraging and justifies a more robust confirmatory clinical studies. An academic, non-commercially funded double-blind placebo controlled RCT is therefore now planned to commence in late 2021.

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Compliance with ethical standards

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Conflict of Interest

None of the authors have any connection with PT Plus Japan or the Peer Ring Breast Group, Tokyo. No member of the research team received money, directly or in kind for this academic evaluation.

Ethical Approval

As a service evaluation of a readily available over-the-counter supplement no formal ethics approval was required.

Consent to Participate

Participants volunteered themselves - no consent was required.

Availability of Data and Material

Readers have full access to all primary data collected and the

authors agree to allow the journal to review the data if requested.

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