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# Effects of Artichoke and Bee Products on Body Weight Gain, Hot Flashes, and Insomnia during Menopause and Climacteric: A Systematic Review

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#### Abstract

We sought to evaluate the effect of ingesting artichoke extract and bee products (royal jelly, honey, pollen), or including them in the diet, on the reduction and/or control of body weight, hot flashes, and insomnia during menopause and climacteric. There are only a few clinical reports that specifically correlate the intake of artichoke (or artichoke extract), in combination with bee products, to the decrease in body weight. In this paper, each of these reports will be examined, together with reports of studies carried out in a menopause model of ovariectomized rats.

A bibliographic search was carried out in PubMed and Google Scholar databases, from January 2010 to January 2021. The results were tabulated for an easy comparison of the experiments performed.

Doses of 20g Tualang honey and 1,000 mg of royal jelly show benefits in reducing menopausal symptoms such as hot flashes, sweating, and sleep disorders. Royal jelly at a dose of 10 ml/day has an activity that is similar to that of estrogens, in addition to antioxidant, and antihypercholesterolemic activity; these activities result in 70% improvement of menopausal symptoms. As for artichoke, 1.8 g of artichoke extract improved the levels of total cholesterol, triglycerides, HDL, and LDL. Hypoestrogenism has been related to physiological changes that are largely responsible for weight gain during menopause, which constitutes a problem for women due to the increase in abdominal fat. Such a situation encourages women to seek alternatives to reduce body weight, hyper-cholesterolemia, the frequent increase in triglyceride levels, and cardiovascular conditions. In such instance, alternative medicine plays an important role as an option to reduce body weight; specifically, through the reduction of abdominal fat, appetite, and anxiety for sweet foods. Alternative medicine can also provide options to reduce insomnia (specifically improving the quality of REM sleep), irritability, hunger, and appetite (since the consumption of bee products generates a feeling of fullness and satiety). As a result, artichoke and bee products dietary supplementation may represent an effective, inexpensive option for individuals with menopause and overweight.

Keywords: Artichoke; Honeybee; Royal Jelly; Menopause; Body Weight; Hot Flashes; Insomnia

## Abbreviations

RJ: Royal Jelly; ALE: Artichoke Leaf Extract; TH: Tualang Honey; HRT: Hormonal Replacement Therapy; OVX: Oophorectomy; SH: Sham Operated

#### Introduction

Overweight and obesity are defined as abnormal or excessive accumulation of fat that can be detrimental to health [1]. Obese individuals have a lower quality of life and a shorter life expectancy

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than the average individual. Epidemiological studies have shown that obesity is a risk factor that can be both the cause or consequence of different diseases [2,3].

The treatment of obesity represents a great economic cost for the health system; this condition involves 1% to 3% of total health care expenses in most countries (5% to 10% in the United States), and its costs could increase in the coming years, due to the presence of complications or diseases associated with this condition [3,4].

Currently, Mexico and the United States are the first places in the world's obesity prevalence for the adult population (30%), which is around 10 times that of countries such as Japan and Korea (4%). In Mexico, overweight and obesity show a constant prevalence increase, according to different national surveys [4]. From 1980 to date, the prevalence of obesity and overweight has tripled, reaching alarming proportions [2,4].

According to the National Health and Nutrition Survey (ENSA-NUT 2018), 40.2% of the female population over 20 years of age is obese, and more than 76.8% of this population is overweight [5,6].

Obesity has also been associated with a delay of about a year in the onset of menopause. At each life stage, the development or presence of obesity shows specific characteristics [7-9]. The mechanisms underlying obesity, as a consequence of the imbalance between energy intake and expenditure, are not well understood. However, the effect of overeating and physical inactivity on obesity are irrefutable.

Menopause is defined as the cessation of menstrual periods (6 - 12-month amenorrhea). Although menopause is a well-defined event over time, the ovarian function begins to decline a few years before, alternating normal ovulatory cycles with anovulatory periods of variable duration; this period, and up to a year after the last menstrual period, is called perimenopause [9]. Several studies have shown that, regardless of age, menopause is associated specifically with weight gain (estimated to be around 6%), which occurs in conjunction with an approximate 17% increase in fat mass [10-12].

The etiology of weight gain during menopause is not completely clear. However, some causes of weight gain are not directly related to menopause, but rather to age. On the other hand, other causes of weight gain depend on the decrease of endogenous estrogens [7,13,14].

During childbearing years, the ovarian follicle and the corpus luteum produce 95% of the circulating estradiol. During menopause, the main sources of endogenous estrogens are the aromatization of androstenedione to estrone and the peripheral conversion of estrone to estradiol [14,15]. Estrogens regulate and stimulate the production of different compounds such as leptin, which is a protein secreted in the adipose tissue that is responsible for informing the brain about the magnitude of energy reserves [14,16].

At the same degree of adiposity, women have higher levels of leptin than men. In women at childbearing age, leptin levels are higher during the luteal phase, but its concentration declines after menopause [7,14,16]. Estrogens also appear to play a role in appetite regulation [14], as the feeling of satiety is stimulated by cholecystokinin, which in turn is stimulated by estrogens [7]. A positive correlation has been found between cholecystokinin and estrogen levels, and it has been found that cholecystokinin concentration increases after estrogen replacement therapy [7,17,18]. Ovarian hormones have a marked effect on the progressive decrease in food consumption during the follicular phase of the menstrual cycle [7]. The loss of estrogens after oophorectomy increases food intake and body weight in monkeys, rats, and mice, which suggests that, in general, higher food consumption, accompanied by lack of exercise, contributes to increased adipose tissue after menopause, although there is no conclusive evidence yet [18-21].

In addition, there is a physiological difference in terms of eating habits between men and women; obese men identified foods rich in fat and protein among their favorites, while obese women identified foods rich in fat and carbohydrates (especially foods rich in sugar) among their favorites. People who had proper weight did not show these differences in preference. These differences may be due to sex differences in the hedonic taste experience, and it is thus important to determine if these differences arise before people become obese, or if they are a consequence of obesity [7,22,23].

The lifetime prevalence of psychiatric eating disorders, and of other eating disorder symptoms, are approximately three times higher in women than in men [24,25]. Subclinical symptoms of eating disorders are also more common in women than men, recovery from eating disorders is slower in women than in men, and remission rates are higher in women [7,26,27]. These eating disorders affect the levels of gonadal steroid hormones [28-30].

Binge eating episodes refer to eating an abnormally large amount of food at one time, causing a feeling of loss of control when

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overeating; binge is an uncontrolled way of eating that occurs especially in girls and women [29,31]. A time series analysis of binge eating tendencies and ovarian hormone levels throughout the menstrual cycle suggested that estrogens inhibit emotional bingeing (eating to improve mood) and that progestins counteract the effect of estrogens; i.e, they indirectly stimulate emotional binge eating [14,15,32,322]. This is the strongest indication that progestins are clinically important in uncontrolled eating in women [14,32,34].

Figure 1 is a graph made by Asarian., *et al.* [7], which correlates food consumption (Kcal/day) to each phase of the ovarian cycle. These authors found that sex-specific physiological mechanisms, especially estrogen-mediated effects, play an important role in the development of obesity in women, as well as in the development of pathophysiological consequences of obesity. Therefore, understanding the full impact of the amount of adipose tissue on women's health will require taking into account the hormonal status in each of these processes [7,14,18].

Although weight gain is not the only symptom of menopause, it is perhaps one of the most obvious, and is in turn related to other symptoms such as hot flashes, night sweats, depression, difficulties for starting and/or maintaining sleep, pain during sexual intercourse, hair loss, and forgetfulness [8,9,35]. All of these are



Figure 1: Daily food intake during the different stages of the ovarian cycle in women. Note the progressive decrease in energy intake during the follicular phase around ovulation, and the high level of energy intake during most of the luteal phase. Data are Kcal ingested per day (data represent mean and standard errors of the mean) calculated from three studies in which food intake was measured by weight, and the phase of the cycle controlled with luteinizing hormone tests in urine and menstruation reports (n = 34 women). In each study, data were averaged for the early follicular (eF; 4d), middle follicular (mF; ~ 9d), periovulatory (PO; 4d), and luteal (L; ~ 11d) phases. Asterisks (\*) represent significant differences from the luteal phase [7,14].

common problems of menopausal women with different treatment approaches, among which the use of natural extracts and/or compounds has gained relevance [17,35-37].

32

The main pharmacological actions of artichoke (Cynara scolymus) are related to the digestion processes; as it has choleretic, cholagogue, hepatoprotective, and hypocholesterolemic activities. In addition, artichoke has an effect on hyperglycemia, in which caffeoylquinic derivatives seem to intervene, especially cynarin, chlorogenic acid, and sesquiterpenic lactones (e.g., cynaropicrin); these effects have been documented both in experimental and clinical animal studies [38,39]. Cynarin, enhanced by the other components of artichoke, produces intense choleretic (increased bile secretion) and cholagogue (facilitates emptying of the gallbladder) effects, increases diuresis (urine production) and hypoglycemic actions [40,41].

The effects of dried artichoke leaves extracts have been evaluated in patients with dyspepsia, who showed a 71% reduction of digestive disorders during the treatment period. Cynara scolymus leave extracts have produced a significant improvement of the symptoms of functional dyspepsia (by significantly increasing the amount of bile secretion in the duodenum), and at the same time have shown antiemetic and spasmolytic effects [38].

Several authors have evaluated the effects of the aqueous extract of artichoke leaves on cholesterol levels through clinical trials, in which a reduction in total cholesterol levels has been observed. Similar results have been obtained with healthy volunteers receiving a dose of 1.2 g of normalized artichoke extract for 12 weeks; these volunteers showed a significant reduction of total cholesterol. The administration of 1.8 g of artichoke extract per day decreased hyperlipoproteinemia in patients with cholesterol levels above 280 mg/dL [42].

Apitherapy is a type of alternative medicine that uses natural products from bees, such as honey, propolis, royal jelly, bee bread and bee venom; these products have shown their usefulness for the treatment of various disorders during menopause and postmenopause [35-37], including mood changes, anxiety and depression, vasomotor symptoms (hot flashes, night sweats), osteoporosis, and vaginal atrophy [43]. Royal jelly has been traditionally used to treat menopausal symptoms by rebalancing hormone blood levels, lowering follicle-stimulating hormones (FSH), and increasing estrogen levels in aged mice. One study showed that changes in hormone levels resulting from royal jelly intake increased the number of ovulated oocytes and their quality in aged rats [44]. Purified

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peptides from royal jelly inhibited  $\beta$ -amyloid 40 and 42 by regulating beta-secretase, which made them useful to improve diseases such as Alzheimer's disease [45]. Additionally, royal jelly improved structural brain imaging and behavioral dysfunctions in cholesterol-fed rabbits. Royal jelly acted through the reduction of body weight, lipid levels, beta-amyloid, and acetylcholinesterase, which was associated with the increase of choline acetyltransferase in the brain [46]. Unfortunately, there are only a few human clinical trials addressing the effects of bee products in the postmenopausal period, as most studies have been conducted in animal models.

In this review, we sought to evaluate the effect of ingesting artichoke extract and bee products (royal jelly, honey, pollen), or including them in the diet, on the reduction and/or control of body weight, hot flashes, and insomnia during menopause and climacteric.

#### Methodology

#### Literature search and study selection criteria

This review was carried out following the PRISMA guidelines(37). PubMed and Google Scholar databases were searched from the time of the study inception to January 2021 without language restrictions. Randomized controlled trials, and in vivo studies in rats from the last 10 years were included. The following text and MeSH keywords were used: "artichoke" "honeybee" "royal jelly" "menopause" "body weight" "hot flashes" "insomnia". Other studies, such as in vitro studies, review articles, and conferences were excluded.

#### **Study selection**

Relevant studies were included according to the following criteria: (1) artichoke or bee products were investigated as an independent intervention, (2) the group under study consisted of women of menopausal age or female rats with and without induced menopause, (3) artichoke or bee products were administered for at least 2 weeks, (4) the study was a randomized placebo-controlled clinical trial or a randomized or an in vivo study in rats with a control group, (5) the study provided sufficient information on outcomes or markers before and after artichoke or bee product interventions in the control and treatment groups. Three authors independently reviewed all articles. Any disagreement was resolved by consensus between the authors.

#### Data extraction

Data were collected using a pilot-tested data extraction form that included the following items: 1) study characteristics, includ-

ing region, authors, year of publication, sample size, study design, type of study intervention, dose, and duration of the treatment; 2) information on the population, including age, sex, characteristics of the symptoms to be evaluated (BMI, percentage of body fat, test of levels or daily incidences of hot flashes and insomnia). A thorough check was performed to see if there was any disagreement between the extracted data.

#### Studies

#### **Included studies**

Figure 2 shows the inclusion process of the studies under review. From 65 records identified in the literature, 33 articles were selected for full-text evaluation. Subsequently, nine eligible randomized controlled studies were found to meet the inclusion criteria.



#### Study characteristics and quality assessment

The studies included in this review were published between 2010 and 2018, the characteristics of these studies are presented in table 1. These studies were held in Malaysia, Japan, the USA, Germany, and Iran. Six studies were conducted in women; three studies consisted of tests performed on rats. The mean duration of the intervention was 11 weeks, and interventions ranged from 2 to 48 weeks. The mean dose of artichoke used was 0.13 g per day (minimum 0.02 g and maximum 0.24 g) and of bee products 0.6 g per day (minimum 0.02 and maximum 1 g).

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Author										34
year, coun- try	Item name	Sample size	Study design	Dose	Treatment duration	Age	Sex	Symptoms evaluated	Results	Observations
Siti Zubaidah Ab Wahab., <i>et al.</i> 2018 Malaysia [47]	Long-term ef- fects of honey on cardiovascu- lar parameters and T anthropo- metric mea- surements of postmenopausal women	98 women	Two-arm, double-blind, randomized parallel study comparing Tualang honey (TH) with a honey cocktail (HC) (honey, bee bread, and royal jelly)	20 g/day of TH 20 g/day of HC	12 months	45-65 years	Females	BMI,% body fat, waist circumference, blood pressure, total cho- lesterol, triglycerides, HDL, LDL, blood sugar	BMI (kg/m <sup>2</sup> ): No significant differ- ences. TH = initial 27.44-final 28.85. HC = initial 27.07-final 27.04. % Fat: No significant differences. TH = initial 37.21-final 39.61. HC = initial 39.75-final 39.43. Waist (cm): No significant differences. TH = 86.27 initial-87.78 final. HC = 87.48 ini- tial-88 final.	TH promoted significant changes in symptoms and markers different from BMI,% body fat, and waist cir- cumference.
Khatereh Rezazadeh., <i>et al.</i> 2017 Iran [36]	Effects of artichoke leaf extract (ALE) supplementa- tion on meta- bolic param- eters in women with metabolic syndrome: Influ- ence of TCF7L2 - rs7903146 and FT0 - rs9939609 polymorphisms	56 wom- en (7 dropped out)	Parallel, randomized, double-blind, placebo-con- trolled clinical trial	450 mg of ALE or placebo, four times per day	12 weeks	38-44 years	Female	BMI, waist circumfer- ence, hip circumfer- ence, blood sugar at fasting, triglycerides, HDL, LDL, total cho- lesterol, systolic blood pressure, diastolic blood pressure, evalu- ation of the homeosta- sis model for insulin resistance, Quantita- tive Insulin Sensitivity Check Index	No significant differences in weight, BMI, waist and hip circumference. START VALUES ALE-Placebo BMI: 34.7-32.4 Weight: 86.6-78.4 Waist: 106-98.5 Hip: 116.8-114.5 FINAL VALUES ALE-Placebo BMI: 35.0-32.2 Weight: 87.3-77.9 Waist: 105.2-98 Hip: 117.7-114	Supplementation with of the diet with ALE resulted in a significant improvement in serum triglycerides levels in carriers of the A allele of the polymorphism rs9939609 of the FTO gene, a group of patients with a higher risk of obe- sity and Metabolic syndrome.
Nik Hazlina Nik Hussain. <i>et al.</i> 2012 Malaysia [17]	R a n d o m i z e d Controlled Trial on the Effects of Tualang Honey (TH) and Hor- monal Replace- ment Therapy (HRT) on Car- d i o v a s c u l a r Risk Factors, Hormonal Pro- files and Bone Density Among Postmenopausal Women: A Pilot Study	79 wom- en	R a n d o m i z e d controlled trial one group with TH and one group with HRT	20 g TH/day. HRT: Femo- ston®, also known as Femo conti 1/5, (contains 1 mg of estradiol valerate and 5 mg of dydrogesterone)	4 months	5 5 - 5 9 years	Female	Systolic BP, diastolic BP, body mass index waist circumference TC, TG, LDL-C, HDL-C, FBS, FSH, LH, estra- diol, testosterone	No significant differences in weight BMI, and waist circumference. START VALUES TH-Control BMI: 27.73-27.62 Waist: 86.53-85.56 FINAL VALUES TH-Control BMI: 27.34-27.83 Waist: 89.18-89.13	Systolic BP and LDL values were lower in the TH group.
Zhiyi Qiang., <i>et al.</i> 2012 USA [49]	Artichoke Extract (ALE) Lowered Plasma Cholesterol and Increased Fecal Bile Acids in Golden Syrian Hamsters	64 Ham- sters (32 males, 32 females)	4 groups formed by Con- trol and Treat- ment for males and females	4.5 g of ELA/kg food. 0.24 g of ALE/Kg B.W.	42 days	8 weeks	Male and female	Weight, Total choles- terol, HDL, Non-HDL, Triglycerides, Bile acids, Neutral sterols	Weight: No significant differences in weight. Females: Control = 128.3 ±4.5g, Treatment = 125.9 ±7.1 g	There was a sig- nificant decrease in symptoms and markers different from weight.
A. Minami., <i>et al</i> . 2016 Japan [50]	Improvement of neurological disorders in postmenopausal model rats by administration of royal jelly (RJ)	43 rats	4 groups: Sham, OVX, OVX + RJ, OVX + 17B- estradiol	17B-estradiol patch, 0.25mg/90 days; RJ, 10ml/kg B.W./day	82 days	Not specified	Female	Body weight, brain and uterus; myelin protein and galacto- lipid content, includ- ing galactosylce- ramide and sulfatide; depression	Weight: There were significant differ- ences. Sham = 205 g, OVX = 230 g, OVX + RJ = 220 g, OVX + E = 190 g	RJ demonstrated significant effects on symptoms and markers different from weight.
Siti SM Zaid., <i>et al.</i> 2010 Ma- laysia [49]	The effects of Tualang honey (TH) on female re- productive organs, tibia bone and hor- monal pro- file in ovari- ectomised rats-animal model for menopause	35 rats	2 control groups and three test groups. Con- trol groups were sham operated (SH) and ovariecto- mized (OVX) rats	Control SH and OVX rats were fed 0.5 ml of distilled water. The rats in the test groups were fed a low dose of TH, 0.2 g/kg (LTH); a medium dose, 1.0 g/kg (MTH); or a high dose, 2.0 g/kg (HTH), in 0.5 ml of dis- tilled water. Treatments were administered by oral gavage once a day.	2 weeks	2 2 0 - 2 4 0 gr of weight	Female	Body weight, Vagi- nal weight, Uter- us weight, Tibia weight, Estradiol, Progesterone, Free Testosterone, FSH, LH	TH prevented uterine atrophy and atrophy of the vaginal epithelium, promoted increased bone density, and suppressed the increase in body weight seen in the menopaus- al state. Weight: Start-End Sham: 229-234 OVX: 226-261 LMT: 229-259 HMT: 229-258	

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Karsten Münstedt., et al. 2015 Ger- many [50]	Bee pollen and honey for the alleviation of hot flushes and other meno- pausal symp- toms in breast cancer patients	46 wom- en (15 dropped out)	Prospective and randomized crossover trial: 2 groups, one with a mixture of honey + pollen and the other only with honey	One tablespoon a day	14 days, 14 days break plus 14 days with the other treat- ment	Older than 60 years with at least 7 months of anti- hormonal treatment	Female	Body mass index, total cholesterol, triglycerides, HDL, LDL, exhaustion, increased aggressive- ness, hot flushes when ingested, itchy lips and mouth, edema of the lower extremi- ties, fine hair, mouth odor, upper abdomi- nal pain, arthralgia, flatulence, disgust when ingesting the product, nausea, vomiting, heartburn, malaise, headache, red eyes, more severe hot flashes, dizzi- ness, itchy face and extremities	Initial BMI: 26.9 average; end results are not described. For both groups there was an improvement in symp- toms (68% for honey and 70% for honey + pollen). And markers differ- ent from body mass index.	There were no changes in choles- terol, triglycerides, HDL, LDL.
Seyedeh Na- zanin Sharif., <i>et al.</i> 2018 Iran [49]	Effect of royal jelly (RJ) on menopausal symptoms: A randomized placebo- T con- trolled clinical trial	200 women (8 dropped out)	Randomized placebo-con- trolled clinical trial	1,000 mg RJ/day	8 weeks	Age 45- 60 years. At least one year of amen- orrhea	Female	Body mass index, depression, irritabil- ity, heart palpitations, hot flashes, anxiety, sexual problems, sleep disorders, blad- der problems, muscle dysfunction, and vaginal dryness	Initial BMI 28 average. End results are not described. An improvement in menopausal symptoms from 32% to 19% is reported.	
Takashi Asama., <i>et al.</i> 2018 Japan [50]	Royal Jelly (RJ) Supplementa- tion Improves Menopausal Symptoms Such as Backache, Low Back Pain, and Anxiety in Postmeno- pausal Japanese Women	42 women	Double-blind randomized controlled trial with placebo	200 mg of RJ/per tablet, four tablets once a day	12 weeks	54-58 years	Female	BMI, hot flashes, easy sweating, difficulty for falling asleep, difficulty for staying asleep, irritability, anxiety, often irritated by trifles, feeling un- happy or depressed, fatigue, eyestrain, memory problems, dizziness, palpita- tions, chest tightness, headache, stiff neck, back pain and low back pain, pain in the cold joints, cold hands and feet, leg or arm numbness, and sensi- tivity to sounds	There was no significant difference in BMI. Regarding hot flashes, there were significant differences be- tween the two groups after 8 weeks of administration and there were no significant differences after 12 weeks of administration. Hot flashes and sweats were re- duced from 13% to 32%, and be- tween 9% and 21% insomnia and sleep quality.	

Table 1

In artichoke extract studies, only one clinical trial addressed weight evaluation in women. We found no studies dealing with menopausal women that addressed both weight evaluation and menopausal symptoms. The study carried out by Khatereh Rezazadeh., *et al.* [47] indicated that a diet supplemented with 1.8 g of artichoke extract resulted in a significant improvement in serum triglyceride levels in carriers of the A allele of the rs9939609 polymorphism of the FTO gene; patients with this polymorphism are at a higher risk of suffering from obesity and metabolic syndrome.

In the case of studies addressing bee products and their benefits in women with menopause, and in ovariectomized rats (OVX) rats, we found clinical studies evaluating body weight; Siti Zubaidah Ab Waha., *et al.* [36] reported that 20 g of Tualang honey or honey cocktail per day improved blood pressure, total cholesterol, triglycerides, HDL, LDL, and blood sugar, although there were no changes in BMI, body fat percentage, or waist circumference. Similar results were reported by Nik Hazlina Nik Hussain., *et al.* [17]; they found that a dose of 20 g of Tualang honey per day improved systolic blood pressure and LDL values, without changes in BMI and waist circumference. In in vivo studies with rats, A. Minami., *et al.* [49] reported that a dose of 10 ml of royal jelly/kg B.W. reduced the weight of rats with induced menopause and improved the brain and uterus tissues. On the other hand, Siti SM Zaid., *et al.* [35] showed that, in rats with induced menopause, Tualang honey at a dose of 0.2–2 g/kg b.w. prevented uterine atrophy, atrophy of the vaginal epithelium, promoted increased bone density, and suppressed the increase in body weight observed in the menopausal state; the most effective dose against weight gain was 0.2 g of Tualang honey/kg b.w.

## Conclusion

There is a positive effect of bee products on the symptoms of menopause. The effect of bee products on weight control, or weight reduction, could be beneficial, as inducing or reaching menopause is already a determining factor for weight gain. In the case of artichoke, it is not possible yet to assert its benefits for weight control in women; the potential effects of artichoke are even less clear in women at the menopausal stage.

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#### **Conflict of Interest**

The authors declare that they have no conflict of interest in conducting and disseminating this research.

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