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Nutritional needs and supplementation for women across menopausal stages

Final degree project

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1. Abbreviations

ADME: administration, distribution, metabolization, excretion
AMH: anti-müllerian hormone
AMPK: AMP-activated protein kinase
BAT: brown adipose tissue
BMR: basal metabolic rate
ERα: α-oestrogen receptor
ERβ: β-oestrogen receptor
FSH: follicle stimulating hormone
GABA: gamma-aminobutyric acid
GnRH: gonadotropin releasing hormone
HDL: high-density lipoproteins
HDL-C: high-density lipoprotein cholesterol
HRT: hormone replacement therapy
IGF-1: insulin growth like factor
LDL: low-density lipoproteins
LDL-C: low-density lipoprotein cholesterol
LH: luteinizing hormone
LOOP: luteal-out-of-phase
NE: norepinephrine
SDG: sustainable development goals
SERM: selective oestrogen receptor modulator
SWAN: The Study of Women's Health Across the Nation
TG: triacylglycerol
5-HT: serotonin

2. Abstract

Menopause, a universal phenomenon in women's lives, remains insufficiently explored in terms of its interaction with physiology and nutrition, despite its significant implications for quality of life. The objective of this thesis is to examine the nutritional needs of women during menopause and how supplements can help meet these needs, including their potential limitations. During menopause, there is a physiological decline in oestrogen levels, which can cause a range of manifestations affecting various body systems, including hot flushes, sweating, headaches, hair loss, muscle pain, vaginal dryness, insomnia, depression, weight gain, and mood changes. Nutritional interventions, such as supplementation with plant extracts or bioactive compounds, have the potential to positively impact the specific manifestations of menopause and enhance the quality of life of women in this phase of life. Non-hormonal supplementation presents an advantageous risk-benefit profile in comparison to hormone replacement therapy. However, further research is needed on the optimal efficacy and safety of supplements. Current evidence is limited due to the lack of standardisation across studies, which lead to inconclusive results, making it difficult to transversally review and assess studies on supplementation during the menopausal stages. Lastly, women who participated in a survey regarding supplementation and menopause during this bibliographic review, expressed a strong preference for supplementation options based on natural products to alleviate manifestations, without compromising efficacy.

Keywords: menopause; perimenopause; postmenopause; menopausal manifestations; menstrual cycle; oestrogen; oestrogen receptor; supplements; phytoestrogens; plant-based; hormone replacement therapy.

Resum

La menopausa, un fenomen universal a la vida de les dones, continua sent insuficientment explorada pel que fa la seva interacció amb la fisiologia i la nutrició, malgrat les seves importants implicacions per a la qualitat de vida. L'objectiu d'aquesta tesi és examinar les necessitats nutricionals de les dones durant la menopausa i com els suplements poden ajudar a cobrir aquestes necessitats, incloent-hi les seves possibles limitacions. Durant la menopausa, hi ha una disminució fisiològica dels nivells d'estrògens, la qual cosa pot causar una sèrie de manifestacions que afecten a diversos sistemes del cos, com ara els fogots, els mals de cap, la pèrdua de cabell, el dolor muscular, la sequedat vaginal, l'insomni, la depressió, el guany de pes i els canvis d'humor. Les intervencions nutricionals, com ara la suplementació amb extractes vegetals o compostos bioactius, tenen el potencial de tenir un impacte positiu en les manifestacions específiques de la menopausa i de millorar la qualitat de vida de les dones en aquesta fase de la vida. La suplementació no hormonal presenta un perfil de risc-benefici avantatjós en comparació amb la teràpia de reemplaçament hormonal.

No obstant això, cal més investigació sobre l'eficàcia i la seguretat òptimes dels suplements. L'evidència actual és limitada a causa de la manca de normalització entre els estudis, fet que porta a resultats inconcloents, fent difícil revisar i avaluar transversalment els estudis sobre suplementació durant les etapes de la menopausa. Finalment, les dones que van participar en una enquesta sobre suplementació i menopausa durant aquesta revisió bibliogràfica van expressar una gran preferència per opcions de suplementació basades en productes naturals per alleujar les manifestacions, sense comprometre l'eficàcia.

Paraules clau: menopausa; perimenopausa; postmenopausa; manifestations de la menoapausa; cicle menstrual; estrogen; receptor d'estrogen; suplements; fitoestròg ens; a base de plantes; teràpia de reemplaçament hormonal.

3. Integration across fields

This thesis explores the menopause from an integrative approach based in three scientific fields: clinical nutrition, pharmacology and physiology.

The primary field, clinical nutrition, focuses on diet and supplementation to optimize health and cover the specific nutritional needs during menopause. This discipline aims to delve into how certain nutritional interventions can improve key parameters including bone function, cardiovascular health, metabolic health, as well as mitigating menopausal manifestations and minimize risks associated with the development of diseases.

Pharmacology complements this integrative approach by analyzing how bioactive compounds behave in the human body for potential use in supplementation. Aspects including mechanisms of action, biodisponibility, and drug interaction have been assessed, as well as an evaluation of safety and efficacy on current and potential supplements.

Physiology provides a solid foundation to understand how hormonal changes, such as oestrogen decline, affect metabolic and molecular mechanisms during the menopausal stages. This framework has been essential in subsequently identifying potential nutritional interventions.

Through this combination of fields, this thesis offers an integrative comprehension of the challenges and opportunities regarding nutritional interventions during menopause.

4. Sustainable Development Goals (SDG)

This project studies the physiology of the menopause and considers nutritional research as a tool to improve the quality of life for women, thereby contributing to the third SDG, which focusses on **good health and well-being**. Following evidence-based evaluations on supplementation, certain recommendations have been proposed to address the manifestations of menopause and to reduce the risk of associated diseases. Furthermore, the fifth SDG, which advocates for **gender equality**, is also incorporated in this research as it seeks to increase the visibility of women's health and to answer to the specific needs associated

with it. This study promotes empowerment of women through a deeper understanding and management of the hormonal, physical and psychological changes that occur during menopause, while also advocating for equality in research and access to treatment.

The use of scientific research to develop new plant-based products that exhibit higher effectivity and safety for women during menopause, is in advocacy for the ninth and twelfth SDG-specifically, **industry innovation and infrastructure**, as well as **responsible consumption and production**. This research contributes to fostering a robust and solid infrastructure within the supplementation sector. Furthermore, it emphasizes the importance of a responsible and conscientious consumption by endorsing evidence-based supplementation practices, reducing waste, and improving market quality. At the same time, this research opens ways for new opportunities within the nutritional industry, aligning with the eighth SDG, which promotes **decent work and economic growth**. The innovation of such products has the potential to create new employment opportunities and increase the demand for resources aimed at improving women's health.

This research, therefore, contributes to the well-being of women, favours innovation within supplementation industry, and promotes economic growth while keeping a focus on sustainability.

5. Introduction

Overview on stages of menopause

The menopause begins twelve months after the last menstrual period. Most women enter this phase between the ages 45 and 55 as a natural consequence of biological aging. The menopause marks the end of a woman's reproductive life as the ovarian reserve is irreversibly depleted. This means that there is a loss of the follicular function in the ovaries which cause a decrease of reproductive hormones in the blood, such as oestrogen. These changes are usually accompanied with manifestations which can greatly vary depending on the person. This period of progressive transition can be divided into different menopausal stages. Fertile women are in the premenopausal stage. The transition from fertility to menopause is called perimenopause and is characterized by irregular menstrual cycles and presence of some manifestations. Perimenopause can last from a few months to a decade, although the average is around three to four years. A woman reaches the menopause one year after her last menstrual cycle. Lastly, five years after the last menstrual cycle, women enter postmenopause. Manifestations throughout the different stages typically include hot flushes, mood swings, night sweats, vaginal dryness, among other manifestations (1,2,3).

Importance of addressing specific needs in menopause

With increasing life expectancy, women will spend approximately 30% of their lives in the postmenopausal phase (4). In fact, it is estimated that there will be 1.2 billion menopausal or postmenopausal women worldwide by 2030 (5). The demographic shift that is contributing to more women currently reaching the menopause makes it increasingly important to address their specific needs. Despite its prevalence, menopause is often misunderstood, under-discussed and sometimes even referred to as a disease. Normalizing conversations about the menopause and increasing public awareness can help to reduce the stigma, and research into menopausal issues can make an important contribution to the cause.

The transition to the menopause is often associated with manifestations that can affect overall well-being, highlighting the need for a holistic view of the health of the women during this period. Further in-depth studies into both the manifestations and possible interventions can contribute to a higher quality of life of women. Given the higher risk of some conditions associated with menopause, there has been increased interest in menopausal treatments, including non-hormonal therapies. More women are looking for reliable evidence to guide these therapeutic approaches, especially those who cannot or do not want to take hormone replacement therapy (HRT) (6). Thus, supplementation and dietary interventions have gained attention in recent decades, although a lack of standardization across studies has made it difficult to obtain conclusive results on their effects on menopausal symptoms. This has contributed to the uncertainty not only among patients but also among health professionals concerning efficacy and safety of these treatments.

6. Thesis objectives

As life expectancy rises, women will spend more time in the menopausal stage. This is a period of hormonal changes that impact health and nutrition. The objective of this thesis is *to examine the nutritional needs of women during menopause and how supplements can help meet these needs, including their potential limitations. Additionally, it will also evaluate current market options, focusing on the supplement CAPS fem.* This general objective has been delineated into the following specific objectives:

- Describe the basic physiology of menopause and discuss how hormonal changes affect women's nutritional needs.

- Identify the key nutrients and supplementation strategies recommended for menopausal women, assessing their effectiveness and any potential risks.

- Evaluate *CAPS fem* as a case study, comparing its composition and claimed benefits to the recommendations found in the scientific literature.

- Develop practical recommendations for improving supplement formulations and share these findings in a divulgation activity to menopausal women.

7. Research methods

In order to carry out this study, a specific in-depth search was conducted:

- Firstly, a physiological literature review was carried out to understand all the processes and systems involved in menopausal stages.
- Next, more detailed and in-depth information was obtained by reviewing relevant recently published literature in scientific journals, books, professional guidelines, public health reports, among other sources from the past ten years (2014-2024). The search was further refined by including studies that referenced menopausal stages, supplementation and nutrient deficiency, along with those conducted on both animals and humans. The consulted data bases included: PubMed, Scopus, Embase, Cochrane library, Medline, Google Scholar, among others. The search was filtered using specific terms.
- In relation to *CAPS fem*, an analysis of the product was carried out, examining its formulation, potential limitations, and any other related issues.
- Concurrently, a survey was conducted among the demographic target to ascertain user perspectives on supplements and dietary intervention for the menopausal stages.

8. Physiology and hormonal changes in menopause

a. Detailed hormonal and physiological changes. Hormonal balance and regulation of the menstrual cycle and menopause.

The beginning of the menopausal transition occurs between 40-50 years of age, with the gradual depletion of the follicle reserve from the ovaries. As a result, the ovaries are less sensitive to hormonal stimulation. Oestrogen production decreases even though there is abundant secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the adenohypophysis (7). This indicates that the interruption of these cycles is not due to the hypophysis disfunction but because the ovaries stop responding to gonadotropins. As a negative feedback, gonadotropin levels peak as an attempt to stimulate the maturation of more follicles in the ovaries (8). Some manifestations have been observed to align with gonadotropin releasing hormone (GnRH) release peaks. Manifestations can include hot flushes, abundant sweating, headaches, hair loss, muscle pain, vaginal dryness, insomnia, depression, weight gain, and mood changes. These manifestations might appear already during perimenopause, when women start having irregular cycles prior to the menopause until they finally cease. Additionally, during postmenopause there might be atrophy of the ovaries, the fallopian tubes, the uterus, the vagina, the breasts and the external genitals (7).

To better understand the hormonal changes that occur during the menopause and the hormonal pathways involved, it is important to understand the process that takes place during the menstrual cycle.

In the menstrual cycle during a woman's reproductive stage, hormones secreted by the hypothalamus, the anterior pituitary gland and the ovaries modulate the main events. The menstrual cycle can be divided into four phases: menstrual phase, preovulatory phase or follicular phase, ovulation, and postovulatory phase. During the menstrual phase, FSH allows primordial follicles to develop into primary and secondary follicles. The decrease of progesterone levels leads to shedding of the endometrium which results in menstrual bleeding. During the following preovulatory phase, secondary follicles secrete oestrogens and inhibin. After some days, the dominant follicle will continue secreting oestrogens and inhibin which will decrease FSH secretion. This will cause the rest of the follicles to stop developing. The dominant follicle will develop to become a mature Graaf follicle, and its granulosa cells will increase oestrogen production. High oestrogen levels will have positive feedback on the hypothalamus and anterior pituitary, increasing LH secretion. Not only high levels of oestrogen cause positive feedback on cells that secrete LH but also GnRH, leading to ovulation. Ovulation coincides with peak oestrogen and LH levels. In the postovulatory phase, the follicle turns into the luteal body which secretes progesterone, oestrogen, relaxin and inhibin. As days pass and secretion of oestrogens, progesterone, and inhibin decrease, GnRH, FSH and LH increase. This is because the negative feedback is over, causing the start of a new cycle. Fluctuations of hormones throughout the cycle can be sequentially observed in Figure 1 and 2.

In the menstrual cycle, hormones have different roles. Oestrogens increase protein anabolism and lower blood cholesterol, among many other actions that will be discussed further. But regarding direct effects on the reproductive tract and the menstrual cycle, they stimulate proliferation of the basal layer to form a new functional layer after menstruation. They additionally promote the development and maintenance of female reproductive structures and secondary sexual characteristics. Progesterone stimulates endometrial glands to secrete glycogen and lipids as food source for the fertilized ovule before and during implantation if it occurs. High concentrations of progesterone inhibit the GnRH secretion. Inhibin inhibits FSH and, to a lesser extent, LH (7). Some of this hormone regulation can be observed in Figure 3.

Before menopause, there is a gradual loss of oocytes over time, which occurs through a combination of ovulation and atresia. Ovulation refers to the release of an ovule from an ovary during the menstrual cycle (1). Atresia is the physiological aging process in which a follicle fails to develop properly, inhibiting ovulation. The lower number of oocytes results in a reduction of inhibin B secretion, and therefore, there is a less negative feedback of inhibin B on FSH. Consequently, there is an increase in FSH levels, which leads to increased follicular recruitment and accelerated follicular loss, while oestradiol levels remain stable during the

early menopausal transition. Finally, exhaustion of follicles, ovarian inability to respond to high levels of FSH and declined oestrogen levels results in loss of reproductive cycle, hence, loss of reproduction capacity (4).

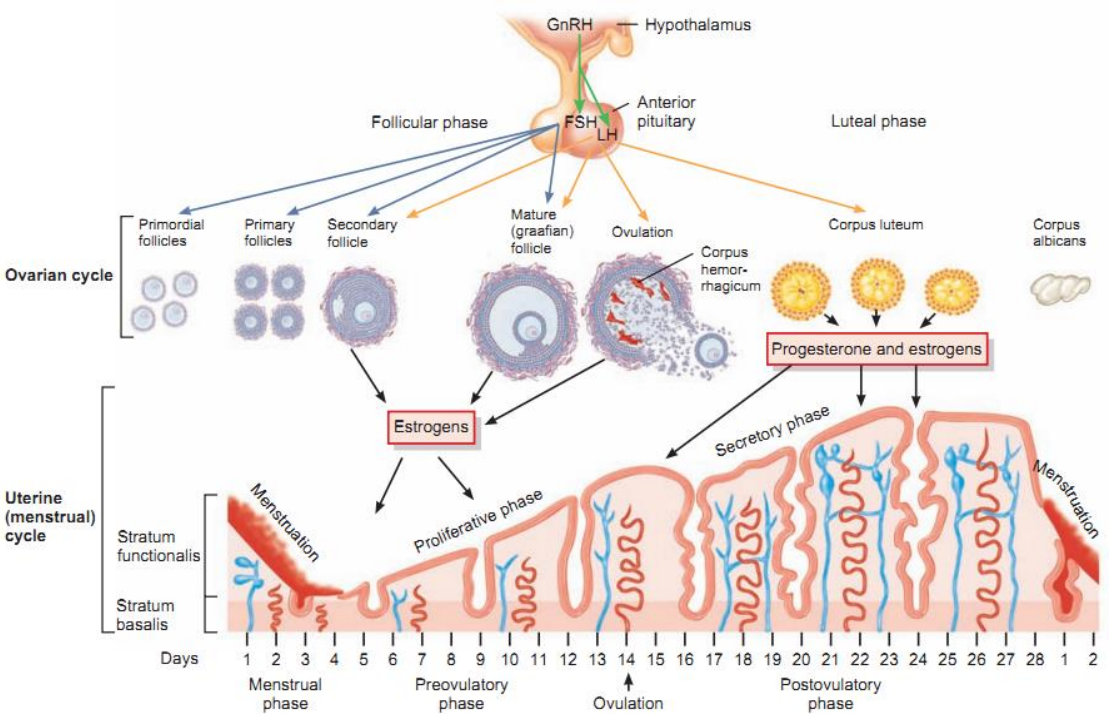

Figure 1. Schematic illustration of the ovarian and uterine cycles, representing the release of hormones and the physiological events during a typical female reproductive cycle. The anterior pituitary secretes gonadotropins, FSH and LH, which regulate ovarian follicle development and ovulation. At the same time, these hormones influence the endometrial lining of the uterus, preparing it for potential implantation. In the absence of fertilization or implantation, the cycle culminates in menstruation, indicating the start of a new cycle (7). GnRH (gonadotropin releasing hormone), FSH (follicle stimulating hormone), LH (luteinizing hormone).

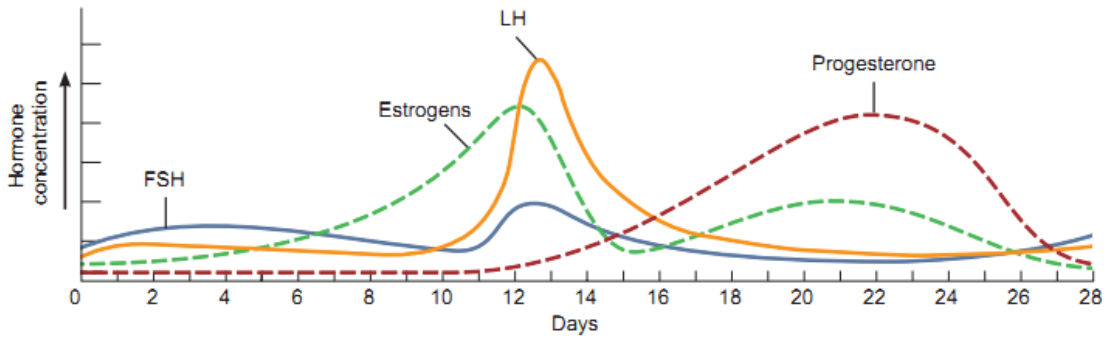

Figure 2. Graphical representation of the relative concentrations of anterior pituitary hormones, FSH and LH, and ovarian hormones, oestrogens and progesterone, throughout the phases of one normal female reproductive cycle. This figure exposes the dynamic interplay between these hormones, with FSH and LH regulating follicular development and ovulation, while oestrogens and progesterone prepare the endometrium for implantation (7). FSH (follicle stimulating hormone), LH (luteinizing hormone).

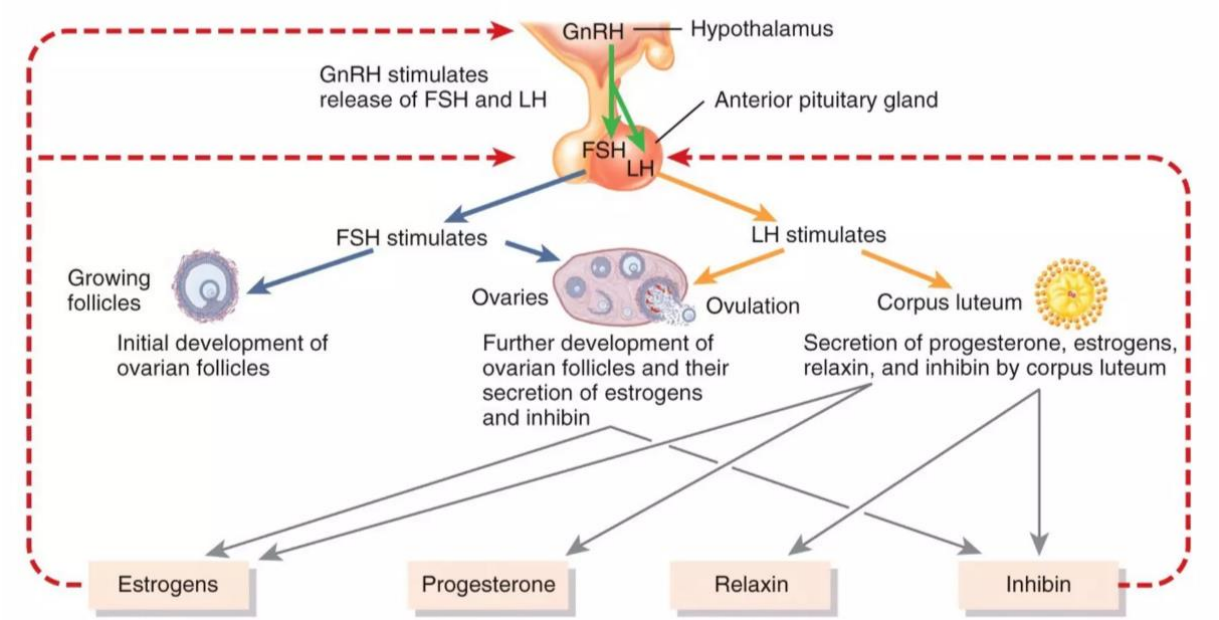

Figure 3. Illustration of the hormonal regulation of female reproductive function, highlighting the interactions between the hypothalamus, anterior pituitary gland, and ovarian hormones, including oestrogens, progesterone, relaxin, and inhibin. This scheme shows the hypothalamic-pituitary-gonadal axis, indicating the secretion of GnRH from the hypothalamus, stimulating the anterior pituitary to release FSH and LH, which will lead to the production of oestrogens and progesterone. Relaxin, produced by the corpus luteum, and inhibin, secreted by the ovaries, inhibit FSH and LH secretion through negative feedback mechanisms, to maintain hormonal balance (7). FSH (follicle secreting hormone), GnRH (gonadotropin realising hormone), LH (luteinizing hormone).

During the menstruation, there are changes in a wide range of hormones. As previously mentioned, oestrogen levels present an abrupt and notable decline, causing an extensive number of manifestations. Progesterone, the second main female sex hormone, also decreases during the menopausal stages. The concentration of androgens, the male sex hormones produced also by women, gradually decreases over the years. This means that the oestrogen-androgen balance is altered, showing a relative increase of androgen levels. This does not imply that androgen levels are increasing, but that the loss of oestrogen is more pronounced. Cortisol can appear elevated throughout the menopausal stages, contributing to menopausal manifestations.

The menopausal transition occurs over progressive changes with reference to hormonal activity, despite the previous definition of the stages of premenopause, perimenopause, menopause and postmenopause. At the start of the progression, there is a compensated follicle failure. Initial hormonal adjustments are clinically silent, as compensatory mechanisms try to maintain regular cycles and potential fertility despite already facing follicular loss. Follicular loss is first compensated by a decrease in anti-müllerian hormone (AMH) and inhibin B, and an increase in FSH. Subsequently, the significant decline in the number of follicles results in the first noticeable changes in the woman's menstrual cycle patterns, either in less regular cycles or in the omission of a whole cycle and resuming after to the previous pattern. The advanced phase of progression occurs with uncompensated follicle failure. This means there are longer interval between periods (>60 days) and eventually more uniform

hypoestrogenic and hypergonadotropic patterns. This occurs during an intermittent uncompensated phase, until finally follicle exhaustion is reached at menopause.

During the menopausal transition, each woman may experience different cycle patterns, which are characterized by irregularities in the menstrual cycle. Five possible patterns have been identified.

1) Firstly, a cycle pattern known as luteal-out-of-phase cycle (LOOP). This cycle consists of follicles being recruited during the luteal phase and reaching maturation at the time of menstruation, leading to a rapid and premature second ovulation. These LOOP events are related to higher luteal oestradiol, and rapid and successive fluctuations of progesterone (9).

2) Some other women have menstrual cycles with hormonal cycle patterns that resemble those of younger, fertile women until the end of their reproductive life. In these cases, the last menstruation is characterised by a decrease of progesterone, an erratic excretion of oestradiol and, finally, an increase in gonadotropin levels as the ovaries deplete their oocyte reserve.

3) Another pattern consists of cycles lacking enough progesterone due to irregular or incomplete ovulation. This pattern is referred to as non-luteal activity cycle. It usually appear in the last three years before menopause and is associated with greater variability in cycle length but not in bleeding duration (10).

4) Another cycle pattern has been classified as evidence of luteal-activity cycle. This pattern indicates there is still ovulatory activity, showed by the presence of a metabolite of progesterone, pregnanediol.

5) Lastly, another possible pattern during transition is cycles with no evidence of luteal activity, which usually do not show ovulation and do not include a clear oestrogen rise compared to ovulatory cycles (9).

<u>b. Hormonal influence on nutrient absorption and molecular pathways.</u>

i. Changes in metabolic pathways and energy balance regulation.

Oestradiol participates in the regulation of fatty acid metabolism by increasing enzymes involved in β-oxidation and lipolysis. However, during menopause, the genes responsible for β-oxidation enzymes decrease, reducing the body's ability to use free fatty acids as fuel. At the same time, the expression of genes related to fat accumulation increases, leading to an increase in adipogenesis. As a result of all of this, catabolism of ATP through β-oxidation decreases and lipid synthesis increases. This clearly alters lipid metabolism and changes energy metabolism potentially leading to weight gain, metabolic disorder and obesity (11, 12). In addition to the decreased level of circulating oestrogen, the lower ratio of oestrogen

to androgen levels may further lead to lipid metabolism dysregulation. This imbalance affects body fat mass, fatty acid metabolism, fat-free mass, basal metabolic ratio, adiposity and other energy-related processes (13). Moreover, changes in oestrogen – together with androgens to a lesser extent – modify receptor activity, thus influencing overall metabolic function (14).

Additionally, there is a likelihood of alteration in circulating lipids, such as lipoproteins, apolipoproteins, low-density lipoproteins (LDL), high-density lipoproteins (HDL) and triacylglycerol (TG). These changes can influence excessive synthesis of fatty acids, adipocytokines, proinflammatory cytokines, reactive oxygen species, among others. In the absence of adequate regulation, these elements can contribute to the development of insulin resistance, abdominal adiposity, and dyslipidaemia (13,15). In this regard, before the menopausal transition, low-density lipoprotein cholesterol (LDL-C) acts as a substrate for ovarian oestradiol production. However, in menopause LDL-C cannot be used for oestrogen synthesis, and therefore its level increases in the blood, raising the risk of cardiovascular disease (16). The Study of Women's Health Across the Nation (SWAN), a widely recognized longitudinal epidemiologic study, revealed that levels of cholesterol, LDL, triglycerides, and lipoprotein peaked during the menopausal transition. Women with higher oestradiol levels showed lower concentration of LDL and cholesterol, while those women with lower FSH levels showed higher amount of LDL-C and cholesterol. Conversely, HDL-C levels increase progressively from premenopause to late postmenopause (17).

There are two types of oestrogen receptors: alfa and beta. The α-oestrogen receptor (ERα) is found in the central nervous system, endometrium, breasts and liver. The β-oestrogen receptor (ERβ) is found in bones, vascular wall, urogenital tract and central nervous system. ERα regulates adipose tissue cells activity and distribution of fat, modulating oestrogenic effects on metabolism. Lack of ERα in ovariectomized mice has been shown to cause almost doubling adipocytes, insulin resistance, hyperlipidaemia and glucose intolerance (13).

ii. Changes in body composition and energy expenditure.

As explained above, the hormonal changes can alter lipid metabolism and lead to changes in body shape through different mechanisms. During menopause, decreased oestrogens and its imbalance with androgens have been associated to body composition changes, including muscle loss and greater abdominal obesity. Decreased oestrogen levels promote an increase in bone marrow-derived adipocytes, which increase visceral fat in postmenopausal women. Additionally, higher lipoprotein lipase activity in visceral adipose tissue elevates the production of free fatty acids, which can cause insulin resistance and metabolic disorders.

At the same time, loss of skeletal muscle reduces the basal metabolic rate (BMR), since skeletal muscle has a metabolic rate over three times higher than that of adipose tissue (11, 18). Moreover, a more sedentary lifestyle and a lower physical activity energy expenditure

has been associated with women during the menopausal stages, which further decreases overall energy expenditure and exacerbates weight gain (19).

Oestradiol, the predominant oestrogen in the human body, greatly influences energy balance by regulating mitochondria function and bioenergetics (20). In animal studies, oestrogens deficiency has been associated with reduced oxygen consumption and energy expenditure leading to weight gain through increased body fat. In contrast, oestradiol supplementation caused an increase in oxygen consumption and energy expenditure, leading to higher insulin sensitivity (18). Beyond these systemic effects, oestrogen facilitates insulin secretion and control of glucose availability, modulates energy substrate selection (favouring lipids if more available than carbohydrates) and provides antioxidant protection (21). In consequence, the lack of oestrogens in menopause, is clearly associated with weight gain, metabolic imbalances and increased oxidative stress.

Some of the most relevant adipokines for the regulation of energy balance include leptin, adiponectin, resistin, and ghrelin. During menopause, leptin and resistin levels increase, while adiponectin and ghrelin levels decrease. These changes are associated with insulin resistance, which contributes to a higher risk for postmenopausal dyslipidaemia (13). Furthermore, these variations in adipokines will influence hunger and satiety cues. In combination with decreased energy expenditure due to loss of lean body mass, a sedentary lifestyle, and risk factors such as smoking, diabetes mellitus, or metabolic syndrome, this increases the risk of menopausal obesity (13).

At the neurological level, oestradiol can modulate hypothalamic regions that control both feeding behaviour and brown adipose tissue (BAT)-mediated thermogenesis (22). Oestradiol can activate anorexigenic POMC neurons, which increase insulin sensitivity, while simultaneous inhibition of orexigenic NPY/AgRP neurons reduces hunger signals. These actions have a direct effect on energy homeostasis through cell-specific rapid physiological responses (23). This might suggest that this pathway might be a therapeutic opportunity for obesity and metabolic disorders.

Moreover, central action of oestradiol inhibits AMPK (AMP-activated protein kinase) in the ventromedial nucleus of the hypothalamus, activating BAT thermogenesis and increasing energy expenditure, leading to weight loss. Therefore, disruption of these pathways, as observed with low oestrogen levels, may therefore favour positive energy balance and adiposity, underlining the importance of oestrogen in maintaining metabolic stability during menopause (24).

iii. Changes in gut health, alterations in gut microbiota and gastrointestinal function.

During the menstrual cycle, hormonal fluctuations can affect composition and function of human microbiome (25), as both oestrogen and progesterone influence the gut microbiome

(26). In fact, these influences are bidirectional, as bacteria can metabolize sex hormones through different enzymes, such as hydroxysteroid dehydrogenase, regulating the balance between inactive and active steroids. Faecal bacteria carry out hydrolysis, reductions and oxidation on androgens and oestrogens through β-glucuronidase, which is secreted by the gut microbiome (26, 27).

High oestrogen levels correlate with increased microbiota diversity, characterised by a predominance of beneficial bacteria and inhibition of harmful ones (28). During the menopause, the progressive decline in oestrogen levels is associated with a lower number of microbial species (29). Early in perimenopause, there is a decrease in beneficial bacteria such as *Lactobacillus* and *Bifidobacteria,* while potential harmful bacteria such as *Enterobacter* increases (28). As menopause progresses into postmenopause, the gut microbiota shifts towards a profile more similar to that of men of the same age (30). This dysbiosis can also decrease circulating oestrogen, in part through impaired β-glucuronidase activity (26). Such changes in the gut microbiome during menopause have been associated with higher risks of obesity (31), including differences in specific populations as *Bifidobacterium animalis* (32).

c. How these hormonal fluctuations translate into manifestations.

The manifestations identified during the menopausal stages have been classified as follows: vasomotor symptoms, changes in weight and body composition, psychological manifestations, sleep disturbances, joint pain, skin changes, and urogenital symptoms. These manifestations can vary in terms of intensity, frequency and nature.

Vasomotor symptoms, such as hot flushes and night sweats, are the main menopausal symptoms which occur due to erratic hormone fluctuation, mainly of oestrogen (9, 33). These symptoms can last from less than five minutes to as long as half an hour and can be triggered by stress, warm environments, hot food or drinks. Evidence suggests that decreased oestrogen concentration alter endorphin levels in the hypothalamus, narrowing the normal thermoregulatory zone and lowering the threshold of temperature for vasodilatation and sweating. As a result, the body is more likely to trigger hot flushes during the menopause. Studies on treatment of vasomotor symptoms have shown a very strong placebo effect. This should indicate the relevance of placebo-controlled randomized trials to assess efficacy of any treatment. In addition, lifestyle factors may influence the frequency of these symptoms, as smoking has been associated with an increased incidence of vasomotor symptoms (4).

Changes in body weight and composition were discussed in detail in the previous section, 8b “Hormonal influence on nutrient absorption and molecular pathways”.

Menopausal women often experience depression, anxiety and cognitive changes. Fluctuating oestrogen levels, together with changes in FSH, are associated with more severe mood disturbances and an increased risk of major depression. Oestrogen exerts antidepressant

effects by regulating the synthesis, metabolism and receptor activity of serotonin (5-HT) and norepinephrine (NE). As a result, declining levels of oestrogen can adversely affect mood (34). In addition, many women report memory problems and age-related cognitive decline. Research suggest that oestrogen decline reduces spine density and impairs synaptic connectivity. Oestrogen depletion also alters neurotransmitter regulation for acetylcholine, dopamine and serotonin pathways, potentially affecting both memory and mood. Additionally, oestrogen reduces oxidative stress and improves mitochondrial energy production, therefore its deficiency can increase neural vulnerability and increase the risk of neurodegeneration (35). Other results on meta-analyses show that postmenopausal women perform worse on test of verbal memory and executive function than premenopausal women (35). Nevertheless, these effects can vary highly among women, without knowing the origin of such variability, which shows the complexity of the mechanisms involved.

Sleep disturbance and poor-quality sleep are often associated with vasomotor symptoms. However, hormonal fluctuations have been related to sleep disturbances independently of vasomotor symptoms. Better sleep in the periovulatory phase was associated with higher hormone stability. Additionally, difficulty falling asleep and night-time awakenings have been associated with lower oestradiol, and higher levels of rapidly increasing FSH (36, 37).

After menopause, the decline in oestrogen levels promotes bone mineral density loss by enhancing osteoclast resorption that exceeds osteoblast bone formation. Ageing of bone tissue occurs because of two main reasons: loss of bone mass and fragility. Loss of bone mass is the result of demineralization, loss of calcium and other minerals from the osteoid matrix. It starts after the age of 30, it accelerates at around 45 as oestrogen levels fall, and continues until there is a 30% loss of calcium at the age of 70. Loss of bone mass also causes deformities, pain, decrease in height and tooth loss. Fragility is due to reduced protein synthesis, particularly collagen, which contributes to the tensile strength of bone. The reduction in tensile strength weakens the bone and exposes it to potential fractures. Risk factors for osteoporosis include family history of the condition, European or Asian ancestry, sedentary lifestyle, smoking, diet low on calcium and vitamin D, more than two daily instances of alcohol consumption and some medication.

Skin and mucosal changes during menopause include thinning and atrophy, dryness and pruritus, wrinkles, sagging, reduced vascularity and poor wound healing. These manifestations differ from malignant lesions or skin aging mainly due to environmental factors, such as sun exposure. Additionally, women might experience hair changes such as reduced scalp hair density, altered hair structure and quality, and increased unwanted facial hair (38). Oestrogen receptors are widely distributed in dermis and epidermis, especially in the genital region, face and lower limbs (39). Oestrogen deficiency impairs the skin barrier, causing dryness due to reduced skin moisture and diminished sebum production; as well as reduced antioxidant function and weakened wound healing (40). There is also a reduction in

the synthesis of elastin and collagen which causes wrinkling and thinning of skin and genital mucosa. Reduced hydration and skin turgescence are observed due to decreased hyaluronic acid in the extracellular matrix (38).

Urogenital symptoms are also common after the menopause, specifically vulvovaginal changes. When oestrogens levels decline, the lining of the vagina thins and turns dry and pale, while the tissue becomes less elastic, narrow and shorten. Brownish or yellow discharge can be a sign of atrophic vaginitis. A higher pH (>5) is usually seen due to a shift in vaginal bacteria, with less acid-producing bacilli. All these changes can result in vaginal symptoms (dryness, itching, irritation, discharge, dyspareunia) and urinary symptoms (frequency, burning, dysuria, recurrent urinary tract infections, nocturia). All these issues can have a negative impact on quality of life and sexual function (4).

Theoretically, there is not such a marked reduction in libido due to suprarenal sexual steroids, as these can lead to the formation of oestrogen after the menopause (7). Nevertheless, the presence of other manifestations, such as psychological or vulvovaginal symptoms, may reduce libido.

Perimenopausal women also show a greater sensitivity to pain and a higher risk of pain disorders such as headache and musculoskeletal pain. Rapid changes in oestrogen levels have been linked to more frequent migraine attacks, particularly in women who already have a faster oestrogen post-luteal decline (9, 41).

9. Nutritional and plant-based interventions in menopause

As previously explained, the postmenopausal state is characterised by changes in body composition, fasting and postprandial metabolic status, diet and sleep patterns, leading to downstream systemic effects such as inflammation, oxidative stress, and increased risk of diabetes and cardiovascular disease (42). The adoption of specific lifestyle behaviours, including dietary interventions, can help to reduce these health risks and menopausal manifestations, improving quality of life (43,44).

Key lifestyle recommendations during the menopausal stages include maintaining a balanced diet, engaging in regular physical activity, and avoiding both smoking and excessive alcohol consumption. Maintaining a healthy body composition - ensuring an appropriate ratio of fat mass to skeletal muscle mass - is also crucial. Supplementation under professional supervision should be considered, taking into account individual food intake, seasonal variations, and any pre-existing diseases (43).

The Mediterranean diet is a good example of a healthy dietary pattern, concerning content and frequency of food groups, since it has been associated with improved vasomotor symptoms, along with numerous benefits in overall health (45). These benefits are attributed

to higher intakes of complex carbohydrates, dietary fibre, minerals, vitamins, phytochemicals, and polyunsaturated fatty acids, which have the potential to reduce inflammation and to promote a more diverse microbiome (42). Nevertheless, it should be noted that these dietary recommendations are not exclusive to menopausal women, as they are often part of dietary guidelines for the general population.

A variety of compounds have been studied for their potential to selectively ameliorate menopausal manifestations. They can be taken as supplements or from food sources though the diet. The most relevant findings from the literature, which have been classified into four main groups, are included below:

a. Phytoestrogens
b. Nutrients and essential compounds
c. Herbal and plant-derived extracts

a. Phytoestrogens and hormonal modulators.

Phytoestrogens are active compounds found in some plants and seeds that act similarly to oestrogens, usually by interaction with oestrogen receptors, but with a weaker action than physiological oestrogens (13). All phytoestrogens have a similar structure to that of 17-β-oestradiol, which enables them to bind to oestrogen receptors (46), which are nuclear receptors that regulate gene transcription in oestrogen responsive-tissues (47, 48). Phytoestrogens act as antioxidants, protecting molecules from oxidative stress. They can also contribute to the regulation of protein synthesis by binding to gene sequences and mimicking hormones influencing blood chemistry. They also present other beneficial properties such as antiangiogenic, antiproliferative, and antitumoral properties. Thus, they have been associated with dietary treatment for menopause manifestations, as a non-steroidal alternative to HRT (13).

As explained previously, there are two main types of oestrogen receptors, ERα and ERβ, which are involved in different signalling pathways. ERα promotes cell growth through its signalling pathways, while ERβ promotes apoptosis and cell cycle arrest by transcriptional regulation (49). Additionally, ERβ is thought to be a safer alternative to conventional HRT because it reduces menopausal symptoms while also decreasing proliferation. On the other hand, the induction of ERα is associated with the proliferative properties of oestrogens (47, 50). Phytoestrogens interact with ERβ preferably by recruiting coactivators more efficiently to β than α (51). Phytoestrogens also have effects independent to their oestrogen receptors. They can reduce angiogenesis by inhibiting tyrosine kinase and DNA topoisomerase, reduce risk of cancer and modulate serotonergic and insulin growth like factor (IGF-1) pathways (52). They also promote antioxidant effects, activating transcription factors that induce the expression of antioxidant enzymes such as catalase, superoxide dismutase, and glutathione peroxidase

(53). Phytoestrogens also present anti-inflammatory effects through inhibition of transcription factors and reduction of pro-inflammatory mediators (54). They also affect epigenetic modifications, as observed with the isoflavone genistein, that can modulate acetylation and methylation reactions, enhancing or decreasing gene expression (51, 55).

Numerous phytoestrogens have been identified and classified into different biochemical groups, as shown in the following figure, with isoflavones, lignans, coumestans, stilbenes, and prenylflavonoids (13).

BIOCHEMICAL GROUP	PHYTOESTROGENIC COMPOUND	EXAMPLES OF FOOD SOURCES
ISOFLAVONES	Genistein, daidzein, biochanin A, puerarin, glycitein, formononetina	Soy flour, soya beans, soya drink, pulses (soya, beans), kudzu, sesame, beer, whole grains, berries, nuts.
LIGNANS	Pinoresinol, podophyllotoxin, enterodiol.	Flaxseed, sesame, soya, cruciferous vegetables, apricots, strawberries.
COUMESTANS	Coumestrol, wedelolactone, plicadin.	Alfalfa, soya bean sprouts, seeds, peas, beans.
STILBENS	Resveratrol.	Grapes (skin and seeds).
PRENYLFLAVONOIDS	Prenylnaringenin, xanthohumol, desmethylxanthohumol, isoxanthohumol.	Hops, beer.

Figure 4. Classification of phytoestrogens into four biochemical groups, with examples of phytoestrogenic compounds and food sources for each group. Adapted from (56, 57, 58).

Isoflavones represent the first and most well-known biochemical group is. They can be found in soy foods, soybeans, and legumes, among others. Soybeans and soy foods, such as tofu and miso, are particularly rich in isoflavones, which contain daidzein, genistein and glycitein. These three compounds are the main phytoestrogenic actives. According to an extensive recent review conducted in 2023, dietary soy consumption may reduce the severity and/or the frequency of vasomotor manifestations (6), and is associated with less vaginal dryness and hot flushes frequency (59). However, information on some safety concerns regarding isoflavones remains limited (59). It is generally considered safe for the menopausal population as a whole, but safety is uncertain for some specific cases, such as breast cancer patients (60).

The isoflavonoid compound daidzein has a metabolite, equol, characterized by its potent oestrogenic activity. This metabolic reaction is conducted by intestinal bacteria, so the variability in the microbiota between individuals, could lead to different responses to soy isoflavones (6). Equol intake has been associated with improved vaginal dryness, sexual problems, and cardiac disorders, contributing to a better quality of life (61). However, the

results from different studies are contradictory, with notable variation in methodology and other elements, making difficult a direct extrapolation of results (6).

Soy extract is an isoflavonoid product from *Glycine soja,* a leguminous plant that is classified within the *Fabaceae* family (62). It is very rich in protein and isoflavones such as daidzein and genistein, which are hydrolysed in the intestine by β-glucosidases resulting in higher affinity for ERβ. Daidzein is specifically metabolised by anaerobic bacteria, through reductase enzymes and dihydrodaidzein racemase, into S-equol, which has even a higher β-oestrogenic affinity than daidzein. Equol production is not homogenous as it presents genetic polymorphism, which may explain variability in its effects on menopausal symptoms. Additionally, both genistein and daidzein from soy present poor bioavailability, resulting in a modest and variable effect on symptoms (47). Soy extract can reduce the frequency of hot flushes, although studies have different conclusions regarding efficacy of treatment. Potential but minor side effects include stomach pain and diarrhea (62).

Red clover (*Trifolium pratense*) is a leguminous plant that belongs to the *Fabaceae* family. It contains different isoflavones, including formononetin and biochanin A, whose chemical structures and metabolic reactions are outlined in Figure 5 (59,63). Biochanin A and formononetin are demethylated in the intestine and liver by cytochrome P450 isozymes, resulting in genistein and daidzein, respectively, which are ERβ selective (47). Red clover has shown beneficial effects on sexual dysfunction in postmenopausal women, as well as in ameliorating vaginal dryness (59, 63). Its consumption has been shown to decrease frequency and intensity of hot flushes (60, 62), although further research is needed to confirm its effects and to ascertain the optimal dosage (6). It is also important to note that red clover may interact with other medications (62).

Kudzu (*Pueraria lobata*) is a plant from the *Fabaceae* family that has been used in traditional medicine for older women's health. Its oestrogenic properties are associated to puerarin, its major isoflavone, which is the C8-glucoside of daidzein (47). It can improve bone formation through stimulation of osteoblast differentiation, suggesting its use for prevention of postmenopausal osteoporosis. Most studies do not follow ideal clinical research practice, making their results difficult to consider (64). Nevertheless, it can be affirmed that *Pueraria lobata* possesses positive effects on cartilage and bone function (65).

Lignans are the second biochemical category of phytoestrogens, and are present in wholegrains, flaxseeds, fruits and vegetables. Lignans possess antioxidant and anti-inflammatory properties, and have been shown to inhibit inflammatory pathways, contribute to lipid lowering, and participate in oestrogen receptor pathways. Moreover, lignans possess therapeutic potential for various menopausal manifestations including psychological disorders and osteoporosis (54). However, the evidence found in the bibliography for

randomised controlled trials is mostly limited to flaxseeds and it does not conclude proven effectiveness in vasomotor manifestation alleviation (6, 54).

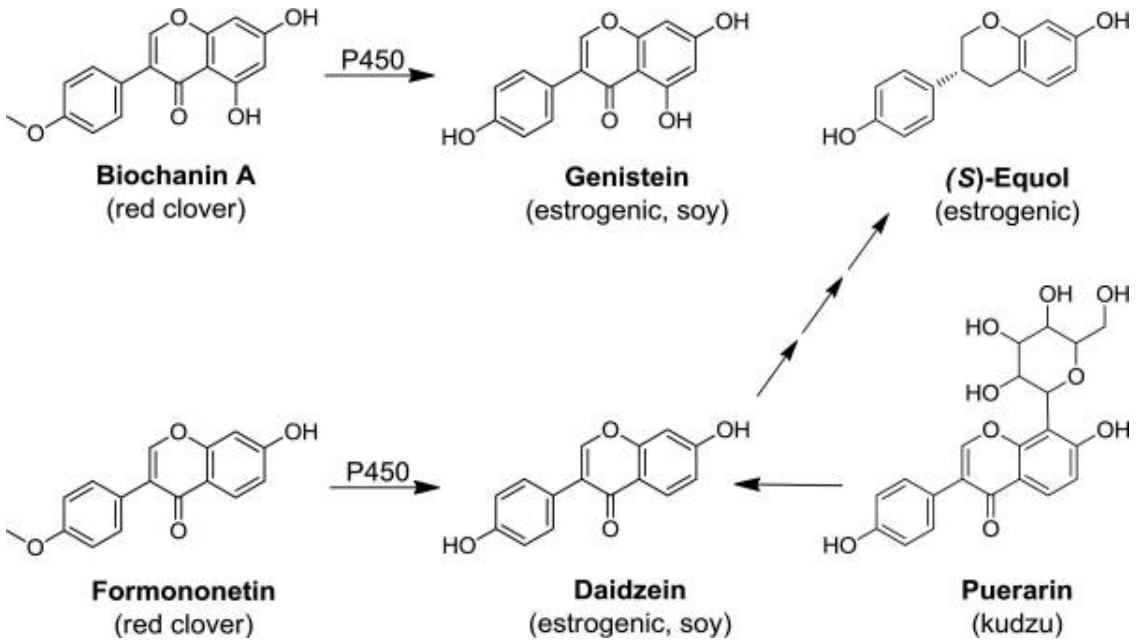

Figure 5. The scheme illustrates the chemical structures of isoflavones found in red clover (biochanin A and formononetin) and soy (genistein and daidzein), highlighting their transformation via cytochrome P450 enzymes into active oestrogenic metabolites. Daidzein is further metabolized by intestinal microbiota into S-equol, a compound with notable oestrogenic activity. Puerarin from kudzu is also included to demonstrate interconversion and its potential oestrogenic effects. Soy contains higher concentrations of genistein and daidzein, its primary isoflavones, compared to red clover (47).

The third biochemical category within the classification of phytoestrogens is coumestans. *Medicago sativa*, commonly known as alfalfa, contains coumestrol, but it is also rich in saponins, which contribute to the lipidic profile. Alfalfa has been reported to be effective against hot flushes, but it is important to note that consumption of alfalfa has been associated with potential infection by *Salmonella*, *Escherichia coli* and *Listeria,* leading to hypokalaemia and digestive disorders (62).

Resveratrol, a polyphenolic compound with phytoestrogenic properties, is the main compound of the fourth biochemical category, the stilbenes group. It is found in grapes, berries and nuts (66). The main effect of resveratrol is the activation of endothelial oestrogen receptors, as well as increasing nitric oxide production and enhancing endothelial vasodilation (67). These actions further involve cardiovascular, cognitive and bone function. In relation to cognitive function, resveratrol can enhance cognitive performance and improve the efficiency of neurovascular activity. Long-term supplementation might mitigate the cognitive deterioration associated with menopause and ageing, although further research is required in this context (67). Regarding bone function, resveratrol supplementation can ameliorate bone mineral density in the lumbar spine and femoral neck of postmenopausal women. In summary, resveratrol has shown potential benefits in the prevention of osteoporosis, due to enhanced bone microcirculation through improved cardiovascular reactivity. However,

additional clinical randomized controlled trials are needed to further investigate this subject (66).

The fifth and final category of phytoestrogens is the prenylflavonoids. *Asparagus racemosus,* commonly known as shatavari, is a medicinal plant used in traditional Indian medicine. Recent studies have shown that Shatavari supplementation enhances musculoskeletal performance in postmenopausal women, improving handgrip strength and increasing myosin contractility, through phosphorylation of the myosin regulatory light chain (68). However, this study remarks further research on the application of shatavari in this field and on oestrogenic compounds that might modulate these effects (68). Another study showed how shatavari can have a significant effect over placebo in reduction of night sweats, hot flushes, anxiety, nervousness and vaginal dryness. It also showed safe use and no major significant adverse effects (69). Nevertheless, this study acknowledges its limitations of sample size, diversity, and symptom-hormone variability (69).

Hops extract originates from *Humulus lupulus* and belongs to the prenylflavonoids due to its content in 8-prenylnaringenin, a strong prenylated flavonoid capable of reducing LH and FSH. This phytoestrogen acts as a ligand and can bind to ERα and ERβ, acting as a full agonist of ERα. In addition, 8-prenylnaringenin inhibits aromatase, which can contribute to protection from oestrogen dependant carcinogenesis. It can also stimulate alkaline phosphatase activity causing positive effects for bone mineralization. Additionally, it can influence the upregulation of mRNA for progesterone receptors (47, 59, 70). Hop compounds can inhibit various P450 enzymes, therefore, the use of medication should be carefully considered prior to supplementation (70).

b. Nutrients and essential compounds.

It is important to note that the following discussion will not focus on general dietary guidelines for the elderly population, but will directly assesses specific nutrients and essential compounds that have been shown to have an effect during the menopausal stages. The majority of western dietary guidelines for menopausal women found in the literature are based on the Mediterranean diet, with few adaptations.

The dietary indications for menopausal women emphasise the consumption of vegetables, fruits, legumes and wholegrain starch, the consumption of high-quality fats (omega 3-6-9), the incorporation of phytoestrogenic food products, sufficient protein intake (higher than before), reduction of caffeine, the increase in fibre intake, the coverage of vitamin B12, vitamin D and calcium levels, and adequate fluid intake for hydration. It is imperative to adapt these dietary recommendations to specific energy needs of individual women, taking into account their level of physical activity and lifestyle. Furthermore, research has identified various specific nutrients and essential compounds that have a significant impact on health

of menopausal women. These compounds are frequently included in dietary supplements or fortified foods.

Vitamin D is an essential micronutrient that performs a wide-range of effects through its receptors, which are located throughout the body. In menopausal women, the supplementation of vitamin D has been shown to help maintain bone density and prevent fractures, thus providing a valuable protection against osteoporosis and musculoskeletal pain (71). Its primary function is to regulate the balance of phosphorus and calcium in the blood, mobilising calcium from skeleton, digestive tract, and kidney when blood levels of calcium are insufficient (13). However, vitamin D acts on multiple systems in addition to those responsible for calcium and phosphate metabolism. The long-term effects of vitamin D deficiency have been associated with weight gain and alterations in body composition, both of which are typical features in the menopause. Another aspect is the potential of vitamin D to reduce the progression to type two diabetes mellitus, considering the decreased insulin action and sensitivity observed during menopause (72). Vitamin D has also been associated with positive effects on cognition and memory, which may reduce the cognitive decline and mood disorders associated with menopause (72). Vitamin D is also related to depression mechanisms due to its metabolic pathways. However, results from randomized control trials are inconsistent and the advantages during menopause remain uncertain (6).

Omega-3 fatty acids possess anti-inflammatory properties, cardioprotective functions, and insulin-sensitising effects. Specifically, eicosapentaenoic acids and docosahexaenoic acids are notable omega-3 fatty acids that have shown these beneficial effects. Alpha-linolenic acid, an omega-3 polyunsaturated fatty acid, is a precursor for eicosapentaenoic and docosahexaenoic acids, although its conversion in the human body is limited and inefficient. These specific omega-3 fatty acids cannot be synthesized by the human body, making them essential fatty acids that must be obtained through the diet (73). Therefore, their supplementation through the diet is highly beneficial. Sources of omega 3 include oily fishes or fish oils, plant-based oils (canola, flaxseed, soybean, walnut, wheat germ; liquid or soft margarine made from canola or soybean oil), nuts, seeds (flaxseeds, soybeans), and human milk (13).

Linoleic acid is a type of polyunsaturated fatty acid, which is part of the omega-6 fatty acids. It can be transformed into other omega-6 fatty acids, including arachidonic acid, prostaglandins, leukotrienes, and thromboxane. Omega-6 fatty acids are beneficial, but excessive consumption may exhibit pro-inflammatory properties and increase risk of cardiometabolic disorders and cancer (74). Thus, supplementation of a low omega-6/omega-3 fatty acids ratio is recommended and can lead towards prevention of inflammation, cardiovascular disease and cancer (73). Omega-6 fatty acids are found in nuts, and seeds such as poppy seeds, sesame seeds, flax seeds, vegetable and seed oils (corn, cottonseed, safflower, sesame, soybean, and sunflower), and poultry fat (75).

Coenzyme Q10, also known as ubiquinone or ubiquinol, is a compound that plays a critical role in cellular energy production. Its synthesis also decreases with age, as well as its absorption through the diet. Coenzyme Q10 intervention can ameliorate oxidative stress and mitochondrial dysfunctions, therefore enhancing cognitive performance. R. Sandhir et al. (76) suggested that cognitive decline during postmenopause is associated with mitochondrial dysfunction and higher oxidative stress, thus coenzyme Q10 may be used for prevention of cognitive decline in postmenopausal women. However, there was insufficient literature regarding coenzyme Q10 use during menopausal stages (76).

Creatine is an important compound that helps to balance cellular energy and its production. It is important for physical performance, muscle mass and strength (77). Creatine shows promise in improving the bone and muscle loss during and after menopause (78).

B vitamins such as vitamin B12 or folate have been shown both positive and negative results regarding improvement of depressive manifestations in menopausal women. Nevertheless, they are still beneficial in overall health (6).

c. Herbal and plant-derived extracts.

Black cohosh (*Cimicifuga racemosa*) is a plant that contains a variety of bioactive compounds: triterpene glycosides, such as actein and cimicifugoside, fatty acids, resins, caffeine, isoferulic acids and isoflavones. It has traditionally been used to treat menopausal symptoms (6). Its triterpene glycosides bind to oestrogen receptors and supress LH secretion in a selective manner, without altering FSH (62). Another mechanism of action has been attributed to the serotonergic system, similar to the action of antidepressants, due to an identified compound that acts as a serotonin receptor agonist (47). However, most randomized control trials are biased due to their methodology, study design and limited information (6, 79), so the results need to be interpreted with caution. NICE guidelines underline the limited evidence concerning formulation, duration, safety and dose of black cohosh formulations, as well as drug interaction (80). Some side effects of black cohosh that can be observed include nausea and vomiting, and inflammation of the stomach lining (62).

St. John's Wort (*Hypericum perforatum*) is a plant known for its antidepressive action. It has been associated with treatment of depression, anxiety, mental complications, lowered libido, vaginal dryness, and urinary problems during menopause (62). However, it remains controversial due to uncertainness of appropriate dosage, persistence of effect, serious drug interaction and variable formulation. Although it has been shown to have some positive effects, NICE guidelines advise against it because of the previous reasons (6). Side effects include gastrointestinal discomfort, sensitivity to light, fatigue and restlessness (62).

Rhodiola Rosea, commonly known as golden root, has been part of the Georgian and Siberian medicinal culture, used as a fertility enhancer. It contains phenylpropanoid glycoside as an

active compound, named salidroside. Its administration has been shown to have beneficial effects on cognitive functions, mental health, cardiovascular function and also has anti-carcinogenic effects (81, 82). *Rhodiola Rosea* improve cardiovascular health via oestrogen-related mechanisms, protecting against oxidative stress, reducing inflammation and maintaining endothelial functions (81). *Rhodiola Rosea* has also been associated with menopause related bone symptomatology. All of this suggests promising alternatives for menopause through *Rhodiola Rosea* in combination with other bioactive compounds. However, studies on *Rhodiola Rosea* extracts have been questioned in some cases due to methodology. Nevertheless, the risk benefit ratio has been considered favourable by the European Medicine Agency since 2012 (81). *Rhodiola rosea* is generally well-tolerated, however, it can cause overstimulation when combined with large amounts of caffeine or other strong stimulants which could result in tachycardia. Doses above 800 mg/day may produce anti-platelet effects. Drug interaction needs further investigation, since *in vitro* studies suggest possible interactions with CYP450 enzymes, human studies have not confirmed these findings, probably due to differences in oral administration, bioavailability and metabolism (81).

Maca (*Lepidium meyenii* and *Lepidium peruvianum*) is a cruciferous root vegetable that can influence the hypothalamus-pituitary axis. It contains macamides and macaenes and glucosinolates, which could help mitigate menopause symptomatology and improve overall health during this phase. However, clinical trials and studies regarding maca use for menopausal stages show inconsistent results. Some studies claim highly significant reduction of hot flushes and night sweats, depression, anxiety, sleep quality, whereas other fewer studies reveal no significance between maca and placebo (83). Nevertheless, all these results expose the importance of further knowledge on maca to obtain valid clinical results**.**

Saffron extract, obtained from the stigmas of *Crocus sativus* flowers, has been associated with enhanced mood in menopausal women. Its mechanisms potentially involve modulation of neurotransmitter activity, the hypothalamic-pituitary-adrenal axis, inflammation, mitochondrial function, oxidative stress and neuroplasticity (84). Alterations of these systems have been identified in both anxiety and depression (85). Studies suggest saffron extract can alleviate psychological symptoms, although further research is required to confirm efficacy on vasomotor and somatic symptoms (86). These results propose saffron as a promising therapeutical option during menopause for psychological manifestations (86). A smaller study stated that saffron, together with other herbs, might be associated with an improvement in perimenopausal manifestations including physical, psychological and urogenital manifestations (87). Another study concluded that saffron was effective and save for postmenopausal hot flushes and depression treatment (88). Inconsistency in results occurs due to different populations, administrations, among many other factors regarding study

methodology and design. Saffron was associated with minor digestive complaints such as flatulence and nausea (86).

Curcumin is derived from turmeric root, *Curcuma longa.* It has been shown to enhance vascular function by reducing inflammation and oxidative stress. This helps to maintain higher levels of nitric oxide, which acts as an important vasodilator among many other relevant functions. These actions support the endothelial function, arterial compliance and overall hemodynamic parameters. Given that menopausal changes predispose to cardiovascular disease, curcumin supplementation has been considered potentially beneficial for vascular health during menopause (89).

Sea buckthorn, *Hippophae rhamnoides*, has been used traditionally to treat uterine and vaginal inflammation. It is rich in vitamins (A, B1, B12, C, E, K, and P), lycopene, carotenoids, phytosterols and flavonoids (90). A study showed that sea buckthorn oil, orally administered, can ameliorate vaginal atrophy by improving vaginal epithelium in postmenopausal women. The bioactive components in sea buckthorn oil had no effect on vaginal pH or epithelial cell maturation, suggesting that it had no influence on oestrogen receptors (91). Another study proved efficacy, safety and tolerability in a gel form of sea buckthorn oil for vulvovaginal atrophy (90).

Pycnogenol, the extract of mediterranean pine bark, has been found to decrease vasomotor manifestations, improving quality of life in menopausal women (92), likely through improvements in circulation, endothelial health, and anti-inflammatory activity (93). Additionally, a study conducted in 2023, concluded that pycnogenol shows potential for treatment of hair loss in menopausal women (94). Nevertheless, further research is needed to obtain stronger conclusions regarding pycnogenol and its role in menopausal treatment (93, 94).

Valeriana officinalis is a herb that contains valerenic acid, which can inhibit gamma-aminobutyric acid (GABA) reuptake, increasing its levels in the synaptic cleft. The plant extract contains high quantities of glutamine, resulting in sedating effects, which can be useful for reduction of hot flushes and night sweats. Additionally, valerenic acid has been identified as a partial serotonergic agonist. No side effects have been identified on therapeutic dosage (62).

Evening primrose, *Oenothera biennis*, is a plant rich in omega-3 fatty acids which are associated with anti-inflammatory properties, and higher prostaglandin and oestradiol levels. It has been used for reduction of hot flushes during the menopausal stages. However, it is important to note that possible side effects can include nausea and vomiting, diarrhea, bloating and reduced seizure threshold in patients under antiepileptic drugs or patients with seizure disorders (62).

Ginkgo biloba, a widely used herbal remedy for menopausal women, has been shown to have antioxidant and anti-inflammatory properties (62). Additionally, *Ginkgo biloba* extract may contribute to reducing brain inflammation and support brain cell function, thus contributing to energy balance regulation (95). Side effects include gastrointestinal disorders, headaches, muscle spasms, arrythmia or heart palpitations, dizziness, increase bleeding after surgery and reduced seizure threshold (62).

Panax Ginseng seems to have anti-inflammatory effects and is used for treatment of weakness, fatigue, and poor concentration. It is therefore associated with the treatment of depression and mood disorders in postmenopausal women. Ginseng also has shown to improve quality of life and sexual function in postmenopausal women (96). Side effects include headaches, nervousness, gastrointestinal disorders, acne, hypoglycaemia and insomnia (62).

10. Pharmaceutical perspective: efficacy and safety

a. Discussion of how plant-based and hormonal formulation can impact efficacy.

Phytoestrogens have been identified as a selective oestrogen receptor modulator (SERM), meaning that they can act as agonist and antagonist, depending on the tissue. Pharmacological SERMs, such as raloxifene or tamoxifen, have been developed for hormone-responsive cancers and osteoporosis (97). There are studies on plant-based formulations in the literature with conflicting results. While some studies are unconclusive, some recent publications show an improvement in menopausal symptoms with the use of phytoestrogens. Improvements reported with plant-based approaches include hot flushes, vulvovaginal manifestations, sleep quality, cognition, bone health, as well as protective cancer effects (4, 97). Despite these findings, HRT, with oestrogens alone or in combination with progesterone, remains the first option for treatment of menopausal symptomatology. The North American Menopause Society claims that no other treatment is as effective as HRT for menopausal vasomotor manifestations, genitourinary symptoms and preventing bone loss and fracture (98).

Although efficacy ranges from uncertain to promising, current research confirms that the use of phytoestrogens during the menopausal stages has positive effects. Published research tends to focus on individual phytoestrogens, but using phytoestrogens in combination may increase the effects and consistency of results. Despite pending additional studies on specific dosage and long-term safety of phytoestrogens, their intake does not show serious adverse events. Phytoestrogens appear to be a positive alternative to HRT although further research is required (97).

There is substantial heterogeneity in rigor and quality among the available studies, which remarks the need for a specific standardization in methodology and analysis. Additionally,

there is still limited knowledge in the outcomes of alternative therapies and their potential benefits. The studies assessing herbal remedies are insufficient. Consequently, there is a lack of information regarding adverse effects of long-term use of plant-based therapies (99).

Plant-based interventions have the added concern of interaction with other medication, which is still in most cases not determined. Vitamins and minerals are relevant for women who are at risk of deficiencies but do not reduce menopausal manifestations. More focus from physicians on alternative methods can contribute to promote its further research and better use (100).

Non-hormonal therapies are valuable for women with an elevated risk of breast cancer, coronary heart disease, venous thromboembolism, or stroke, as well as those who have contraindications to HRT, who prefer to avoid it, or women whom the side effects are intolerable (101).

b. Safety on hormone replacement therapy and phytoestrogenic supplementation.

There is an on-going debate about its benefit-risk ratio of HRT. Although HRT shows a more favourable risk-benefit ratio in younger women, the risk profile is unfavourable in women over 60 or more than 10 years beyond menopause onset – specially in those over 70 or more than 20 years beyond onset. Possible risks include coronary heart disease, stroke, venous thromboembolism, and dementia. Furthermore, oestrogen therapy alone appears safer for long-term treatment than oestrogen-progesterone therapy, although the long-term use of any hormone therapy is associated with an increased risk of breast cancer. Nevertheless, the available data are insufficient to properly confirm this association, and HRT is usually contraindicated in survivors of oestrogen-sensitive cancers unless non-hormonal therapies have failed. Despite all these risks, physicians highlight that the determinants of HRT such as formulation, dose, regimen, route of administration, and timing of initiation, can have different outcomes on safety and should be addressed to the needs of the individual (98). Because of all these concerns, alternatives with fewer risks have been considered for the treatment of menopausal manifestations.

During the menopause, phytoestrogens are often taken as supplements or through dietary sources, particularly soy foods. There have been questions about the safety of soy foods, as their consumption has been associated with an increased risk of oestrogen dependent breast cancer. However, later evidence showed that soy food not only did not increase the risk of breast cancer, but that these compounds had preventive properties. The confusion began as a research misjudgement that turned into public concern. It was early demonstrated that oestrogen exposure in postmenopausal women increased the risk of breast cancer (102). Initially there was a concern that the consumption of soy might have similar effects. However, studies in rodents showed that they metabolise isoflavones differently from humans. Rodents

conjugate isoflavones less efficiently than humans, resulting in considerable higher plasma levels of unconjugated isoflavones. The significant higher concentration in rodents compared to humans invalidated the extrapolation of results from these studies on the effects of isoflavones on breast tissue (103). Additionally, more recent studies have proven how phytoestrogens can contribute to breast cancer prevention. Phytoestrogens act through different mechanisms and targets, increasing their potential to inhibit or prevent breast cancer. *In vitro* studies have shown how phytoestrogens influence specific signalling pathways: NF-kB, involved in inflammation and immune response; PI3K/Akt, involved in cell survival and metabolism; MAPK/ERK, involved in cell growth and differentiation. Through these pathways they can control cell cycle progression, promote apoptotic events, inhibit angiogenesis, inhibit metastasis, exert epigenetic changes, inhibit oestrogen synthesis, and modulate oestrogen metabolism. Nevertheless, further research is needed to translate these in vitro findings into clinical settings, as well as determining concentrations of phytoestrogens and its derivatives that are safe and effective (104). Currently, there is no consensus on the effect of dietary soy on cancer development or its treatment (43). But the main issue is that there is no standardized dosage, duration and other factors of methodology across studies (105).

The EFSA published an assessment of the safety of isoflavones from food supplements in menopausal women. The objective was to evaluate the possible adverse effects on breast, uterus and thyroid gland associated with the intake of food supplements containing isoflavones, in peri and postmenopausal women. Its publication date goes back to 2015 but remains the last published document from the EFSA on the matter. The human and animal studies concluded that there were no adverse effects on endometrial thickness, uterine weight, breast density and histopathology at dosing of 150 mg/day over two years and a half, which is comparable to isoflavone intake from soy-based foods. After *in vivo* and *in vitro* findings, genotoxicity was dismissed. Nevertheless, the EFSA remarks the need for standardization of isoflavone studies and further research on long-term use. It was also noted that the findings of the study were limited to postmenopausal women without oestrogen-dependent tumours in their history (106).

c. Individual variation in nutrient absorption.

Interindividual variation is especially relevant for personalised nutrition that attends the needs of women across the menopausal stages. Nevertheless, there are phenotypic and genotypic factors that can affect the absorption, distribution, metabolism and excretion of plant-derived bioactive compounds (107, 108). The main factors include:

- Variations in genes that encode for metabolic enzymes and transporters can result in differences in how plant bioactives are absorbed and metabolised. Additionally,

epigenetic modifications can further affect gene expression regarding nutrient metabolism.

- Age-related physiological modifications can influence the efficacy and absorption of bioactives from the diet.
- Metabolic disorders or malabsorption syndromes can modify the nutrient absorption.
- The gut microbiota is essential for the metabolism of plant bioactives, but its composition varies greatly among individuals. During the menopause, women experience significant changes in their gut microbiota, which can further increase the variability in nutrient absorption.
- Adiposity and its impact on metabolic rate have been identified as affecting factors although findings are not consistent across all compounds.
- Lastly, lifestyle factors such as dietary habits, physical activity, smoking, and alcohol intake can influence nutrient bioavailability.

Such individual variation in bioavailability, especially for phytoestrogens, as well as the differences in their use, may explain the inconsistent results regarding their effects. One notable factor directly affecting phytoestrogens is the variability in intestinal microbiota, along with the changes that occur during the menopausal transition, as it determines the individual's ability to metabolize phytoestrogenic compounds. The individual's capacity to produce equol, as previously explained, can determine the oestrogenic effect from phytoestrogens (97). Only around 20-30% of western population are estimated to be equol producers (109)**.**

11. Survey on women's nutritional needs and supplement awareness

The objective of the survey was to obtain valuable raw insights from women in the menopausal stage. The survey focused on identifying specific demands, understanding supplement preferences, examining knowledge, assessing awareness of supplementation efficacy, and identifying barriers to supplementation.

The survey, entitled "*Menopause and supplements*", utilised a structured questionnaire with multiple-choice questions, single-rating and open-ended questions, with a duration of five minutes. The survey was distributed in Spain and Austria, with a total of forty-six women participating across various stages of menopause. Specifically, 39% of the participants were in the premenopausal stage, 22% were in the perimenopausal stage, 26% were in the menopause, and 13% were in the postmenopausal stage.

Concerning manifestations, the participants reported a consistent pattern in the following order: hot flushes, mood instability, sleep disturbances, weight changes and bone fragility.

In the survey, 80% of the participants did not take any form of supplementation for menopausal manifestations. The majority of the participants attributed this decision to either a belief that supplementation was unnecessary or a lack of knowledge regarding suitable products. Furthermore, some respondents added a lack of confidence in these types of products. Nevertheless, 89% indicated willingness to try a new menopause supplement. Additionally, all respondents expressed willingness to use non-hormonal supplement that could reduce manifestations such as hot flushes, sleep issues, and mood swings by fifty percent.

Among the 20% of the individuals who took supplementation for menopausal manifestations, every participant used more than one product, with the most common choices being vitamins (30%), followed by calcium and herbal supplements. However, 11% of these women expressed dissatisfaction with the supplements they were using for menopausal manifestations. Furthermore, 64% of the participants received supplement recommendations from healthcare professionals.

A significant 87% of participants expressed greater trust in products purchased from pharmacies compared to those obtained from online shops, drugstores or supermarkets. The majority of surveyed women expressed a preference for natural or plant-based supplements, with safety and minimal side effects ranking as secondary considerations. The most preferred delivery format was capsules or tablets. Furthermore, many respondents desired a simplified supplementation strategy, emphasizing the need for a single combination product that can address multiple menopausal manifestations simultaneously. This approach aimed to minimize the need for multiple products while ensuring significant individual efficacy and a wide spectrum of effects within a single formulation.

12. Analysis of *CAPS fem*

a. Ingredients in *CAPS fem* for women's health.

CAPS fem is a dietary supplement administered in the form of capsules, which is targeted at women throughout their life stages. The product is vegan and contains exclusively natural-source ingredients.

The following ingredients are listed in the product composition: Magnesium citrate, shatavari root extract (*Asparagus racemosus*), damiana leaf extract (*Turnera diffusa*), capsule shell: hydroxypropyl methyl cellulose, lemon balm extract (*Melissa officinalis*), acerola cherry powder (*Malpighia glabra*), maritime pine bark extract (*Pinus pinaster*), iron-enriched *Aspergillus oryzae* powder, 5MTHF-glucosamine (110).

Each ingredient in the formulation has been selected for specific functions:

- Folate, listed as 5MTHF-glucosamine, is the more bioactive form of folic acid. It is an essential vitamin that performs many important functions in cell metabolism.
- Iron-enriched *Aspergillus oryzae* powder is a natural source of iron. It claims to help reduce tiredness and fatigue, which is of special interest for women who often have a higher need for iron during menstruation.
- Acerola cherry powder, from *Malpighia glabra,* is a rich source of vitamin C, which improves the bioavailability of iron.
- Damiana leaf extract, from *Turnera diffusa,* has been considered a natural aphrodisiac in traditional medicine, supporting female sexuality.
- Shatavari root extract, from *Asparagus racemosus,* helps regulate the menstrual cycle while contributing to well-being during menopause.
- Magnesium citrate is a magnesium salt which supports hormonal regulation.
- Lemon balm extract, from *Melissa officinalis*, contributes to higher quality sleep.
- Maritime pine bark extract, from *Pinus pinaster*, acts as an antioxidant.
- The capsule shell is made of hydroxypropyl methyl cellulose, a vegan-friendly capsule material which acts as a structural component of the supplement.

b. Assessment of the formulation for menopause.

The formulation contains ingredients that are beneficial for the overall health of women. This section evaluates each ingredient in the context of the menopausal stages.

Folate is an essential vitamin and is therefore necessary for all population. It plays an important role in cell division, DNA synthesis and red blood cell production. However, women in the menopausal stages are not in special need of higher amounts of it. Moreover, folate needs should be covered with a healthy diet containing green-leaf vegetables and legumes.

Iron intake is particularly relevant for menstruating women as iron levels drop with each cycle due to the loss of blood. It is also important to note that an additional factor should be considered in iron necessities: the increasing tendency towards vegan and vegetarian diets in recent years. These dietary choices imply the need of careful supplementation in most cases, as they can lead to potential deficiencies, including iron deficiency, if not assessed carefully. All these aspects add importance of iron consumption. However, women in the menopausal stage have lower iron requirements compared to menstruating women. While menstruating women need 18 mg of iron daily, non-menstruating women require only 8 mg per day (111).

Acerola cherry powder increases iron absorption and bioavailability due to the ascorbic acid originated from vitamin C. As commented above, iron is not a high priority for non-menstruating women with a healthy and varied diet.

Damiana leaf extract originates from *Turnera diffusa*, a plant with oestrogenic effects. Although it is described as an aphrodisiac in some studies, there is no significant evidence of its efficacy during the menopausal stages (112).

Shatavari has supporting evidence on helping with the reduction of night sweats, hot flushes, anxiety, nervousness and vaginal dryness. It has also been associated with a better musculoskeletal performance, making it an interesting compound for menopausal women (68,69).

Magnesium is an essential mineral necessary for regulating body temperature, synthesizing nucleic acids and proteins, and maintaining the electrical potentials of nerve and muscle cells. During pregnancy, it can benefit foetal development (113). Additionally, magnesium supports bone mineral density and reduces fracture risk, which is important during the menopausal stage (114).

Lemon balm extract, from *Melissa officinalis*, is used for sleep disruption manifestations (62). It has sedative and anxiolytic compounds that influence neurotransmitter activity such as GABA. This characteristic benefits all population in general. But it can also contribute with special interest to women in the menopausal stages since lower quality sleep and anxiety are common manifestations.

Maritime pine bark extract, from *Pinus pinaster*, is rich in pycnogenol. It can alleviate menopausal vasomotor manifestations as well as menstrual symptoms through action on circulation and inflammation (92, 93). Additionally, this circulatory action can be beneficial against hair loss during menopause (94).

The capsule shell made of hydroxypropyl methyl cellulose acts as an inactive excipient, offering structure to the formulation.

c. Limitations in the current formulation and alternative ingredient considerations.

The current formulation contains four ingredients associated with menopausal symptom management, out of a total of eight. Incorporating additional ingredients supported by robust evidence could strengthen its effectiveness. Furthermore, the synergistic combination of different compounds may result in more beneficial outcomes for specific menopausal manifestations. However, safety considerations must be carefully assessed, given the insufficient evidence regarding the safety and effectiveness of such combinations.

Based on the review presented in section nine, “Nutritional and plant-based interventions in menopause”, specific ingredients have been identified to address these limitations and augment the overall formulation.

1. For the management of hot flushes and night sweats, the most reported manifestations, the following ingredients may be considered, listed in order of the strength of evidence: soy isoflavones (6, 59), red clover (59, 60, 62, 63), black cohosh (6), saffron (87, 88), maca (83), shatavari (69), pycnogenol (92), valerian, and evening primrose (62).

2. To address mood changes and cognitive health, the following ingredients may be considered, listed in order of the strength of evidence: vitamin D (6, 72), black cohosh (6, 47), saffron (84, 85, 86), golden root (81, 82), maca (83), resveratrol (67), ginseng (96), coenzyme Q10 (76), omega-3 fatty acids (115, 116, 117), shatavari (69), vitamin B12 (6), and valerian (62).

3. For support in bone health, beyond magnesium citrate, the following ingredients may be considered, listed in order of the strength of evidence: vitamin D (13, 71, 72), resveratrol (67), creatine (77, 78), shatavari (68), kudzu (64, 65), hops (47, 59, 70), and golden root (81). There is supporting evidence for the synergistic combination of vitamin D and resveratrol (118).

4. For a higher content of antioxidants, the following ingredients may be considered: plant flavonoids, soy isoflavones (61, 62), lignans (6, 54), and vitamins A, β-carotene, C, and E.

6. To support cardiovascular health, the following ingredients may be considered, listed in order of the strength of evidence: resveratrol (66, 67), omega-3 fatty acids (73, 74, 115), probiotics, golden root (81, 82), pycnogenol (93), and curcumin (89).

7. For skin and hair enhancement use of resveratrol (67) and pycnogenol (93, 94) may be considered.

8. For a stronger anti-inflammatory action, the following ingredients may be considered: phytoestrogens (13, 47, 48, 49, 50, 52, 53, 54), omega-3 fatty acids (73, 74, 115), golden root (81, 82), lignans (6, 54), curcumin (89), saffron (84), gingko (62, 95), ginseng (96), and pycnogenol (93).

9. For sexual dysfunction and urogenital symptoms, the following ingredients may be considered: red clover (59, 63), shatavari (69), saffron (87), and sea buckthorn (91).

Although some of the listed compounds may still require further research to fully understand their mechanism of action and evaluate their efficacy and effectiveness, existing studies indicate promising potential for their use in future formulations. The reviewed collection of compounds presents a wide range of prospective options for incorporation into the management of women during the menopausal stages.

13. Discussion of limitations and opportunities in women's supplements

While HRT is highly effective, it is also associated with significant high risks, including coronary heart disease, stroke, venous thromboembolism, dementia, and an increased risk of breast cancer with long-term use. Conversely, non-hormonal approaches such as dietary supplements present lower and less proven efficacy but generally they carry fewer serious risks. However, their potential long-term risks that have not yet been proven, cannot be completely dismissed, despite the general perception of safety associated with the use of these compounds, given the absence of reported serious adverse effects. What should be considered more carefully is the potential for drug interaction, as this may have significant repercussions, particularly for drugs with a narrow therapeutic window. In conclusion, safety should not be overlooked; however, due to the apparent innocuous nature of its components, it should not be a source of considerable concern when compared to HRT. Nevertheless, it would be very beneficial to better understand both the optimal and safest dosage.

Another aspect to consider is the availability of treatment. HRT has very clear guidelines for its use, and health professionals are generally well informed about it. However, non-hormonal treatments lack specific recommendations for use and knowledge among healthcare professionals, which creates an additional barrier for patients to access these treatments. Again, the scattered evidence and the lack of transversality in studies make it difficult for professionals to make evidence-based recommendations. The decision to use hormonal or non-hormonal therapy is ultimately assessed by a qualified physician. This decision should be based on the circumstances and conditions of the individual, but it may be biased by the lack of information about alternative treatments. Nevertheless, this issue is gradually gaining prominence in response to patient demands.

It is also worth mentioning how the different regulatory frameworks in pharmaceutical medicine significantly influence the circumstances of available evidence. In industry, more rigorous evaluation studies and regulations prior to commercialization lead to higher standardization of processes and a better control over variables. Conversely, this is not the case regarding supplements.

During the development of this project, some challenges and limitations have been identified in supplementation research. Primarily, the diversity of the studies has made difficult to make direct comparisons and to draw generalizable conclusions. Furthermore, the evidence on alternative approaches, such as non-hormonal treatments, is limited compared to HRT. There are four direct factors that contribute to this statement, in addition to the previous explanations. First, HRT consists of only two treatment options, oestrogen therapy or progesterone-oestrogen therapy. The alternative methods include a large number of different compounds, substances, and plants, with a great variability between them in terms of efficacy and knowledge. A second element to consider is how different dosage forms

undergo different ADME (administration, distribution, metabolization, excretion) processes, which may affect efficacy. A third and very relevant aspect is the variation in dosage, extraction and preparation of the compounds, which is concerningly variable across studies. Lastly, study design and methodology can critically compromise the validity of the process, and the results obtained. All these factors progressively create an exponential increase in variability, resulting in very limited comparable evidence available in the bibliography and consequently positioning alternative methods in a subordinate state to HRT.

In this project, as information found in the literature lacked homogeneity among compounds, some were presented in more depth than others. This was highlighted in section nine, titled "Nutritional and plant-based interventions in menopause", where the volume of information and the nature of the content exhibited variability depending on each compound.

Finally, the survey conducted on women's nutritional needs and awareness of supplements revealed some potential implications for product development. While participants recognized a lack of knowledge about supplementation during the menopause, they expressed a willingness to explore and learn more about such supplements. This provides new opportunities for product development to meet the desired improvements. There is a strong preference for the use of natural and plant-based ingredients, a demand for transparency regarding the contents of the supplements, as well as an emphasis on product safety. Despite the popularity of formats, such as gummy supplements, the participants still favoured capsules or tablets as their preferred delivery method. But most importantly, women are looking for a practical solution with a streamlined approach that still guarantees effective results.

14. Conclusions

The following conclusions can be drawn from this in-depth work on nutritional needs on the menopause:

1. The nutritional needs of menopausal women are conditioned by the decrease in oestrogen, which alters various systems throughout the body. These physiological changes can benefit from diet adaptations and supplementation to target manifestations and prevent potential deficiencies.

2. Key nutritional elements, including phytoestrogens, specific nutrients and essential compounds, as well as herbal and plant-derived extracts, have demonstrated beneficial effects on menopausal manifestations. Nevertheless, certain compounds may also exhibit potential risks, including the possibility of drug interaction.

3. This project highlights the importance of addressing the menopausal symptoms from a multidisciplinary perspective, including nutrition as a relevant element of treatment.

Nevertheless, certain limitations have been identified, such as the exclusive reliance on published literature and the lack of transversal results across studies on dietary supplements.

4. The product evaluated, *CAPS fem*, presents a positive basis; however, certain limitations have been identified in its targeting of menopausal manifestations. Some recommendations have been proposed to enhance its formulation.

5. Future research opportunities include the establishment of standardized methodologies for the study of various compounds, the long-term efficacy and safety of supplements, the combination of phytoestrogens within a single formulation and its effects and safety, the determination of optimal and safest dosages for the different compounds, the optimization of bioavailability through optimal dosage forms, and the evaluation of the efficacy of the compounds on manifestations.

Non-hormonal supplementation can be a valuable option for women going through the menopause, potentially relieving symptoms with fewer systemic risks than HRT. However, more well-designed studies are needed to standardize dosing, ensure long-term safety and clarify how these interventions interact with individual physiology. Continued research and clinical vigilance will help health care providers offer informed guidance and expand therapeutic options for women at all stages of the menopause.

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16. Annex

In this annex, the results of the survey conducted to assess women's nutritional needs and supplement awareness are presented.

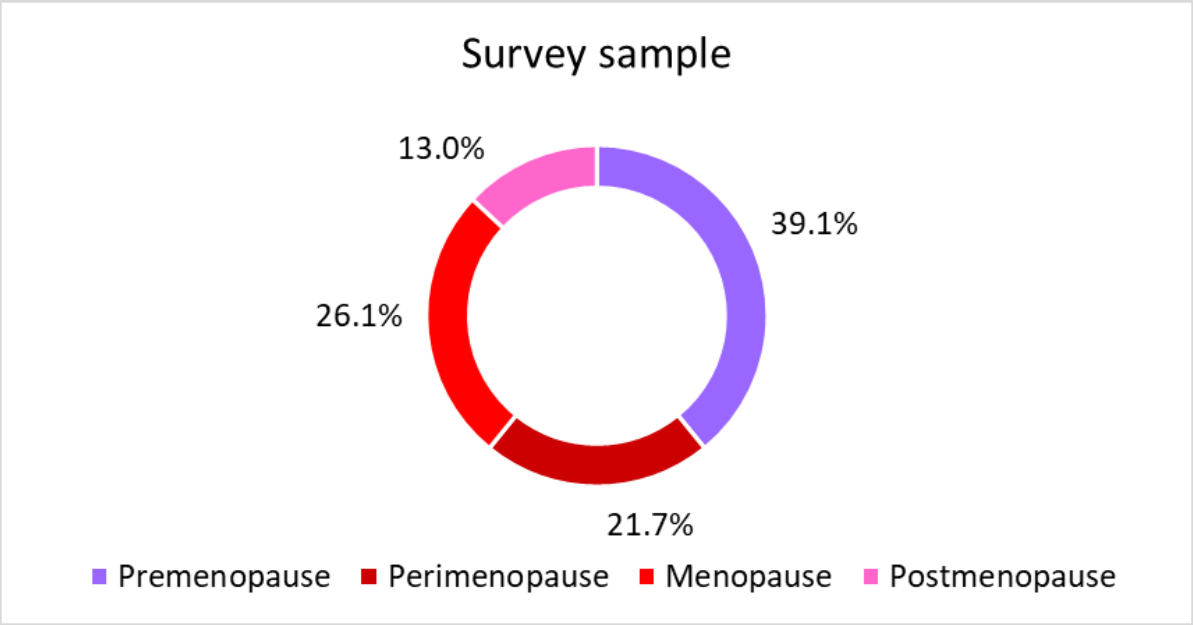

Figure 6. The total number of participants was 46, with 39% experiencing regular menstruation without symptoms in premenopause, 21% having irregular menstrual cycles and symptoms in perimenopause, 26% being more than twelve months since their last menstrual period in menopause, and 13% being more than five years since their last menstrual period in postmenopause.

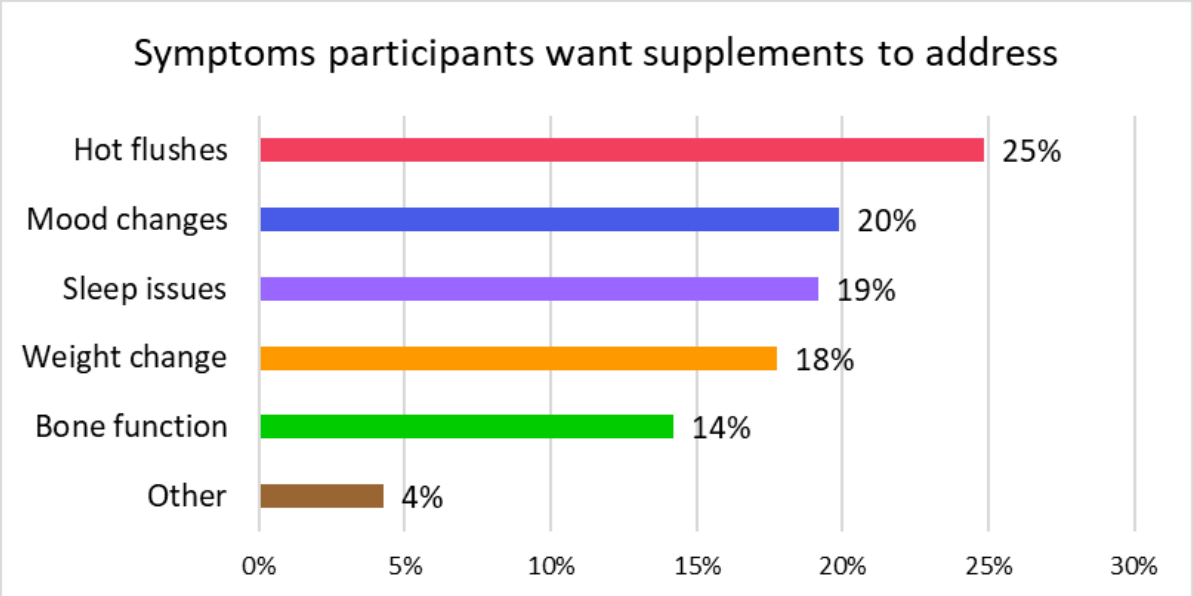

Figure 7. This graph illustrates the symptoms that participants wish menopausal supplements could address most effectively. The most reported symptom was hot flushes, followed by mood changes, sleep issues, weight gain, and bone function. Participants who selected "other" did not provide any specifications.

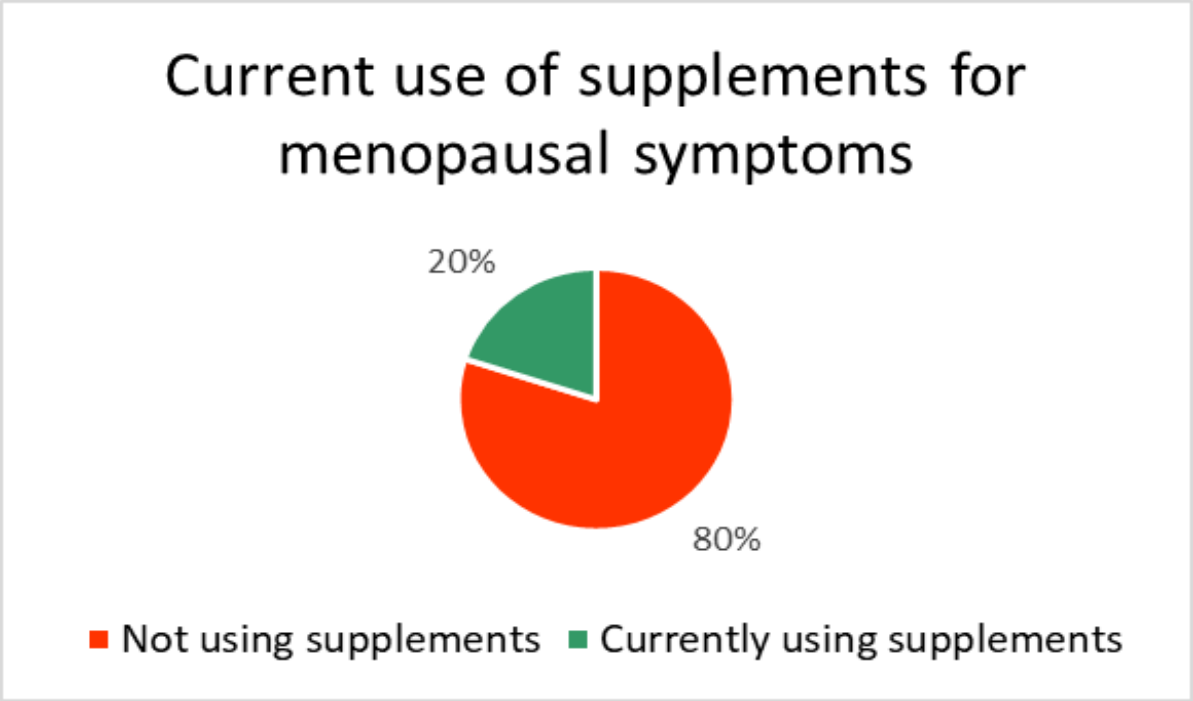

Figure 8. This chart illustrates whether the participants were currently taking any supplements specifically for menopause symptoms. 80% of the participants reported not using any supplements for menopause.

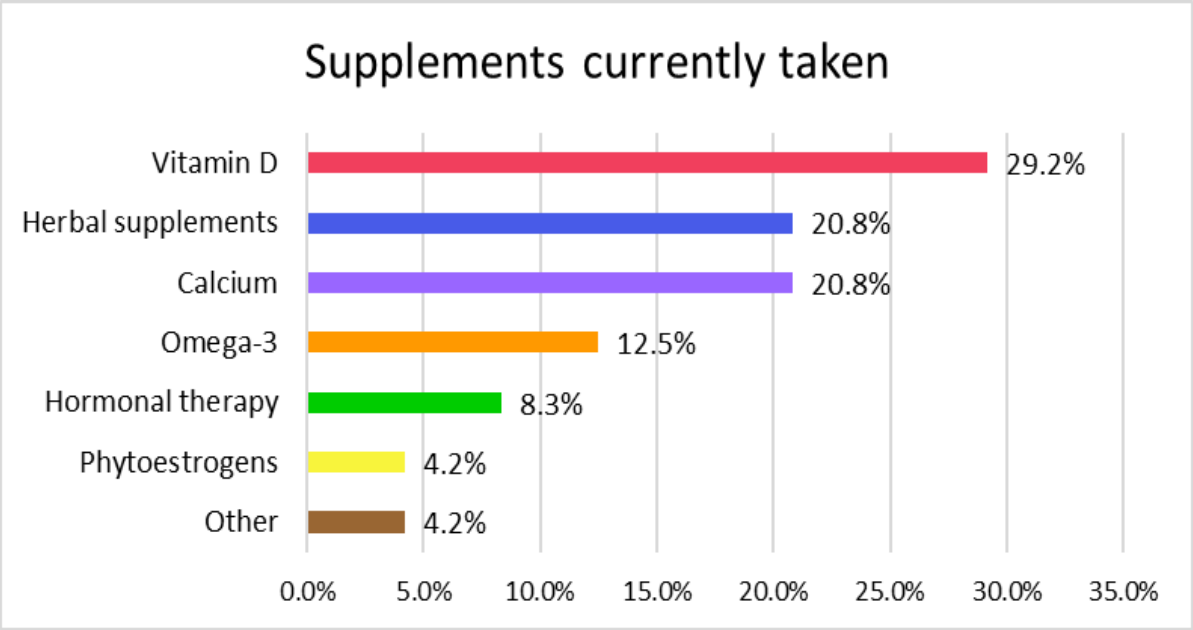

Figure 9. This graph illustrates the supplements for menopause taken by the 20% of the participants from the previous chart. The participant who selected ”other” referred to a drink containing a mixture of various vitamins.

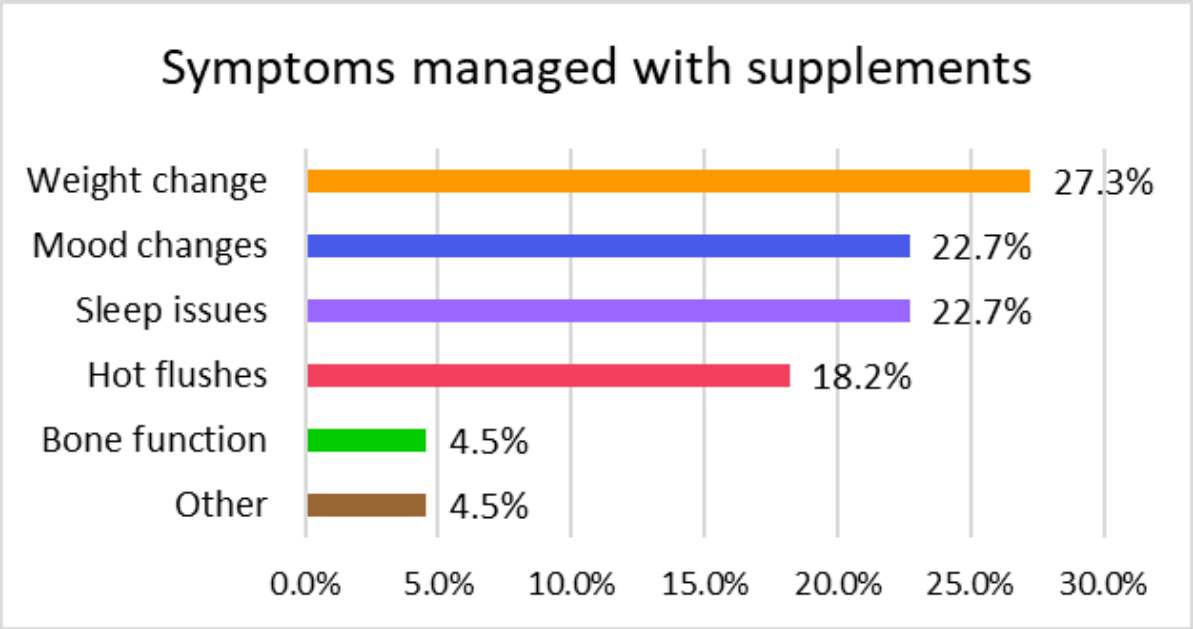

Figure 10. This graph illustrates the symptoms targeted by the participants from the previous graph with their menopausal supplementation. The participant who selected ”other” referred to hair and skin.

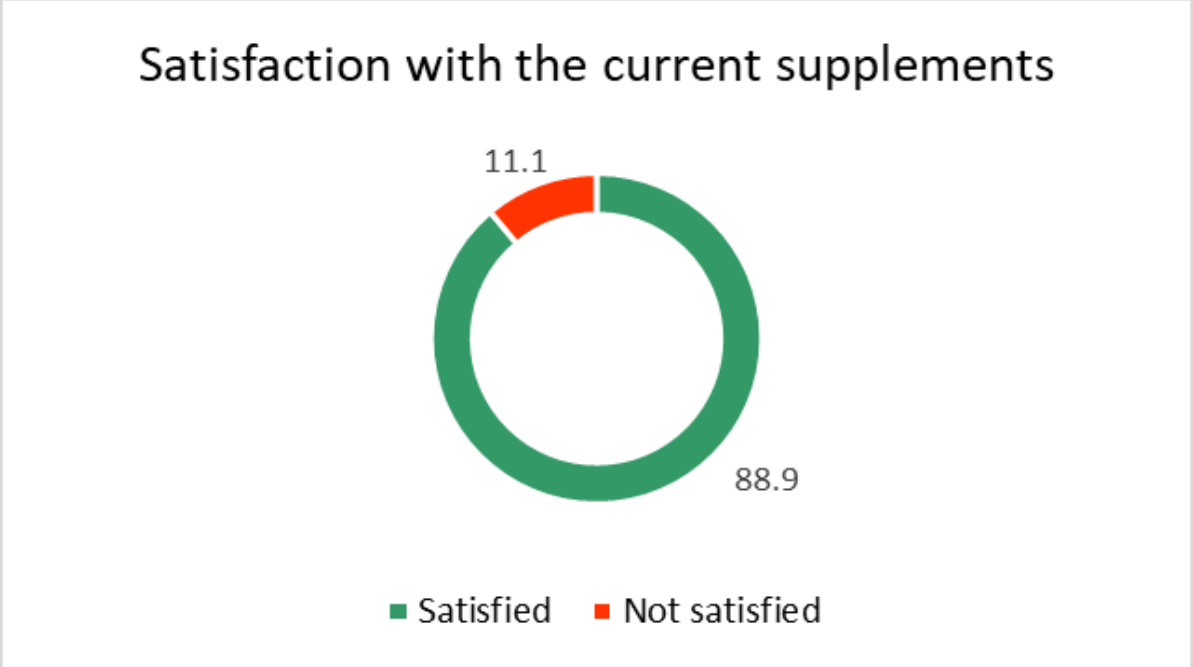

Figure 11. This chart illustrates whether the participants from the previous graph were satisfied with the supplements they were taking at that time. Almost 89% expressed satisfaction. One participant specified that she was not satisfied with her current supplementation, as she would prefer a single product that addressed all of her needs.

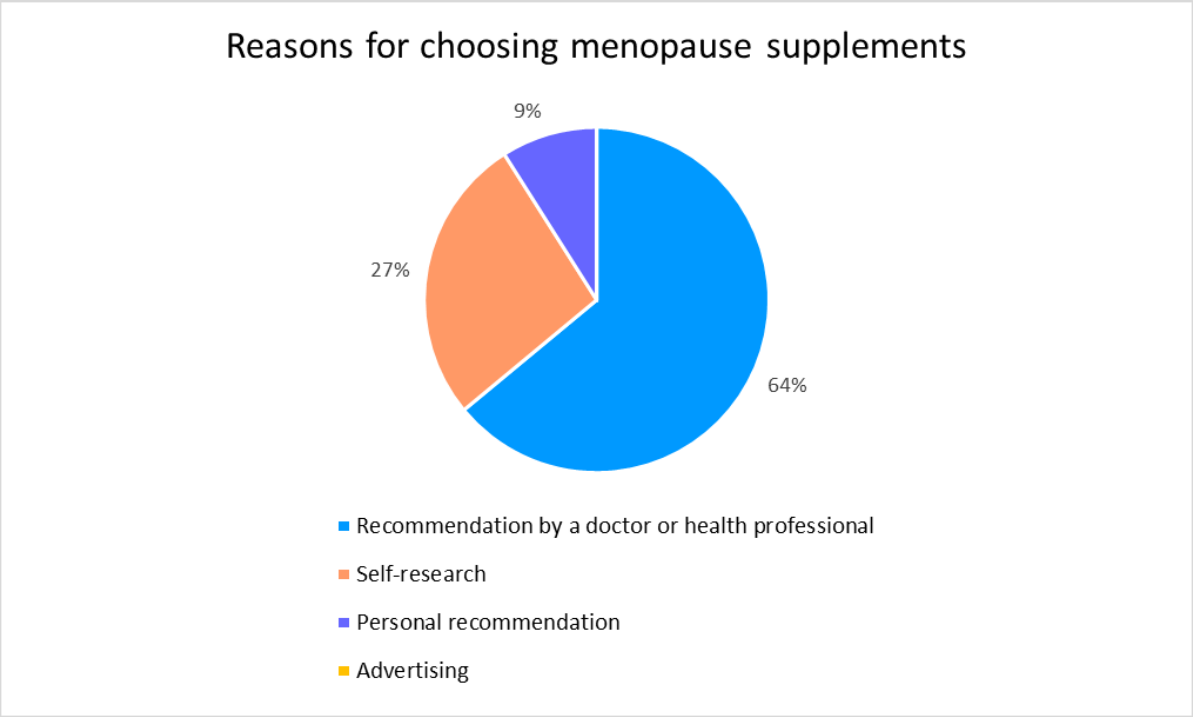

Figure 12. This chart illustrates the reasons why the participants chose the supplements mentioned previously. The majority selected supplementation based on recommendations from a doctor or health professional, followed by self-research and personal recommendations. No participants chose advertisements as a factor.

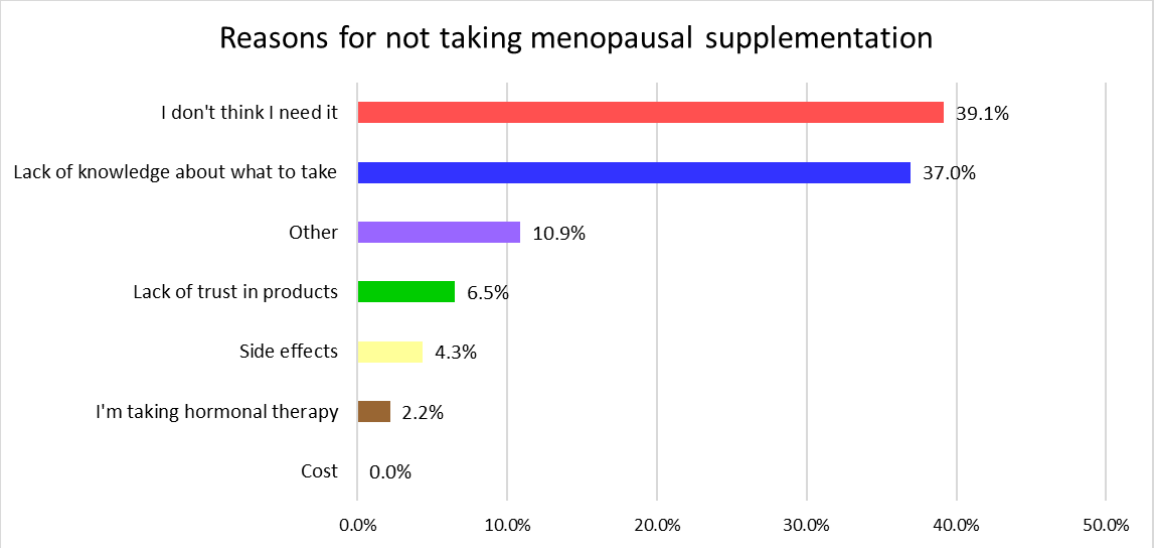

Figure 13. This graph illustrates the reasons why the 80% of the participants chose not to take menopausal supplements. The majority stated they do not need them, followed by a second major group who expressed a lack of knowledge about which supplements to take, concerns about a lack of trust in supplements, potential side effects, and already being on HRT. No participants selected cost as a factor. The participants that selected ”other” specified that they had not encountered symptoms or were not explicitly concerned with them.

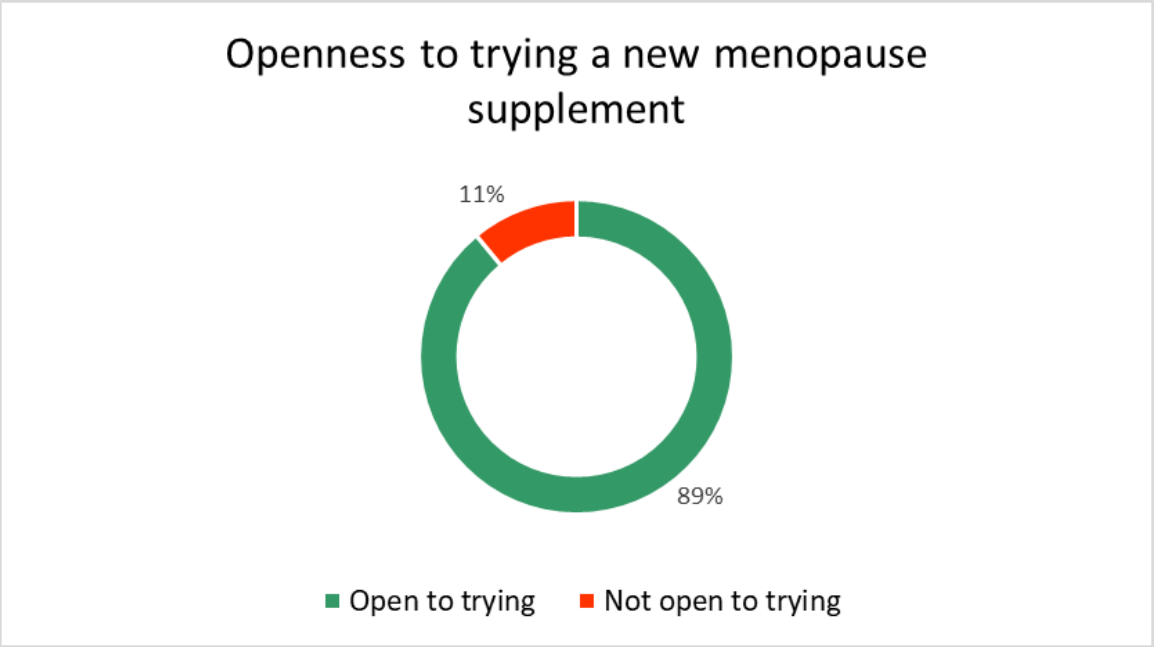

Figure 14. This chart illustrates whether the participants would be open to trying a new menopause supplement. 89% of them expressed openness to it.

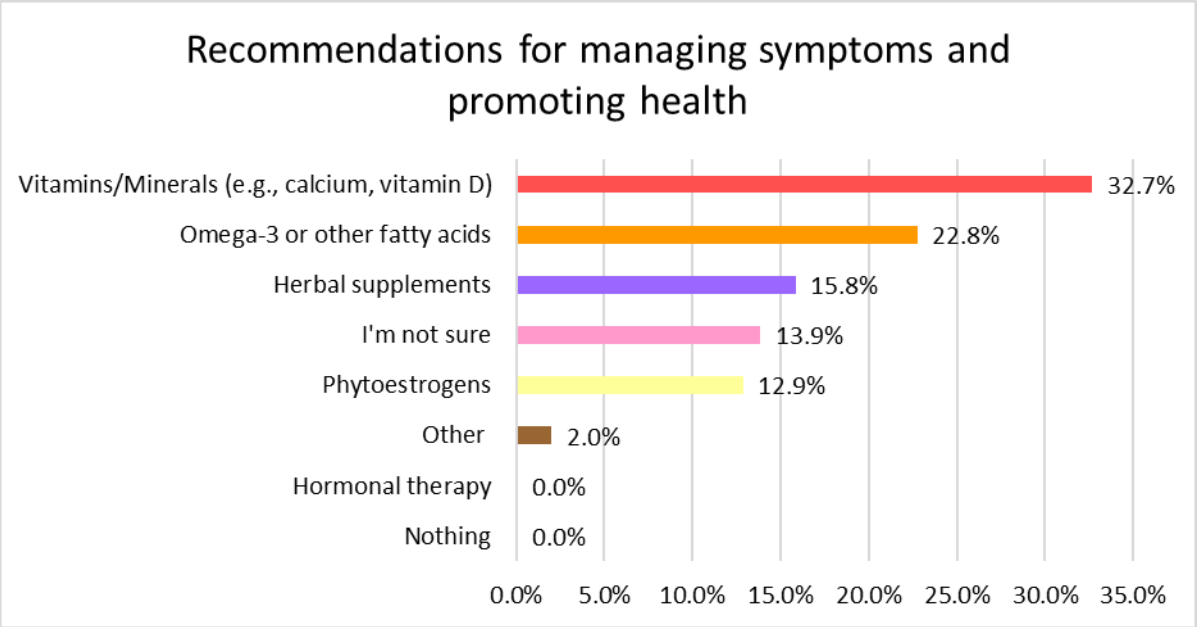

Figure 15. This graph illustrates what the participants believe women in menopause should take to manage symptoms or maintain health. The participants that selected ”others” did not specify any further recommendations.

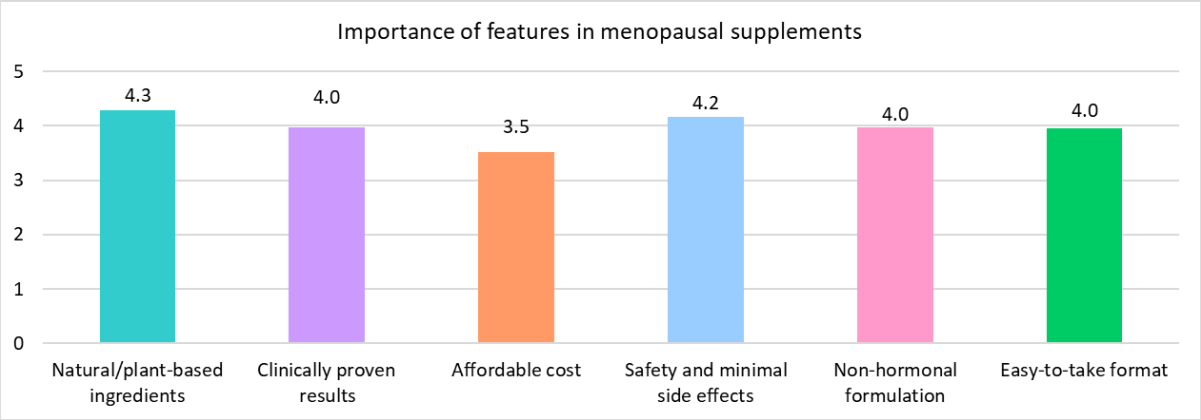

Figure 16. This graph illustrates the importance of the following features in a menopause supplement, rated on a scale from 1 to 5 (1 being not important and 5 being very important). The greatest concern was placed on having natural/plant-based ingredients, closely followed by safety and minimal side effects. Clinically proven results, non-hormonal formulation and easy-to-take format all received equal relevance. Affordable cost was considered the least important.

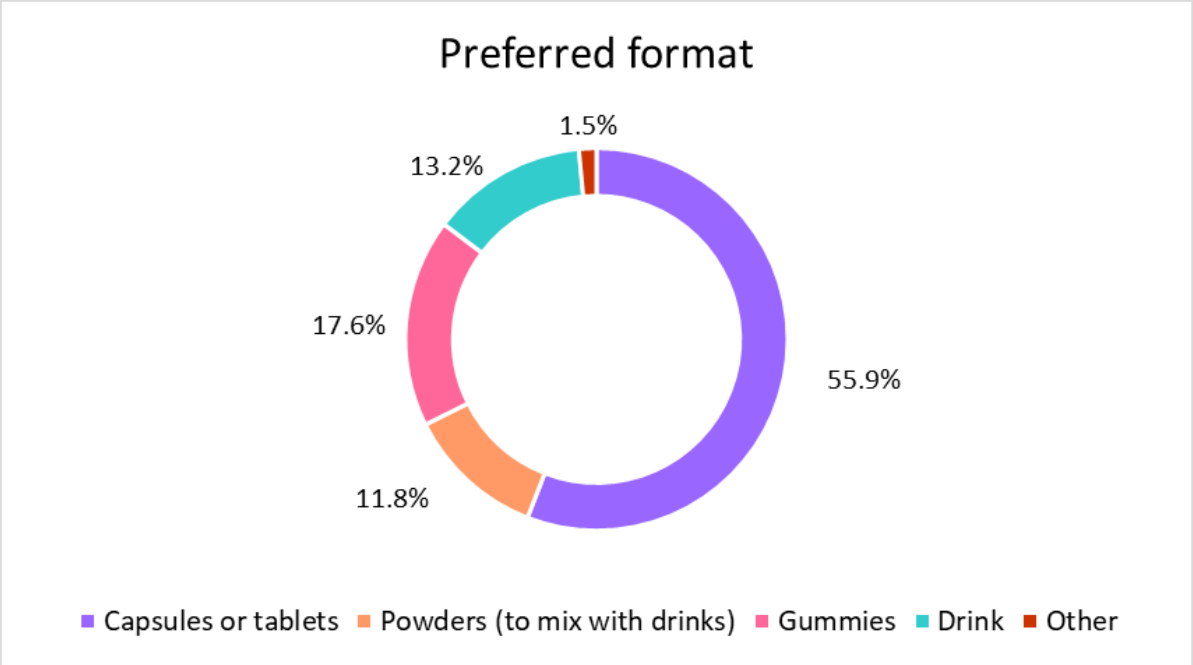

Figure 17. This chart illustrates the preferred format for a menopause supplement. Nearly 56% of the participants selected capsules or tablets as their preferred dosage form. The participants who selected ”other” did not specify an alternative dosage form.

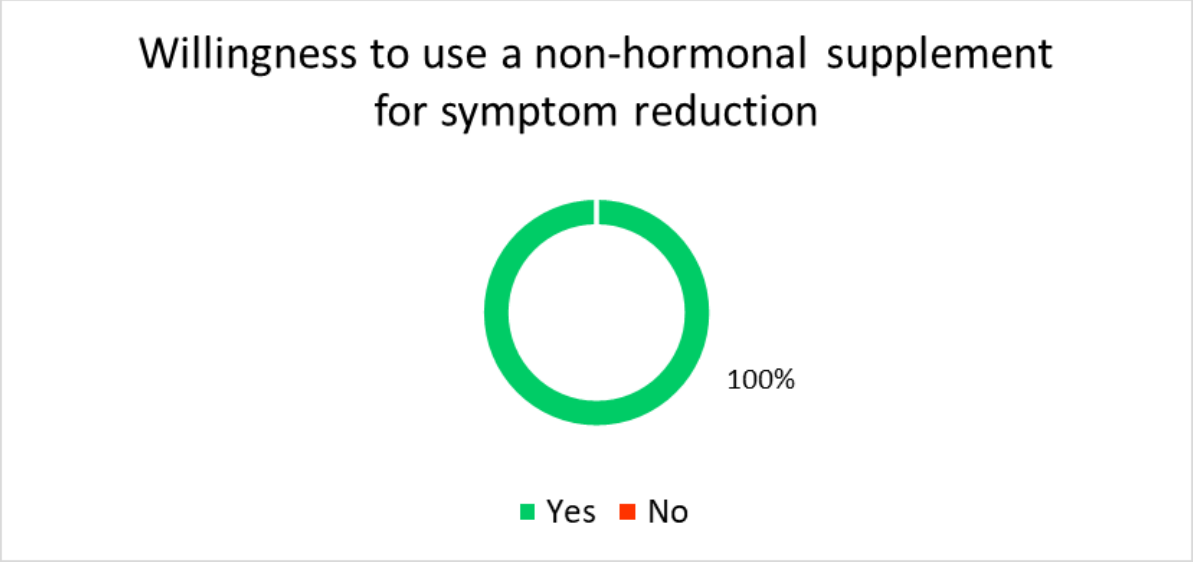

Figure 18. This chart illustrates the participants' willingness to take a non-hormonal supplement that could reduce symptoms such as hot flushes, sleep issues, or mood swings by 50%. All of the participants stated they would use it.

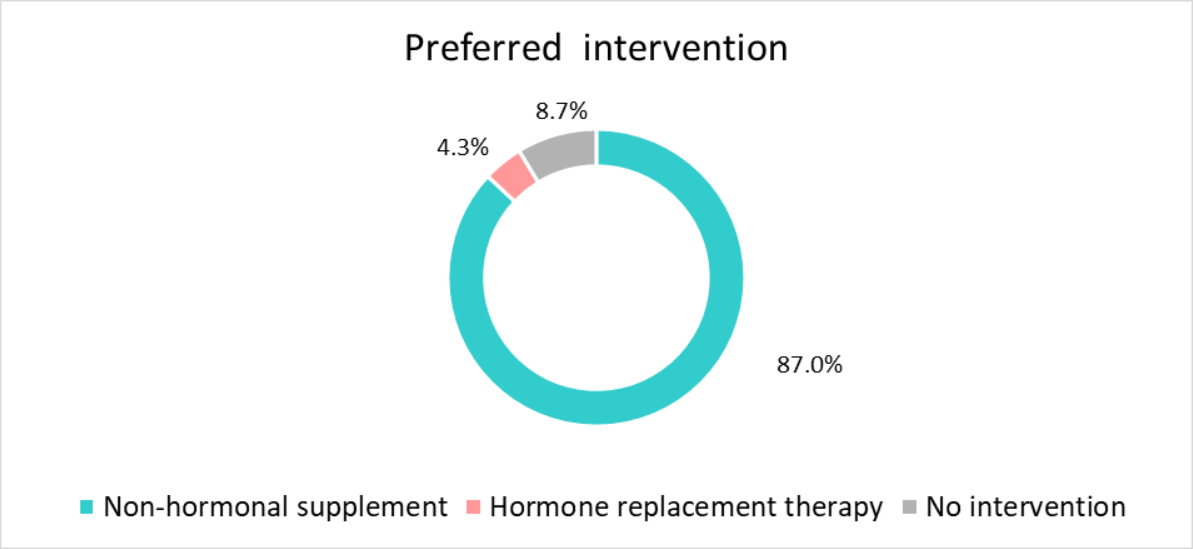

Figure 19. This chart illustrates the preferred menopausal intervention if the participants were required to choose. 87% selected non-hormonal supplements over HRT and no intervention.

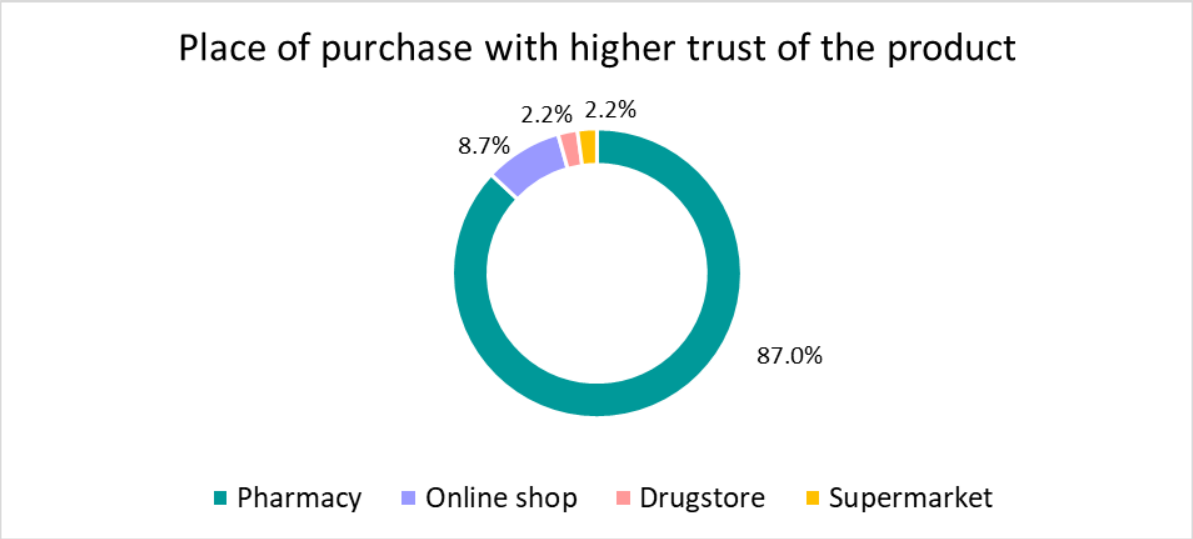

Figure 20. This chart illustrates where participants would be more likely to trust the product. 87% selected pharmacies, over online shops, drugstores and supermarkets.