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Nutritional practices to manage menstrual cycle related symptoms: a systematic review

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Abstract

Certain nutritional practices may reduce menstrual-related symptoms, but there is no current consensus on what foods/supplements are sufficiently evidenced to warrant promotion to reduce menstrual symptoms of naturally menstruating individuals. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Two online databases were searched for published experimental studies that investigated the effects of foods/supplements on menstrual-related symptoms in eumenorrhoeic women. Extracted data and study characteristics were tabulated and grouped on the basis of food/supplement intervention and dosage compared with UK dietary reference values (DRV) and safe upper limits. In total, twenty-eight studies and twenty-one different foods/supplement interventions were included in the review. None of the studies reported a negative effect on symptoms, twenty-three reported a positive effect and five had no effect. Eighteen different ways of measuring menstrual-related symptoms were described across the studies. The results indicate a lack of consistency in studies to confidently provide information to eumenorrheic, naturally menstruating women regarding the use of foods/supplements to reduce menstrual symptoms. Determination of menstrual-related symptoms varied along with dose and duration of food or supplements provided. These data provide some evidence for the use of vitamin D, calcium, zinc and curcumin to reduce menstrual-related symptoms of non-hormonal contraceptive users, on an individual basis; however, further investigation is required prior to implementation with a focus on robust protocols to determine and measure changes in menstrual symptoms, with interventions adhering to DRV and safe upper limits.

Key words: **Menstrual cycle: Women: Food: Diet: Supplement: Symptoms**

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Key findings & implications

- There is inconsistency in information recommending nutritional interventions to women experiencing a natural menstrual cycle when aiming to reduce menstrual-related symptoms, resulting from the wide range of symptoms and unknown mechanism of cause. We recommend treating symptoms on an individual case basis, adapting and personalising the nutrition intervention for the individuals' symptoms and dietary/supplement preferences.
- Curcumin, vitamin D, calcium, magnesium and zinc may reduce menstrual-related symptoms; however, further investigation is required, considering the mechanisms and reporting individual responses.
- Future studies should focus on investigating nutritional strategies to manage menstrual-related symptoms, ensuring DRV and safe upper limits of supplementation are adhered to.

Introduction

The menstrual cycle is a biological rhythm, whereby cyclic fluctuations in endogenous sex hormones such as oestrogen and progesterone are observed [1–3]. The changes in hormone levels and associated interactions with the brain and wider bodily functions can cause a variety of menstrual cycle related symptoms.

Worldwide estimations of pre-menstrual symptom prevalence range from 10 to 98%[4], with up to 80% of women experiencing at least one symptom of menstrual related symptoms during their lifetime[5]. Pre-menstrual symptoms can reduce quality of life, limit work capacity and cause absenteeism

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from school, work and social activities[6–8]. The most common symptom is primary dysmenorrhoea, otherwise known as cramping pain in the lower abdomen before or during menstruation without any evident disease or pathology[9]. The pain associated with dysmenorrhoea, can also reduce mood and sleep quality compared with the pain-free phase after menstruation[10]. Other common symptoms include changes to mood, bloating, food cravings, fatigue and breast pain[11]. However, many women do not consult a doctor whilst experiencing menstrual symptoms, which has been attributed to medication avoidance[9].

The exact aetiology of menstrual related symptoms is unclear, there are multiple theories suggesting the involvement of several hormones released with ovulation, diets with nutritional deficiencies, family medical history, progesterone and GABA neurotransmitter aberrations[12] and circulating gonadal steroids[13]. Alternatively, inflammation has been proposed as a potential mechanism as medications such as non-steroidal anti-inflammatory drugs are typically used to reduce menstrual-related symptoms such as abdominal cramps. High-sensitivity C-reactive protein is an acute phase inflammatory marker which has been positively associated with pre-menstrual mood, abdominal/back pain, food cravings, weight gain, bloating and breast pain but not menstrual headaches[14]. In some cases, suppression of ovarian hormone secretion attenuates menstrual related symptoms, although differences in ovarian steroid hormones have not consistently been observed between symptomatic and asymptomatic individuals[14]. It has been acknowledged that biological, social, demographic and behavioural factors have been associated with menstrual related symptoms[15–17] and due to the broad spectrum of symptoms and potential mechanisms, symptom relief is a main challenge and effective treatments are limited[18].

Hormonal contraceptives (HC) are frequently used to manage symptoms caused by fluctuating reproductive hormones[19]. HC are exogenous steroid hormones that inhibit ovulation and result in consistent low endogenous sex hormones[20,21]. Suppression of ovarian hormone secretion has markedly attenuated menstrual related symptoms[22]. HC inhibit hypothalamic gonadotrophin releasing hormone which prevents pituitary secretion of follicle stimulating hormone and luteinising hormone. Contraceptives provide pharmacological control of the reproductive cycle by consistently promoting a negative feedback loop to prevent endogenous oestrogen or progesterone release[23]. As synthetic hormones, their actions differ from endogenous hormones, the differences in mechanisms of which extend beyond the reproductive system and contradict responses and actions of other bodily systems such as cardiovascular and metabolic systems[23], including but not limited to oxidative stress and inflammatory response[24]. Therefore, although HC may manage menstrual related symptoms, individuals have been hesitant to use this approach due to the synthetic hormones associated and unknown effects on other systems beyond the reproductive system, or frequently experiencing side effects of the synthetic hormones – commonly mistaken for menstrual related symptoms.

Following a healthy diet and managing stress have been reported as important factors in naturally preventing and managing menstrual related symptoms, specifically fresh, unprocessed foods, avoiding foods rich in refined carbohydrates or fats, salt, alcohol and simulating beverages has been reported[25]. Whilst other research has found no correlation between macronutrients and menstrual related symptoms[26], reports of micronutrients, such as zinc, to provide anti-inflammatory and neurotrophic factors have been stated[18]. Further dietary interventions could ameliorate inflammation[27] such as fruits, vegetables and food legumes which contain high levels of phytochemicals that show anti-inflammatory effects[28], whilst several other nutraceuticals have been investigated that may reduce menstrual related symptoms, these include vitamin D, vitamin C and curcumin[27].

Currently there is no treatment universally recognised to prevent or manage menstrual-related symptoms. Given the ease of implementation of non-pharmaceutical strategies to manage menstrual symptoms[29], and potential solution it offers to prevent symptoms disrupting daily life, nutritional interventions may provide a viable option. However, to the authors knowledge, no review exits that provides practical recommendations and guidance to practitioners or individuals on food, nutrition or supplements for the purpose of menstrual cycle symptom management[30].

Based on the above reasoning, the aim was to systematically review all studies investigating changes in menstrual-related symptoms in eumenorrhoeic women using foods or supplements as interventions for management.

Methods

This review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines[31].

Study inclusion and exclusion criteria

Considerations of Population, Intervention, Outcomes and Study design were used to determine the parameters within which the review was conducted[32]:

Population. Participants included healthy women who were (a) naturally menstruating (menstrual cycle length >21 d and <35 d resulting in nine or more consecutive periods in a year;[33] (b) not using HC, (c) free from menstrual-related dysfunctions (such as amenorrhoea, endometriosis, polycystic ovarian syndrome) or any other condition that could affect menstrual function (e.g. pregnancy, eating disorder or disordered eating), (d) not overweight or obese, and (e) not using hormone treatment/therapy.

Individuals using HC were excluded from this review due to differences in mechanisms and action of synthetic hormones that extend beyond the reproductive system[18]. The cause of symptoms and therefore management related to a natural menstrual cycle is different to side effects that may be experienced using HC. In the instance side effects of HC are experienced, a different type or brand of HC is prescribed due to the cause being related to the synthetic hormone being ingested/released.

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Intervention. The selected studies had to include one or more food, diet, supplement or nutritional intervention, without being focussed on weight loss or changes in energy intake. Each intervention was required to be completed for at least one menstrual cycle.

Outcome. The primary outcome was menstrual-related symptoms. For the purpose of this review, menstrual symptoms included any symptoms on the pre-menstrual syndrome scale (PMSS) or dysmenorrhoea (abdominal/pelvic/lower back pain).

Study design. Experimental studies were considered for analysis if they met the following criteria to ensure sensitivity and robustness of results: (a) published in full in a peer-reviewed journal, (b) had primary or secondary objectives of assessing changes in menstrual-related symptoms due to food, diet, supplement or nutritional intervention, (c) interventions included groups that did not combine the use of pharmaceutical medication with the nutritional intervention, (d) non-steroidal anti-inflammatories were not used unless a statement of control was provided, and (e) Cochrane risk-of-bias 2 categorised as low risk or some concern. Single case studies, review articles, study protocol papers and conference abstracts were excluded. Only full texts that were published in English or had existing translation were examined. There was no limit on the date of publication; the studies returned range in publication date between 1953 and 2020 and within the final review between 1985 and 2020, the last search was conducted 11 February 2021.

Search strategy for identification of studies

A systematic electronic literature search was conducted by N.B. to identify relevant articles using two online databases (PubMed, ScienceDirect). The searches were performed using the following search terms ('Diet', OR 'Supplement', OR 'nutrition', OR 'food', OR 'nutraceuticals', OR 'dietary patterns', OR 'micronutrients', OR 'carbohydrate', OR 'protein', OR 'fat', OR 'alternative medicine', OR 'herbal medicine') AND ('menstrual cycle symptoms', OR 'premenstrual symptoms', OR 'premenstrual syndrome', OR 'dysmenorrhea'). The reference lists of obtained relevant articles and review articles were hand-searched to identify any further studies and were added manually.

Data selection

Selection of studies. Two reviewers (N.B., D.M.) independently reviewed the titles, abstracts and access to full text paper of the identified articles for inclusion and any duplicates or review articles were removed. Three reviewers (N.B., R.F., L.F.) independently reviewed the full texts against the inclusion and exclusion criteria and any conflicts between the reviewers were resolved in meetings.

Extraction of data. Initial data extraction was conducted by one reviewer (N.B.) and verified independently by another member of the review team (R.F.). Once compiled into a preliminary table, other members of the research team (G.B., M.W., D.M.) confirmed data inclusion in the final analysis and presentation of results.

Study quality assessment. Study quality was assessed by two reviewers (N.B., R.F.) using Cochrane risk-of-bias 2 tool for randomised trials[34]. This process ensured studies were randomised controlled trials with the purpose of assessing the effect of assignment to the intervention (intention-to-treat effect). Studies were assessed for randomisation, risk of bias due to deviations from the intended interventions, missing outcome data, measurement of the outcome and selection of the reported result. All domains required the studies follow a pre-determined algorithm for suggested judgement of risk of bias, categorising studies as low risk, some concern or high risk. An overall risk of bias judgement was provided and only those studies classified as low risk or some concern were considered. Studies judged to be of some concern were due to the research team of the study in question not being blinded from the intervention, but where due control was detailed and deemed by the reviewers to not affect the outcome results. This risk-of-bias 2 process addressed studies with missing data, only one author was contacted due to missing number of participants in each trial arm. As this data was not available, the study was excluded at this stage. The remaining studies were screened by two reviewers (N.B., R.F.) to ensure participants met the inclusion criteria outlined in the study. In addition, sample size was assessed for power (R.F.) to ensure quality and consistency of studies included for data extraction, a minimum sample size of 20 for each arm (experimental, control, placebo) was applied.

Data synthesis

Studies were grouped on the basis of food/supplement intervention and dosage compared with UK DRV and upper limits for safety of supplementation[35,36]. Data were also extracted to tabulate measurement of pre-menstrual symptom or dysmenorrhoea to allow comparison between interventions whilst informing the quantity of studies investigating each of these menstrual-related symptoms.

Meta-analysis of effect estimates and extensions were not possible due to the small number of studies for each intervention type, leading to limited evidence due to the infancy of robust studies in the research area. Extracted studies also suffered from different interventions and effect measures investigated[37]. Effect sizes could not be summarised as this data was not available.

Heterogeneity arises in systematic reviews due to a variety of factors pertaining to the participants, methodologies, intervention exposure and outcomes. This review included several different interventions (nutrition, food products, supplements) in the treatment of PMS and dysmenorrhoea measured using different outcome measures, indeed the only clinical heterogeneity was that all participants were female, were naturally menstruating and were not taking any form of HC.

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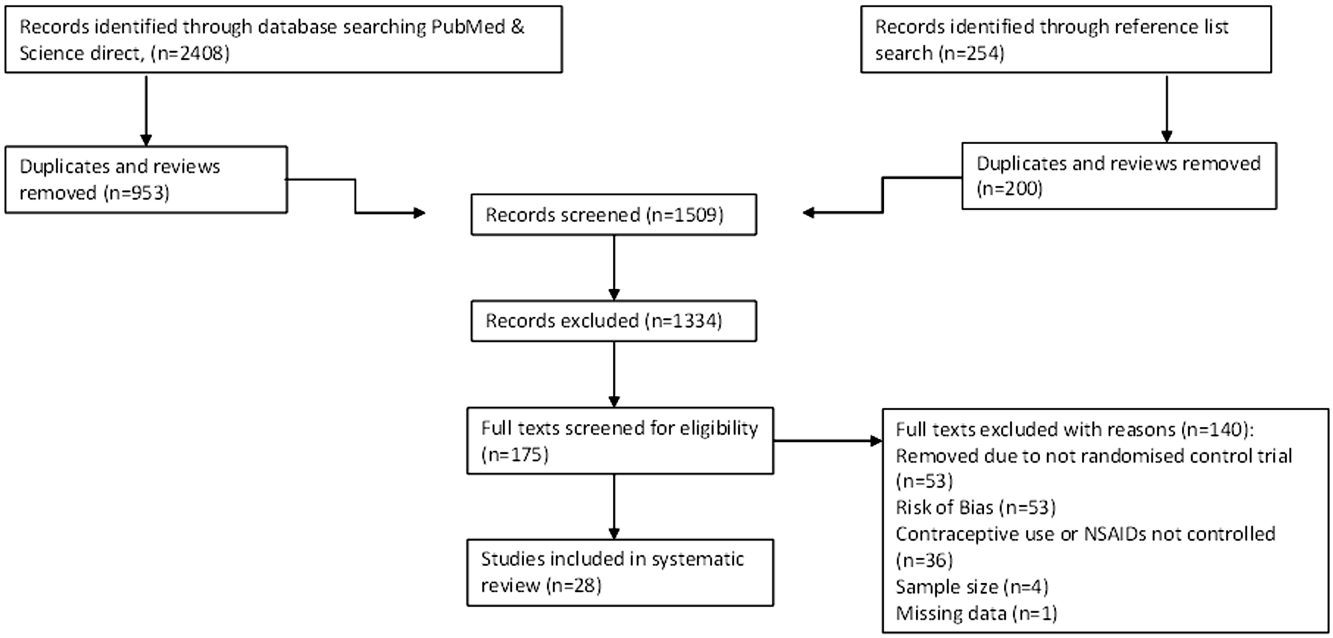

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines flow chart for literature search and study selection

Results

Study selection and characteristics

The literature search and selection of studies are presented in Fig. 1. In total, twenty-eight studies with a total of 2621 participants were included in the review. Details of the included nutritional interventions are shown in Table 1 and individual studies are shown in Table 2.

Risk of bias

A proportion of twenty-six of the studies (93%) were classified as low risk. Where assessment resulted in some concerns for the studies included in this review, this was due to assessors knowing the intervention received by the study participants, as it was not possible to blind from the intervention (e.g. increasing whole grains in the diet). These papers were not excluded as precautions were stated which resulted in the review authors concluding the assessment of the outcome was not influenced by knowledge of the intervention received[52].

All studies were reviewed in accordance with Consolidated Standards of Reporting Trials for randomisation and concealment. Despite all studies stating randomisation with evidence provided within methodological figures, only twenty-one (75%) studies provided details of the method of randomisation[38,39,41–43,45,46,51,54–57,59,60,62–65,67–69]. A total of sixteen studies (57%) provided clear details on randomisation implementation reporting either external, manufacturer or principal investigator not involved in treatment. All except one study[52] stated both participants and experimenters were blinded and matched for method of administration. A total of five studies did not state, or it was unclear, if the intervention and control were matched on appearance[49,52,54,60,65], in ten studies it was unclear if groups were matched for taste[38,41,49,52,54,59,60,65,67,68] and twelve studies lacked clarity on matching based on smell[38,41,44,46,49,52,54,57,60,65,67,68].

Results of individual studies

Table 2 presents a summary of results for each study. The studies have been grouped and displayed based on similarities in type of food or supplement intervention.

Results of synthesis

A total of twenty-one food or supplement interventions, including individual and combined supplements were identified in the analysis of studies as interventions for management of menstrual-related symptoms (Table 1). Overall, fourteen studies investigated the effect of a food or supplement intervention on general pre-menstrual symptoms (ten positive results, four no significant effect) and fourteen studies (thirteen positive results, one with no significant effect) investigated use specifically for dysmenorrhoea. The results were variable between interventions, despite some consistencies in the prescribed type of food/supplement. This variability could be attributed to differences in dose, length of intervention, participant characteristics (e.g. deficiency in vitamin under study, age, age at menarche, Table 3) and methodological variation in determination of symptoms. In the latter case there were few consistencies in determination of pre-menstrual symptoms and dysmenorrhoea (Table 4). A total of eighteen different ways of measuring pre-menstrual symptoms were described across the studies and seven different methods to determine dysmenorrhoea pain were extracted from the twenty-eight studies. This prevented any further comparisons between the studies.

Of the twenty-eight studies reviewed, two were crossover study design, whereas twenty-six were parallel controlled trials. None reported a negative effect on symptoms nor investigated

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Table 1. Supplement/foods included within the reviewed studies, including associated dietary reference/safe upper limit in the UK

Supplement/food and references	Category	Dietary reference value for females	Safe upper limit	Dosage from extracted studies
Vitamin D (Abdollahi *et al.*, 2019[38]; Moini *et al.*, 2016[39])	Vitamin/mineral supplement.	RNI 10 μg/d (400 IU/d) of vitamin D, for everyone aged 4 years and above, throughout the year[40].	Upper limit of 100 μg/d (4000 IU/d) for adults set by EFSA[40], except for those at risk of hypercalcaemia. Doses of 7500 μg (300 000 IU) at intervals of 3 months or longer would not be expected to cause adverse effects in adults[40].	50 μg (2000 IU) vitamin D tablet, every other day for 12 weeks. 50000 IU (1250 ug) oral vitamin D, one per week after food for 8 weeks.
Vitamin D and calcium combined (Khajehei *et al.* 2010[41]; Zarei *et al.*, 2016[42])	Vitamin/mineral supplement	RNI 10 μg/d (400 IU/d) of vitamin D, for everyone aged 4 years and above, throughout the year[40].	Upper limit of 100 μg/d (4000 IU/d) vitamin D for adults, except for those at risk of hypercalcaemia. Doses of 7500 μg (300 000 IU) at intervals of 3 months or longer would not be expected to cause adverse effects in adults[40].	500 mg of calcium plus 200 mg (200 000 ug) vitamin D twice daily from 15th to 24th day of menstrual cycle for two consecutive cycles.
		Calcium RNI 800 mg/d for age 11–14 years or 700 mg for 19 years and above[35].	Insufficient data from studies to establish a safe upper level for calcium. Doses of 1500 mg/d are likely to be safe[36].	One tablet per day of 1000 mg calcium and 5000 IU vitamin D3, or one tablet/day 1000 mg calcium only. Taken from 15th day of menstrual cycle until disappearance of menstrual pain in the following cycle.
Calcium and magnesium (Charandabi *et al.*, 2017[43])	Vitamin/mineral supplement	Calcium RNI 800 mg/d for age 11–14 years or 700 mg for 19 years and above[35].	Insufficient data from studies to establish a safe upper level for calcium. Doses of 1500 mg/d are likely to be safe[36].	600 mg/d calcium and 300 mg/d magnesium sterate or 600 mg/d calcium only. Taken on 15th day of cycle until no pain in the following cycle. Intervention: two menstrual cycles.
		Magnesium 280 mg/d for 11–14 year olds, 300 mg/d for 15–18 year olds or 270 mg/d for 19 years and above[35].	Insufficient data to establish a safe upper level for magnesium. 400 mg/d supplementation seems well tolerated[36].	
Vitamin B6 (Hagen *et al.*, 1985)[44]	Vitamin/mineral supplement	1·2 mg/d for age 15 years and above or 1 mg/d for 7–14 year olds[35].	Doses of 200 mg/day vitamin B6 or more taken for long periods are associated with reports of neuropathy in some human subjects[36].	Total 100 mg/d vitamin B6 (one tablet taken twice daily). Intervention: two menstrual cycles.
Zinc (Jafari *et al.*, 2019[45]; Zekavat *et al.*, 2015[46])	Vitamin/mineral supplement	7 mg/d for age 15 years and above or 9 mg/d for 11–14 year olds[35].	50 mg/d for adults[36].	30 mg/d zinc gluconate for 12 weeks. 50 mg/d zinc sulphate beginning on first day of menses and continuing 3 d prior to end of menses. Intervention: three menstrual cycles.
Omega-3 (Sohrabi *et al.*, 2013[47])	Lipid supplement	(Cis) Omega-3 fatty acids should provide a minimum of 0·2% of total energy in the diet[35].	Daily supplemental intakes of 5 g of long-chain omega-3 fatty acids raise no safety concerns for adults[48].	2 g/d as 2 × 1g soft gels. Intervention for 3 months.
Alpha lipoic acid (ALA or Thioctic acid) (Yousefi *et al.*, 2019[49])	Lipid supplement	None	Upper limit of safe intake of alpha-lipoic acid of 0·6 mg/kg body weight per day, indicating a maximum daily dose of 42 mg alpha-lipoic acid for a person weighing 70 kg[50].	600 mg/d for 5 d (2 d before menses and 3 d after) for one cycle.
Phosphatidylserine and phosphatidic acid complex (PAS) (Schmidt *et al.*, 2018[51])	Lipid supplement	None	None, but authors advise caution in those with a soya allergy from which it is often derived.	Total of 400 mg/d PS and 400 g/d PAS – prescribed as three capsules daily for three menstrual cycles.
Whole grains (Esmaeilpour *et al.*, 2019[52])	Foodstuff	Dietary fibre 30 g/d for adults, 25 g/d for children aged 11–16 years of which whole grains could supply a variable amount[53].	Intakes of total fibre greater than 43 g/d are not believed to be beneficial[53].	Replace at least four servings of daily refined grain consumption with whole grains daily for three cycles. Also list of whole-grain food items. Given 840 g of whole bread each week to replace refined bread.
Wheat germ extract (Atallahi *et al.*, 2014[54])	Plant extract	None	None	
Curcumin (Fanaei *et al.*, 2014[55]; Khayat *et al.*, 2015[56])	Plant extract	None	None	

Table 1. (*Continued*)

Supplement/food and references	Category	Dietary reference value for females	Safe upper limit	Dosage from extracted studies
Ginger (Kashefi *et al.*, 2014[57])	Plant extract	None	None	
Cinnamon (Jahangirifar *et al.*, 2018[58])	Plant extract	None	None	
Fenugreek seed (Younesy *et al.*, 2014[59])	Plant extract	None	None	
C. Sativus (saffron) (Agha-Hosseini *et al.*, 2008[60])	Plant extract	None	None. Supplement contained magnesium stearate. Insufficient data to establish a safe upper level for magnesium. 400 mg/d supplementation seems well tolerated[36].	
Hypericum perforatum (St John's wort) (Hicks *et al.*, 2004[61]; Canning *et al.*, 2010[62])	Plant extract	None	None	
Psidii guajavee folium (guava leaves) (Doubova *et al.*, 2007[63])	Plant extract	None	None	
Chlorella (Haidari *et al.*, 2018[64])	Plant extract	None	None	
Vitex Agnus Castus (chaste-berry) (Turner *et al.*, 1993[65]; He *et al.*, 2009[66])	Plant extract	None	None	
Achillea millefolium (yarrow) (Jenabi *et al.*, 2015[67])	Plant extract	None	None	
Salix (willow) (Raisi Dehkordi *et al.*, 2019[68])	Plant extract	None	None	
Prasaplai (Thai herbal remedy) (Vannabhum *et al.*, 2016[69])	Plant extract	None	None	

µg/d, microgram per day; IU/d, International Units per day; RNI, Reference Nutrient Intake; EFSA, European Food Safety Authority; PS, Phosphatidylserine.

Table 2. Summary of reviewed studies

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Vitamin D and calcium								
Khajehei (2010)[41]	A comparison between the efficacy of dydrogesterone and calcium plus vitamin D in improving women's general health.	151 undergraduate medical students, eumenorrhoeic, not taking vitamins.	5 mg dydrogesterone tablet, 500 mg of calcium plus 200 mg vitamin D 2× daily from 15th to 24th day of their menstrual cycle for two consecutive cycles.	Placebo tablet twice daily from 15th to 24th day of their menstrual cycle for two consecutive cycles.	Not stated.	General health scores in dydrogesterone 19·6 (SD 3·97) B versus 4·33 (SD 2·69) PI; Calcium + vit D 18·93 (SD 4·73) B versus 6·2 (SD 3·55) PI; placebo 19·41 (SD 3·37) B versus 14·39 (SD 3·45) PI. Both interventions more effective than placebo ($p < 0·05$).	Both dydrogesterone, and calcium and vitamin D were more effective than placebo to reduce menstrual related symptoms; dydrogesterone was more efficient than calcium plus vitamin D.	Positive
Moini (2016)[39]	The effect of vitamin D on primary dysmenorrhoea with vitamin D deficiency.	50 women, 18–30 years, four painful menstrual cycles in 6 months, low vitamin D concentration (<30 ng/ml). Primary dysmenorrhoea, vitamin D deficient 2013–2014.	50 000 IU oral vitamin D, 1× week after food for 8 weeks.	Placebo 1× per week for 8 weeks.	Not stated.	Pain severity decreased in treatment group ($p < 0·001$).	A weekly high dose of vitamin D for 8 weeks in patients with primary dysmenorrhoea and vitamin D deficient could improve pain intensity.	Positive
Zarei (2016)[42]	Effects of calcium vitamin D and calcium alone on pain intensity and menstrual blood loss in women with primary dysmenorrhoea.	84 medical students, 18–32 years, eumenorrhoeic, maximum pain intensity between 5 and 9·1 according to VAS with primary dysmenorrhoea pain features.	One tablet per day of 1000 mg calcium + 5000 IU vitamin D3; or one tablet/day 1000 mg calcium only. Taken from 15th day of menstrual cycle until disappearance of menstrual pain in the following cycle.	One tablet daily placebo – lactose and starch.	Yes	Pain intensity significantly reduced with calcium + vitamin D 6·2 (SD 1·6) B versus 4·6 (SD 2·6) PI; calcium only 6·3 (SD 1·8) B versus 3·6 (SD 2·2) PI. Placebo no difference 5·8 (SD 1·5) B versus 5·7 (SD 1·7) PI. Calcium only versus placebo $p = 0·001$.	Intake of calcium alone was effective in reducing menstrual pain intensity.	Positive
Abdollahi (2019)[38]	The effect of vitamin D supplement consumption on pre-menstrual syndrome in vitamin D deficient young girls.	130 university students suffering from PMS, age 18–30 years, serum-(OH)-D <20 ng/ml, eumenorrhoeic, not taking vitamin D.	2000 IU vitamin D tablets, every other day 12 weeks.	Tablet – maltodextrin and had a similar appearance to the vitamin D tablet.	Yes	No difference of fourteen symptoms after 12 weeks ($p > 0·05$).	2000 IU vitamin D in vitamin D-deficient young girls with PMS had no impact on PMS symptoms.	No effect

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Charanadabi (2017)[43]	Calcium with and without magnesium for primary dysmenorrhoea.	61 students, eumenorrhoeic, moderate to severe primary dysmenorrhoea.	600 mg calcium carbonate and 300 mg magnesium stearate or 600 mg calcium carbonate from 15th day of cycle until no pain on the following cycle. One pill daily. Intervention: two menstrual cycles	Placebo	Not stated	Pain intensity calcium + magnesium 6·0 (SD 2·3) B versus 3·91 (SD 2·1) PI; calcium only 5·2 (SD 2·0 B versus 4·2 (SD 2·0) PI ($p < 0·001$). Placebo no difference 5·4 (SD 2·2) B versus 5·3 (SD 3·3) PI. Calcium + magnesium versus placebo −1·9 (− 2·2 to −1·7) ($p < 0·001$); calcium only versus placebo −0·9 (−1·2 to −0·6) ($p < 0·001$); calcium + magnesium versus calcium only −1·1 (−1·4 to −0·8) ($p < 0·001$).	Both combined calcium plus magnesium and calcium alone groups had better outcomes than placebo groups in pain intensity. Calcium plus magnesium had significantly better pain relief.	Positive
Crocus sativus (saffron)								
Agha-Hosseini (2008)[60]	*Crocus sativus L* (saffron) in the treatment of premenstrual syndrome.	47 women aged 20–45 years, eumenorrhoeic, experiencing PMS for at least 6 months.	Capsule *C. Sativus* 30 mg/d (15 mg twice a day) for two menstrual cycles.	Placebo capsule (twice a day) for two menstrual cycles.	Not stated	19 (76%) responders ($p < 0·0001$) in intervention and 2 (8%) in placebo. Significant effect of saffron on total daily symptom rating ($p < 0·0001$). Difference between two protocols was significant at the endpoint ($t = 5·92$, df = 48, $p < 0·001$).	Saffron was effective in relieving symptoms of PMS. Decrease observed in efficacy of saffron in cycles three and four in total premenstrual daily symptoms	Positive
Wheat germ								
Atallahi (2014)[54]	Effects of wheat germ extract on the severity and systematic symptoms of primary dysmenorrhoea.	80 women, 20–45 years old, BMI 19·8–26 kg/m^2, no smoking, eumenorrhoeic.	Three capsules of 400 mg wheat germ extract daily, from 16th day to 5th day of next menstrual cycle for 2 months.	Three capsules placebo daily.	Not stated	Reduction in pain severity in wheat germ group ($p < 0·001$). 4·791(1·916–6·666) B versus 0·606 (0–1·553) PI. Placebo 4·999 (1·666–6·874) versus 3·610 (0–0·666) ($p = 0·203$).	Pain severity decreased only in the wheat germ extract group ($p < 0·001$) and no statistically significant change in the placebo group.	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
St John's wort								
Canning (2010)[62]	The efficacy of *Hypericum perforatum* (St John's wort) for the treatment of pre-menstrual syndrome.	32 women, 18–45 years old, eumenorrhoeic, suffering from PMS.	*Hypericum perforatum* 900 mg/d for two menstrual cycles (75 tablets per box – 2 boxes).	Placebo tablets for two menstrual cycles.	Not stated	Total symptoms 5·8 reported versus 6·58 placebo. Significant main effect of treatment ($F(1·30) = 4·82$; $p = 0·04$; partial $\eta^2 = 0·14$).	*Hypericum perforatum*, statistically superior to placebo in improving physical and behavioural symptoms of PMS. No effect for mood and pain-related PMS.	Positive
Hicks (2004)[61]	The significance of non-significance in randomised controlled studies: a discussion inspired by a double-blinded study on St John's wort for pre-menstrual symptoms.	125 women, symptoms 30% more severe the week preceding menstruation than week after.	Two tablets of St John's wort (each containing 300 mg; 600 mg total), two cycles.	Two tablets daily containing lactose and cellulose.	Not stated	Both treatment and placebo groups significantly lowered PMS scores in cycles two and three compared with B ($p < 0·001$). No significant difference between groups ($p > 0·66$). St John's wort 326 (SD 198·33) B versus 230·28 (SD 172·57) PI; placebo 317·02 (SD 204·49) B versus 221·12 ± 174·03 PI.	Trend for St John's wort to be superior to a placebo but not significantly different.	No effect
Psidii guajavae								
Doubova (2007)[63]	Effect of *Psidii guajavae folium* extract in the treatment of primary dysmenorrhoea.	197 female students, 17–25 years, eumenorrhoeic.	*Psidii guajavae folium* group 1 – one capsule 3 mg/d, group 2 – two capsules 6 mg/d, group 3 – one capsule placebo per day (300 mg/d starch), group 4 – one 400 mg capsule ibruprofen. All 5 d, start 24 h before menstruation. Complete for three cycles	Placebo and ibuprofen.	Yes	Menstrual pain intensity phyto-drug 3 mg/d 5·37 (SD 2·12) B versus 3·39 (SD 2·18) PI; phyto-drug 6 mg/d 5·59 (SD 2·28) B versus 4·31 (SD 2·5) PI; placebo 4·75 (SD 1·91 B) versus 3·18 (SD 2·08) PI; ibuprofen 4·83 (SD 2·43) B versus 3·22 (SD 2·05) PI. Phyto-drug 6 mg/d $p < 0·001$ versus placebo and ibuprofen.	At a dose of 6 mg/d *Psidii guajavae folium* extract reduced menstrual pain significantly compared with placebo.	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Whole grains								
Esmaeilpour (2019)[52]	Diets enriched with whole grains reduce pre-menstrual syndrome scores in nurses.	76 female nurses, 18–45 years old, eumenorrhoeic.	Replace at least four servings of daily refined grain consumption with whole grains daily for three menstrual cycles. Also list of whole-grain food items including whole-wheat bread, brown rice, brown spaghetti, homemade cakes and cookies using whole wheat. Given 840 g of whole bread each week to replace refined bread.	Continued regular daily consumption of grains.	Yes	General pre-menstrual scores significantly reduced $p < 0{\cdot}001$.	Daily consumption of whole grains in place of refined grains can contribute to improvement in PMS symptoms.	Positive
Curcumin								
Fanaei (2016)[55]	Effect of curcumin on serum brain-derived neurotrophic factor levels in women with pre-menstrual syndrome.	63 female students, eumenorrhoeic.	Curcumin three menstrual cycles, 10 d in each – two capsules daily for 7 d before menstruation and 3 d after menstruation. 100 mg/12 h.	Three menstrual cycles, 10 d in each – two capsules daily for 7 d before menstruation and 3 d after menstruation. 100 mg/12 h.	Not stated	Total severity of PMS significantly reduced with curcumin after 2 months ($p < 0{\cdot}001$). Curcumin 102·1 (SD 40·1) B versus 44·61 (SD 26·4) PI; placebo 106·06 (SD 40·1) B versus 94·66 (SD 51·3) PI.	Curcumin BDNF levels were significantly higher and mean scores of PMS were significantly lower.	Positive
Vitamin B6								
Hagen (1985)[44]	No effect of vitamin B6 against pre-menstrual tension.	34 women, eumenorrhoeic, suffering from PMS.	Vitamin B6 one tablet taken twice daily. 100 mg/d, two menstrual cycles.	Placebo tablets for two menstrual cycles, one tablet taken twice daily.	Yes	Median score VAS 6·6 cm, after treatments 5·8 cm (range 1·0–10·0). Median relative improvement 4·2% (range 90·0–82·0).	Vitamin B6 no better than placebo.	No effect
Khayat (2015)[56]	Curcumin attenuates severity of pre-menstrual syndrome symptoms.	63 female students, eumenorrhoeic, at least 5 symptoms diagnosed as PMS.	Curcumin, two capsules curcumin powder daily (100 mg/12 h) for 7 d before menstruation and for 3 d after menstruation. Three cycles.	Brown sugar capsules. daily (100 mg/12 h) for 7 d before menstruation and for 3 d after menstruation. Three cycles.	Not stated	Total severity of PMS score curcumin 102·06 (SD 39·64) baseline versus 42·47 (SD 16·37) post-intervention; placebo 106·06 (SD 44·12) versus 91·60 (SD 43·56) ($p < 0{\cdot}001$). Difference between mean changes was significantly (mean difference 45·14, 95% CI: 6·10–14·98).	Curcumin reduced severity of PMS symptoms in students.	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Chlorella								
Haidari (2018)[64]	Effect of *Chlorella* supplementation on systematic symptoms and serum levels of prostaglandins, inflammatory and oxidative markers in women with primary dysmenorrhoea.	44 women, 18–35 years, eumenorrhoeic, moderate to severe dysmenorrhoea.	1500 mg/d of *Chlorella* as five soft gel. 8 weeks.	Soft-gel placebo.	Not stated	*Chlorella* significantly reduced the severity of menstrual pain ($p = 0{\cdot}001$). *Chlorella* 7·45 (SD 1·50) B versus 4·22 (SD 2·22) PI ($p < 0{\cdot}001$); placebo 7·15 (SD 1·80) B versus 6·78 (SD 2·34) PI ($p = 0{\cdot}202$).	*Chlorella* supplementation could decrease the severity of pain and systemic symptoms in women with primary dysmenorrhoea	Positive
Vitus agnus-castus								
He (2009)[66]	Treatment for pre-menstrual syndrome with *Vitus agnus-castus*.	202 healthy Chinese women, 18–45 years old, eumenorrhoeic, suffering from PMS.	*Vitus agnus-castus* Administered orally once daily for three menstrual cycles as a tablet.	Tablet – once daily for three menstrual cycles.	Not stated	After treatment for three menstrual cycles, PMS scores were significantly lower between the two groups ($p < 0{\cdot}001$). *Vitus* 29·13 (SD 7·88) B versus 6·41 (SD 7·94) PI; placebo 28·14 (SD 7·59) B versus 12·64 (10·35) PI.	*Vitus agnus-castus* is a safe, well-tolerated and effective drug for treatment of Chinese women with moderate to severe PMS	Positive
Turner (1993)[65]	A double-blind clinical trial on a herbal remedy for pre-menstrual syndrome.	217 women, 18–46 years, suffering from PMS	*Vitex agnus-castus*, dose not stated.	Placebo	Not stated	No statistical significance.	No difference between groups on symptoms, *Vitus agnus-castus* not effective compared with placebo.	No effect
Zinc								
Jafari (2020)[45]	Effect of zinc supplementation on physical and psychological symptoms, biomarkers of inflammation, oxidative stress and brain-derived neurotropic factor in young women with pre-menstrual syndrome.	57 female medical students, 18–30 years old, BMI 18·5–24·9, eumenorrhoeic.	30 mg zinc gluconate for 12 weeks.	Placebo for 12 weeks.	Yes	Physical symptoms of PMS were significantly decreased by zinc; 0·66 (SD 0·62) B versus 0·32 (SD 0·29) PI ($p = 0{\cdot}006$). Placebo no change 0·47 (SD 0·31) B versus 0·45 (SD 0·3) PI ($p = 0{\cdot}20$). Psychological symptoms of PMS were significantly decreased by zinc; 0·62 (SD 0·43) B versus 0·31 (SD 0·36) PI ($p < 0{\cdot}001$). Placebo: no change 0·47 (SD 0·29) B versus 0·48 (SD 0·4) PI ($p = 0{\cdot}77$).	Beneficial effects of 12 weeks zinc supplementation on physical and psychological symptoms of pre-menstrual syndrome, total antioxidant capacity and brain-derived neurotrophic factor	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Zekavat (2015)[46]	A randomised controlled trial of oral zinc sulphate for primary dysmenorrhoea in adolescent females.	120 females, 14–18 years old, eumenorrhoeic, history of primary dysmenorrhoea.	Capsule containing 50 mg/d zinc sulphate beginning on first day of menses and continuing 3 d prior to end of menses for three menstrual cycles.	Placebo beginning on first day of menses and continuing for 3 d prior to end of menses.	Not stated	Pain severity reduced with zinc; 7·3 (SD 2·43) baseline versus 4·23 (SD 1·69) post-intervention. No change in placebo 7·23 (SD 1·44) baseline versus 6·58 (SD 1·60) post-intervention. $p < 0·001$.	Both pain duration and pain severity were decreased by taking zinc.	Positive
Kashefi (2014)[57]	Comparison of the effect of ginger and zinc sulphate on primary dysmenorrhoea.	140 students, 15–18 years, eumenorrhoeic, primary dysmenorrhoea.	250 mg ginger powder capsules. 220 mg zinc sulphate capsules. Capsules taken three times a day for 4 d, starting the day before commencement of menstruation to third day of bleeding. Two cycles.	Placebo lactose capsules. Capsules taken three times a day for 4 d, starting the day before commencement of menstruation to third day of bleeding. Two cycles.	Not stated	Severity of pain was significantly different between interventions and placebo ($p < 0·001$). Ginger 7·97 (SD 1·4) baseline versus 3·08 (SD 1·52) post-intervention; zinc 8·01 (SD 1·12) baseline versus 3·12 (SD 1·2) post-intervention; placebo 7·76 (SD 1·3) baseline versus 6·95 (SD 1·67) post - intervention.	Ginger and zinc sulfate positive effect on improving primary dysmenorrhea pain	Positive
Cinnamon								
Jahangirifar (2018)[58]	The effect of cinnamon on primary dysmenorrhoea.	58 women, mean age 22·2 (SD 2·2) years, eumenorrhoeic.	Capsules containing 1000 mg cinnamon 3× a day for first 72 h of menstruation for two menstrual cycles.	Capsule placebo contained 1000 mg starch three times a day for first 72 h of menstruation for two menstrual cycles.	Not stated	Mean intensity of dysmenorrhoea pain was significantly different between cinnamon and placebo ($p = 0·002$). Cinnamon 5·7 (SD 1·7) B versus 3·2 (SD 2·4) PI ($p < 0·001$); placebo 5·8 (SD 1·4) B versus 5·9 (SD 2·1) PI.	Cinnamon can reduce the intensity of primary dysmenorrhoea.	Positive
Achillea millefolium								
Jenabi (2015)[67]	The effect of *Achillea millefolium* on relief of primary dysmenorrhoea.	91 female students, 19–23 years, eumenorrhoeic, with primary dysmenorrhoea.	*Achillea millefolium* (4 g in tea bag). First 3 d over two menstrual cycles. Tea was prepared by pouring of boiling water on the tea bag with *Achillea millefolium* powders and keeping for 10 min. Three teacups in morning, noon and night with each meal (teabag in 300 ml hot water).	Placebo teabags (starch).	Not stated	Mean change in pain score in the *Achillea millefolium* group was significantly greater than that in the placebo group at 1 month ($p = 0·001$) and 2 months ($p < 0·0001$) after treatment.	*Achillea millefolium* is effective in minimising the pain severity in primary dysmenorrhoea.	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Salix								
Raisi Dehkordi (2019)[68]	A double-blind controlled crossover study to investigate the efficacy of *Salix* extract on primary dysmenorrhea.	96 female students, 18–28 years old, eumenorrhoeic, with primary dysmenorrhoea.	*Salix* 200 mg capsules – three capsules daily. One of the *Salix* capsules in each pack was a placebo. Salicine 240 mg for daily use. Administered 1 h after onset of dysmenorrhoea. Continue medication only while dysmenorrhoea and symptoms present. One menstrual cycle.	Mefenamic acid 250 mg, three capsules daily. One menstrual cycle.	Not stated	77·39 (SD 16·18)% of *Salix* group showed no symptoms followed by 22·18 (SD 14·08)% experienced mild symptoms. Mefenamic group 44·58 (SD 20·16)% had mild symptoms and 28·12 (SD 15·29)% had moderate symptoms.	*Salix* extract significantly decreased dysmenorrhoea in comparison with mefenamic acid.	Positive
Phosphatidic acid complex (PAS)								
Schmidt (2018)[51]	A lecithin phosphatidylserine (PS) and PAS reduces symptoms of pre-menstrual syndrome.	40 women, 18–45 years old, eumenorrhoeic, who suffer from PMS.	400 mg PS and 400 mg PAS per day, three capsules daily for three menstrual cycles.	Placebo maize starch capsule, three capsules daily for three menstrual cycles.	Yes	Reduction in symptom severity was significantly larger in PAS group ($p = 0·001$).	Beneficial effects of PAS over three cycles on symptom levels.	Positive
Omega 3								
Sohrabi (2013)[47]	Evaluation of the effect of omega-3 fatty acids in the treatment of premenstrual syndrome.	124 women, 20–45 years old, eumenorrhoeic, BMI 19–26, who suffer from PMS.	2 g omega 3 – once daily single dose of two 1 g soft gels for 3 consecutive months.	Two placebo soft gels once daily for 3 consecutive months.	Not stated	Reduction in use of sedatives after 90 d in Omega-3 group (25%) versus placebo group (73·3%) $p = 0·001$. Severity of symptoms after 90 d lower in omega-3 group for depression (0·95; SD 0·73 versus 3·43; SD 0·65), anxiety (0·79; SD 1·04 versus 3·89; SD 0·91), concentration (1·48; SD 1·26 versus 5·63; SD 1·32), bloating (0·74; SD 0·15 versus 2·41; SD 0·19) and nervousness (2·15; SD 0·93 versus 6·09 ± 0·86).	Omega-3 fatty acids may reduce psychiatric symptoms of PMS including depression, nervousness, anxiety, lack of concentration and may reduce bloating, headache and breast tenderness. Longer duration of treatments increased effectiveness.	Positive

Table 2. (*Continued*)

First author and date	Title	Sample details	Intervention and dose	Control	Adherence to intervention	Results	Overall outcome	Effect
Fenugreek								
Younesy (2014)[59]	Effects of fenugreek seed on the severity and systemic symptoms of dysmenorrhoea.	101 female students, eumenorrhoeic, primary dysmenorrhoea.	Fenugreek seed, first 3 d of menstruation, 2–3 capsules containing fenugreek seed powder (900 mg) were given three times daily for two menstrual cycles.	Placebo – potato starch.	Not stated	Pain severity decreased, fenugreek 6·4 (SD 1·83) B versus 3·25 (SD 1·5) PI ($p < 0·001$); placebo 6·14 (SD 1·89) B versus 5·96 (SD 1·87) PI ($p = 0·016$).	Fenugreek seed powder during menstruation can reduce severity of dysmenorrhoea.	Positive
Alpha-lipoic acid (ALA)								
Yousefi (2019)[49]	Effect of ALA at the combination with mefenamic acid in girls with primary dysmenorrhoea.	98 women, eumenorrhoeic, BMI below 30, primary dysmenorrhoea.	ALA and mefenamic acid administered in 600 mg and 250 mg, respectively, for 5 d (2 d before menstruation and 3 d after onset). ALA + mefenamic – one ALA 600 mg and one mefenamic acid 250 mg daily.	Placebo, 5 d (2 d before menstruation and 3 d after onset).	Not stated	Pain intensity significantly reduced in ALA 7·12 (SD 0·82) B versus 5·42 (SD 0·4) PI ($p = 0·046$); mefenamic 7 (SD 1·01) B versus 6·01 (SD 0·4) PI ($p = 0·045$); ALA + mefenamic 7·61 (SD 0·9) B versus 4·3 (SD 0·07) PI ($p = 0·041$) compared with no change in placebo 7·19 (SD 1·07) B versus 7·06 (SD 1·01) PI ($p = 0·803$).	ALA supplement more efficient than mefenamic acid.	Positive
Prasaplai formula (PPF)								
Vannabhum (2016)[69]	The efficacy of Thai herbal PPF for treatment of primary dysmenorrhoea.	40 females, 18–45 years old, eumenorrhoeic, primary dysmenorrhoea.	Thai herbal PPF, two capsules = 1000 mg orally (each capsule 500 mg PPF) first and then three capsules per day before meals for 3 d starting from the first day of menstruation.	Placebo capsule (500 mg starch) orally three times per day before meals for 3 d starting from first day of menstruation.	Not stated	Average pain scores: no significant difference between groups 0·25 (SD 1·11) B versus 3·86 (SD 3·07) day 1–3 of PPF; 0·20 (SD 1·43) B versus 3·18 (SD 2·57) day 1–3 placebo.	PPF no different in pain relief from dysmenorrhoea than placebo	No effect

B, baseline; BMI, body mass index; g, grams; mg, milligrams; IU, International Unit; kg/m2, kilograms divided by height in metres squared; PI, post intervention; PMS, premenstrual symptoms; VAS, Visual Analogue Scale

Table 3. Participant characteristics

Reference first author	Number of participants	Age (years)	Country of origin	Type of participant
Abdollahi[38]	Vitamin D ($n=64$) Placebo ($n=66$)	22·5 (SD 2·6)	Iran	University students
Agha-Hosseini[60]	Saffron ($n=24$) Placebo ($n=23$)	35·10 (SD 7·79) 33·45 (SD 7·61)	Iran	Not specified
Atallahi[54]	Wheat germ ($n=42$) Placebo ($n=38$)	33·452 (SD 5·89) 32·842 (SD 5·58)	Iran	Women in hospitals affiliated with Hamadan University of Medical Sciences
Canning[62]	St John's wort first ($n=17$) Placebo first ($n=15$)	35·3 (SD 5·9)	All Northern European, except one British-born Asian and one Eastern European	Not specified
Charandabi[43]	Calcium + magnesium ($n=20$) Calcium ($n=20$) Placebo ($n=21$)	21·0 (SD 2·0) 21·3 (SD 2·5) 20·8 (SD 2·2)	Iran	University students
Doubova[63]	Psidii Guajavee 3 mg/d ($n=52$) Psidii Guajavee 6 mg/d ($n=57$) Ibuprofen ($n=46$) Placebo ($n=42$)	19·6 (SD 2·0) 19·4 (SD 1·7) 19·5 (SD 1·9) 19·9 (SD 2·2)	Mexico	University students
Esmaeilpour[52]	Whole grains ($n=38$) Placebo ($n=38$)	34·5 27·5	Iran	Nurses
Fanaei[55]	Curcumin ($n=32$) Placebo ($n=31$)	23·86 (SD 5·7) 25·21 (SD 9·2)	Iran	University students
Hagen[44]	Vitamin B6 ($n=34$) Placebo ($n=34$)	37 (24–46 range)	Norway	Not specified
Haidari[64]	Chlorella ($n=22$) Placebo ($n=22$)	22·68 (SD 3·32) 22·95 (SD 3·25)	Iran	Not specified
He[66]	Vitus ($n=104$) Placebo ($n=104$)	34·51 (SD 7·34) 35·27 (SD 6·16)	China	Not specified
Hicks[61]	St John's wort ($n=61$) Placebo ($n=64$)	37·2 (SD 5·1)	UK	Not specified
Jafari[45]	Zinc ($n=27$) Placebo ($n=30$)	23·04 (SD 2·97) 22·53 (SD 1·85)	Iran	University students
Jahangirifar[58]	Cinnamon ($n=30$) Placebo ($n=28$)	22·2 (SD 2·2) 22·3 (SD 2·7)	Iran	University students
Jenabi[67]	*Achillea millefolium* ($n=45$) Placebo ($n=46$)	21·66 (SD 5·77) 20·37 (SD 6·0)	Iran	
Kashefi[57]	Ginger ($n=45$) Zinc ($n=53$) Placebo ($n=42$)	17 (SD 4·3)	Iran	High school students
Khajehei[54]	Dydrogesterone ($n=53$) Calcium+vitamin D ($n=55$) Placebo ($n=51$)	20·84 (SD 1·64)	Iran	University students
Khayat[56]	Curcumin ($n=32$) Placebo ($n=31$)	25·21 (SD 9·2) 23·86 (SD 5·7)	Iran	Not specified
Moini[39]	Vitamin D ($n=23$) Placebo ($n=27$)	25·91 (SD 3·74) 26·81 (SD 2·92)	Iran	Patients
Raisi dehkordi[68]	*Salix* first ($n=48$) Placebo first ($n=48$)	20·48 (SD 1·64) 21 (SD 1·83)	Iran	University students
Schmidt[51]	PAS ($n=22$) Placebo ($n=20$)	33·64 (SD 7·37) 32·65 (SD 7·41)	Germany	Not specified
Sohrabi[47]	Omega 3 ($n=63$) Placebo ($n=61$)	31·18 (SD 6·54) 31·64 (SD 8·37)	Iran	University students

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Table 3. (*Continued*)

Reference first author	Number of participants	Age (years)	Country of origin	Type of participant
Turner[65]	*Vitus* ($n=105$)		UK	Not specified
	Placebo ($n=112$)			
Vannabhum[69]	PPF ($n=20$)	22·5 (SD 4·2)	Thailand	Not specified
	Placebo ($n=20$)	26·6 (SD 7·5)		
Younesy[59]	Fenugreek ($n=51$)	19·56 (SD 1·52)	Iran	University students
	Placebo ($n=50$)	20 (SD 1·56)		
Yousefi[49]	ALA ($n=24$)	23·02 ± 2·17	Iran	University students
	Mefenamic ($n=25$)	22·49 ± 2·21		
	ALA + mefenamic ($n=25$)	23·41 (SD 3·08)		
	Placebo ($n=23$)	23·11 (SD 2·33)		
Zarei[42]	Calcium+ vitamin D ($n=29$)	22·7 (SD 2·4)	Iran	University students
	Calcium ($n=28$)	23·8 (SD 3·0)		
	Placebo ($n=28$)	24·5 (SD 3·9)		
Zekavat[46]	Zinc ($n=60$)	15·2 (SD 1·7)	Iran	Outpatients
	Placebo ($n=60$)	14·8 (SD 2·1)		

PAS, Phosphatidic acid complex; PPF, Prasaplai formula; ALA, Alpha-lipoic acid.

any potential placebo effect, twenty-three reported a positive effect (Table 2) and five had no effect or were inconclusive (Table 2). Additional factors such as lack of control of dietary intake when investigating omega-3 or other vitamins and minerals naturally found in food prevented conclusions being drawn of the use of additional supplements. Furthermore, there was variation in dose of intervention used and duration of intervention across the studies preventing further analysis (Table 1).

Where more than one paper was reviewed of the same intervention type, further synthesis of results was completed. This included thirteen studies and six different nutritional practices: vitamin D, calcium (and magnesium) St John's wort, *Vitus agnus-castus*, curcumin and zinc. Synthesis highlights seven of these studies report no other form of vitamin or mineral supplement ingested prior to and during the intervention; interventions where this control was not stated were St John's wort and *Vitus agnus-castus*. There was variation in identification of deficiency, for instance, serum vitamin D measures included blood ELISA analysis[38], electrochemiluminescene[39] or self-reported diet lacking consumption of vitamin D[41,42]. In some cases[41,42], levels were not measured. Self-reported food diaries were also used to establish calcium intake and determination of insufficient quantities consumed (e.g. less than 1000 mg calcium consumed per day deemed as deficient[42]).

When differentiating the outcome measures of the four studies which included vitamin D, only two looked solely at vitamin D supplementation, one for the treatment of dysmenorrhoea[26] and one for the treatment of pre-menstrual symptoms[38]. Disparity existed between the outcome of vitamin D on treatment of pre-menstrual symptoms with one overall report of no effect[38]. Both studies included participants of the same age range, deficient in vitamin D (<0.03 mg/l or <0.02 mg/l) and not taking any vitamin D or other vitamin/mineral supplements. There was variation in dose and length of time; 50 µg every other day for 12 weeks compared to 530 mg once a week for 12 weeks. Although Adbollahi *et al.*[38] reported results as overall no effect, vitamin D significantly improved anxiety, providing evidence that vitamin D may impact on mood related symptoms; however, consistency in length and dose amount need to be controlled along with outcome measure to determine any effect on symptoms.

A combined intervention of vitamin D and calcium identified dydrogesterone was more efficient to manage menstrual-related symptoms[41] or calcium alone[42] to reduce dysmenorrhoea and pain intensity. However, in another study calcium plus magnesium was reported to have a greater effect of reducing dysmenorrhoea than calcium alone[43]. Across the calcium and vitamin D studies there was variation in dose and duration of intervention; 500 mg of calcium plus 200 mg (200 000 ug) vitamin D were prescribed twice daily from the fifteenth to twenty-fourth day of the menstrual cycle for two consecutive cycles. Whereas one tablet per day of 1000 mg calcium and 5.3 mg vitamin D3, or one tablet per day 1000 mg calcium only were taken from the fifteenth day of menstrual cycle until the disappearance of menstrual pain in the following cycle. Whilst high, this calcium dose is below the likely safe upper limit of 1500 mg/d[36]. Calcium doses were consistent across the studies, however

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Table 4. Reported measurements from twenty-eight studies to determine pre-menstrual symptoms and primary dysmenorrhoea

Premenstrual symptom measurement	Primary dysmenorrhea measurement
Interview and validated Iranian version PMS screening tool (PSST)*	Self-reported checklist intensity of primary dysmenorrhoea
Checklist of 17 pre-menstrual symptoms rated 0–4 severity – Four subscales mood, behaviour, pain and physical	Pain measure VAS*
State scale of the state-trait anxiety inventory (STAIS)*	Amount of pain relief used
Aggression questionnaire (BPAQ)	Pain measure VAS 0–10*
Barratt Impulsiveness scale version (BIS-II)*	Number of days in pain
Daily record questionnaire 19 symptoms (based on DSM)	Multidimensional verbal questionnaire to evaluate systemic symptoms
VAS for PMS symptoms completed during interviews*	Multidimensional verbal scoring system, 0 = none, 3 = severe
Rank severity of list of PMS symptoms	
Chinese version PMS diary (PMSD) 17 items*	
Pre-menstrual tension syndrome self-rating scale (PMTS) 36 items*	
Menstrual diary PMS 25 items scored using VAS	
Daily record questionnaire 30 symptoms based on DMS = VI*	
General health questionnaire (GHQ-28) 28 items divided into 4 subscales: somatic symptoms, anxiety, social dysfunction, depression. 4-point scoring scale.	
Daily record questionnaire 19 items based on DSM-IV	
Daily record of severity of problems (DRSP)*	
SIPS questionnaire (German version PSST)	
Questionnaire based on The American College of Obstetrics and Gynaecology	
Menstrual distress questionnaire	

* Indicates validated measure.PMS, pre-menstrual syndrome; PSST, pre-menstrual syndrome screening tool; VAS, visual analogue scale; DSM VI, Diagnostic and Statistical Manual of Mental Disorders 6; DSM IV Diagnostic and Statistical Manual of Mental Disorders 4

vitamin D doses varied. Duration of supplementation did vary between the studies reviewed. Intervention duration ranged from two consecutive cycles[41] or categorised as 8 weeks in another paper[39] to three cycles[42] or 12 weeks[38].

Zinc reduced physical and psychological symptoms associated with the menstrual cycle[45] and dysmenorrhoea[46], with results also highlighting zinc combined with ginger can reduce primary dysmenorrhoea pain[57]. Studies spanned age ranges of 14–30 years, with interventions ranging from approximately 4 weeks to 12 weeks and variation in zinc dosage of 30 mg/d, 50 mg/d and 220 mg/d (Table 1) taken 4 d prior to onset of menstruation or on the first day of menstruation for 3 d or 3 d prior to the end of menstruation. It should be noted that Kashefi *et al.*[57] provided doses significantly higher than the recommended safe upper limit for zinc of 50 mg/d for adults[36].

Curcumin reduced the severity of menstrual related symptoms in female eumenorrhoeic students with total scores reducing from 102·06 (SD 39·64) at baseline to 42·47 (SD 16·37) post intervention, with placebo reducing to 91·60 (SD 43·56) ($p < 0·001$). Curcumin was taken in capsules over three menstrual cycles, two capsules were taken daily (100 mg/12 h) for 10 d in total – seven before menstruation and three during menstruation in both studies[55,56].

Studies investigating St John's wort and *Vitus agnus-castus* were inconsistent in results with only one study of each showing an effect. There was variation between intervention dose (e.g. St John's wort) preventing any conclusions being drawn on effectiveness of these nutritional practices.

Overall, vitamin D, calcium (and magnesium), zinc and curcumin were effective in reducing pain or severity of menstrual related symptoms. A maximum of three papers were reviewed under each of these interventions; therefore, despite positive results, caution should still be taken when applying the results widely.

One extreme case which should be interpreted with caution investigating the effect of *Psiddi guajavae folium* extract for treatment of dysmenorrhoea[63]. Reported results over emphasized the benefit of the extract compared with ibuprofen. Treatment combined with compliance for ibuprofen was not reported, despite completing this for both 6 mg/d and 3 mg/d *Psiddi guajavae folium* extract treatment groups. By the end of treatment there was no difference in pain reported between any of the groups. Compliance was reported with similarities between groups, but the number of participants in each group varied for analysis (fifty-seven 6 mg/d extract participants compared with forty-two placebo participants and forty-six ibuprofen participants). All interventions were identical and labelled with codes only known by the investigators who manufactured the products. However, there was no clarification if these were the same investigators completing the research and details of double blinding the interventions to prevent bias lacked clarity.

Eight of the reported interventions involved nutrients with UK DRV and safe upper limits recommended (Table 1). Of note, some of the supplement interventions included lactose in the preparations for instance Agha-Hossini *et al.*[60] and Hicks *et al.*[61], which could be problematic for those with lactose intolerance. In addition, lactose was included as a placebo in some studies[42,57] which needs consideration if recruiting for further studies.

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Discussion

The aim of this systematic review was to determine the influence of nutritional practices on symptoms related to the menstrual cycle. The results indicated that there are food/supplements which may be used by women to reduce severity of menstrual-related symptoms (based on single studies) including pain caused by primary dysmenorrhoea if guidelines are followed and any contraindications are considered. However, there is a lack of consistency regarding determination of menstrual related symptoms and dose/duration of food or supplement to make recommendations in practice.

Within this review, various foods and supplements have found a positive effect on reducing menstrual related symptoms and dysmenorrhoea including vitamin D, calcium (and magnesium), zinc and curcumin, but in these instances a maximum of two to three papers were reviewed for each treatment, with variations in intervention duration and dose, alongside inconsistent outcome measures, thus preventing direct comparison between the studies. Foods such as whole grains in place of refined grains and omega-3 may contribute to improved menstrual related symptoms, whilst cinnamon may reduce the intensity of dysmenorrhoea; however, these studies did not explore the mechanisms related to these findings and only one study was reviewed on each preventing definitive recommendations from being provided.

Current pharmacological treatments for women suffering from menstrual-related symptoms and primary dysmenorrhea can include non-steroidal anti-inflammatory drugs, HC, antipyretic medication and analgesic medication. However, these medications have a reported failure rate of 20–25%[70,71], and can have associated unwanted outcomes, such as diarrhoea, stomach-ache and nausea[72] along with long-term health implications. Furthermore, some women might not wish to use medication or contraceptives for the relief of symptoms and pain, and some have religious or cultural conflicts with the use of these medications[73]. Alternative options are required; despite inconsistencies in current literature reviewed, there may be vitamins, minerals or other nutritional interventions for the treatment of menstrual related symptoms and dysmenorrhoea. Results of this review have informed the specific sections below on vitamin D, calcium and magnesium, zinc and curcumin.

Calcium and vitamin D

From the studies reviewed, one study identified calcium and vitamin D combined were more effective than a placebo in reducing pre-menstrual symptoms in participants self-reporting a deficiency of calcium or vitamin D in their diet[42]. No measures determined participants' serum levels of either vitamin or mineral to recognise previous suboptimal levels prior to intervention and nor were any measures included in the study design to determine the biological mechanism causing a difference in the results. However, in more recent years, it has been noted that blood levels of calcium and vitamin D, the latter facilitating calcium absorption, fluctuate across the menstrual cycle[74]. Disruption of calcium regulation has been proposed as an underlying factor for increasing incidence and severity of menstrual pain[22].

From the perspective of a reduction in pain associated with primary dysmenorrhoea, calcium alone was identified as being more effective than when combined with vitamin D in the studies reviewed[42]. Differences in protocols may explain these results, with supplements only being taken from the fifteenth day of the menstrual cycle. Again, all measures were self-reported, including determining calcium deficiency using a food diary; those classed as deficient if consuming less than 1000 mg/d. Analysis of each group showed that 93% of participants were deemed to be deficient in the calcium and vitamin D group, 86% deficient in calcium alone group and 89% deficient within the placebo. These results highlight calcium supplementation may be beneficial to women deficient in calcium to reduce dysmenorrhoea; however, there was limited mechanistic insight provided by the study to draw any conclusions.

Two studies considered solely vitamin D supplementation; the studies were inconsistent in outcome measures (dysmenorrhoea or pre-menstrual symptoms) with further disparity between dose and duration. It has been shown that vitamin D has anti-inflammatory effects[75]. It reduces production of prostaglandins[76], which have been found to have a major role in the pathophysiology of PMS[77] and dysmenorrhoea[78]. Previous research has shown that vitamin D may influence several different mechanisms related to dysmenorrhoea and PMS, including reduced expression of cyclooxygenase-2 and, accordingly, reduced prostaglandin production, up-regulation of 15-hydroxyprostaglandin dehydrogenase, increased prostaglandin inactivation, regulation of the expression of prostaglandin receptor, and consequently reduced pain intensity[75]. This may highlight the beneficial effects reported in the reviewed studies for women deficient in vitamin D but may be limited to this population.

One study in the present review investigated the use of calcium alone or combined with magnesium[43]. Previous research has reported serum magnesium acts as a transit pathway between electrolyte uptake and excretion, bone stores and actively metabolising tissues; these processes are affected by several hormones, including sex steroids[79]. Deficiency can cause muscle cramps, anxiety and signs of inflammation[79]. There is evidence of reduced levels of prostaglandin F2α, involved in pain and inflammation[80], which may play an important role in pain modulation of primary dysmenorrhoea. Out of the studies reviewed, one study investigated the use of calcium alone or calcium and magnesium combined, with results identifying the addition of magnesium had an increased effect on reducing pain intensity. However, no details were provided on participant levels of calcium or magnesium prior to the intervention. Consistent with previously reported findings, no measures to determine biological mechanisms affecting the reduction in self-reported pain were included in the study design.

Zinc

Serum zinc concentrations change during the menstrual cycle; zinc deficiency can reduce the zinc serum concentrations and consequently may cause the glucocorticoid's production to be irregular and lead to some neuropsychological symptoms such

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as irritability, depression and emotional instability[81], along with being associated with dysmenorrhoea[82].

Within this current review, findings of Jafari *et al.*[45] demonstrated that taking zinc supplements for 12 weeks in women with PMS resulted in significant increase in brain-derived neurotrophic factor (BDNF) compared with the placebo. There has been no other study that assessed the effect of zinc supplementation on serum levels of BDNF in PMS subjects[45]. However, it is believed zinc induces the matrix metalloproteinase that activates tropomyosin-related kinase proteinase, and this leads to release of pro-BDNF from cells and then converts to BDNF[83]. Previous studies have shown that BDNF has a role in a women's reproductive physiology and some of the actions of sex hormones are mediated by BDNF[84]. Recent studies in PMS women revealed serum BDNF levels in luteal phase are significantly different than women without PMS, with studies reporting both higher[85] and lower[84] BDNF levels associated with menstrual-related symptoms. However, there is consensus between studies suggesting that circulating serum BDNF levels are associated with incidence of PMS symptoms and may play a role in the pathophysiology of PMS[84,85].

Alternative research has suggested zinc promotes microcirculation and prevents ischaemia[86], inactivates free oxygen radicals by increasing the dismutase enzyme level[87], down-regulates inflammatory cytokines[88] and decreases and regulates the level of the cyclooxygenase-2 enzyme[89] to reduce dysmenorrhoea. Additionally, inflammatory markers are significantly associated with severity of menstrual symptoms in women[90]; since zinc functions as an anti-inflammatory agent[91], it may affect inflammatory markers, such as high-sensitivity C-reactive protein [92] and, therefore, alleviates PMS symptoms as well.

The tolerable uptake level of zinc suggested by the UK safe upper limit is 50 mg/d and popular multi-vitamins supply more than 15–30 mg of zinc as a dietary supplement[93]. The recommended daily dietary allowance of elemental zinc for women is 8 mg/d, and long-term supplementation with more than 20 mg elemental zinc per day would be unsafe[94]. Within studies included in this current review, the dose of zinc was much greater in the study by Kashefi *et al.*[57], reporting 220 mg zinc sulphate capsules taken for 4 d approximately at the start of menstruation, and Zekavat *et al.*[46] reported an intervention of 50 mg/d of zinc sulphate for 4 d. Although Jafari *et al.*[45] reported use of a lower dosage (30 mg/d zinc gluconate) this was prescribed every day for 12 weeks. The studies included in this review reporting use of zinc supplements should be applied with caution, checking the dose first, and further research is required to determine dose quantity of zinc to improve PMS and dysmenorrhoea experienced by women.

Curcumin

The results from the studies included in this systematic review[55,56] both reported a beneficial effect of curcumin. Fanaei *et al.*[55] identified that BDNF levels were significantly higher and mean scores of PMS were significantly lower following supplementation of curcumin for 10 d repeated for three menstrual cycles; a daily dose of 100 mg/12 h was prescribed. This study supported the proposed mechanisms related to BDNF and subsequent impact on mood and behaviour regulation[55].

Curcumin, otherwise known as turmeric, has recently been involved in research indicating its medicinal, health[95] and anti-inflammatory effects [96]. Studies have demonstrated that curcumin can have beneficial effects on physiological and pathological conditions[95]. Curcumin is proposed to have a neuroprotective effect, it is observed that it acts through modulating the release of certain neurotransmitters, such as BDNF[97].

Both reviewed studies were consistent in protocol, Khayat *et al.*[56] prescribed 100 mg/12 h over 10 d and repeated for three menstrual cycles. There was consistency in the results and protocol implemented and there is no daily recommended dose or safe upper limit for this plant-based extract which may therefore be deemed safe to supplement. Similarly, cinnamon was reported to have a beneficial effect on pain intensity of primary dysmenorrhoea and requires further research to support the one study reviewed[58].

Measurement of menstrual symptoms and outcome measures

To date, although over 200 menstrual cycle-related symptoms have been described, a universally accepted definition and/or conventional diagnostic criteria for PMS are still lacking[98]. Although no specific physical finding or laboratory test is currently available for the diagnosis of PMS, the American College of Obstetricians and Gynecologists published a list of diagnostic criteria for PMS[99,100], establishing that PMS could be diagnosed if at least one of the affective and one of the somatic symptoms were reported 5 d before the onset of menses in the three previous menstrual cycles[101]. Symptoms must be prospectively recorded in at least two cycles, must cease within 4 days from the onset of menses, and should not recur before day twelve of the next cycle[101]. In addition, symptoms must be recorded in the absence of pharmacologic therapy in patients not taking hormones, drugs and alcohol[101]. However, dysmenorrhoea alone may be defined as a menstrual cycle-related symptom, but under the diagnostic criteria this would exclude a participant from being diagnosed with PMS.

Criteria were not consistent between the studies reviewed, there were instances when multiple diagnostic criteria were included. For instance, Abdollahi *et al.*[38] recorded the cycles for 3 months; the individual presented with one or more somatic symptoms for 5 d before a period and symptoms did not start until day thirteen of the cycle. Future research should determine PMS diagnostic criteria and studies should implement these criteria as a minimum when examining the efficacy of a food or supplement on menstrual-related symptoms.

To further improve the quality of the studies, longitudinal tracking of symptoms over time to allow for other lifestyle influences which may affect symptomology should be considered. Where possible, sex hormones should be measured to confirm the changes in hormones across menstrual cycle phases coinciding with presentation of symptoms, along with physiological markers, to assist with

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investigation of underlying mechanisms of interventions to support self-reported measures.

Participant characteristics

The age of participants varied in the review (Table 3) with one study[46] investigating the effect of intervention on participants as young as 15 years with no information provided in the methodology stating eligibility to participate based on age of menarche. Peri-pubertal girls can be more symptomatic with hormone secretions more likely to be atypical[102]; this may add variability to the effect of the intervention on outcomes measures and findings reported. Vitamin and mineral deficiencies were considered in some studies, but not all; the level of determination of deficiency varied as well. Future studies need to measure and report method of measurement of deficiency status in participants to understand if supplementing elevated to a 'normal' level and the consequential impact on symptoms.

Limitations and future research

Limitations of evidence reported within this review should be considered, there was consistently a lack of alignment in outcome measures with further variation noted between studies regarding intervention in terms of food or supplement investigated and dose and duration of interventions. Furthermore, the majority of studies did not investigate physiological mechanisms associated with symptoms related to the menstrual cycle. Self-reported outcome measures are important in understanding severity and frequency of symptoms experienced, but biological mechanisms are an additional requirement in understanding nutritional practices and interventions in management of menstrual cycle symptoms.

Another limitation of reviewed studies is the lack of consideration or discussion relating to the placebo effect, despite research identifying many types of placebo responses driven by different mechanisms depending on the particular context[103]. As placebo factors have neurobiological underpinnings and affects the brain and body, placebo mechanisms should be considered in clinical trial design[103]. Research has evidenced that placebo effects can be strong in the first cycle of intervention[104] but should begin to decline to baseline as the study continues[105]. Therefore, study design should consider this with interventions completed for at least two cycles. Conversely, not all studies provided clear detail on how the placebo/control was equally matched to the active intervention[54,62] which may influence the study findings. Future research should consider the placebo/control within methodological design to ensure it is evenly matched on the basis of appearance, taste and smell and ensure more than one cycle of intervention is completed.

The reviewed studies included individuals naturally menstruating, excluding those using HC and eliminating multiple studies from the review. It is acknowledged that this reduces the practical application of the review to only those naturally menstruating; however, the mechanisms causing side effects of HC vary significantly due to the differences in exogenous versus endogenous hormones and are not comparative and therefore are beyond the scopes of this review. Furthermore, individuals experiencing side effects of HC can change the type and brand, associated with different levels of synthetic hormone and composition, to actively manage side effects. Future research is needed to explore the mechanisms of symptoms related to the menstrual cycle and HC to enable application of interventions to manage these two groups.

Future research specifically should investigate the effect of vitamin D, calcium, magnesium and zinc prescribed within safe upper limits and measured physiological changes in both normal and deficient women.

Conclusion

This is the first systematic review to examine the use of food or dietary supplements to help with management of menstrual related symptoms. These data provide some evidence for the use of vitamin D, calcium (and magnesium), zinc and curcumin to reduce pre-menstrual symptoms. However, further investigation is required to understand the physiological mechanism relating to these nutritional interventions and how specific symptoms related to the menstrual cycle may be improved rather than grouped as PMS. Future studies should focus on the general quality of the methods used, to allow direct comparisons between studies to be made and conclusions to be drawn from studies and implemented in practice.

Availability of data materials

Not applicable.

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Authorship

N.B., R.F., D.M., M.W. and G.B. contributed to conceptualisation; N.B., D.M., R.F., L.F., M.W. and G.B. were involved in review; N.B. and R.F. wrote the original draft; N.B., R.F., D.M., M.W. and G.B. reviewed and edited subsequent drafts. All authors read and approved the final manuscript.

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All authors declare that they have no conflicts of interest relevant to the content of this review.

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Ethical statement

Not applicable.

Consent for publication

Not applicable.

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