MS-10®

Famenity

Women's health



US FDA Notification

MSDS Approval

Health Canada Approval

Clinically-proven

Menopause Support

White Paper: MS-10® for Women's Health

A Proprietary Blend of Natural Botanical Ingredients Clinically-Proven to Alleviate Menopausal Symptoms*



INTRODUCTION

MS-10® is a proprietary blend of natural botanical dietary ingredients extracted from Thistle and Thyme. In a series of published, peer-reviewed *in vitro*, *in vivo* and double-blind, randomized, placebo-controlled human clinical studies researchers found that **Famenity's MS-10® exerted significant improvement in alleviating menopausal symptoms, regulating estrogen receptor activity, and improving bone health blood serum markers in menopausal women.** [1,2,3,4] In addition to clinically-proven efficacy, a suite of toxicology studies were conducted on MS-10® and found that it is a safe, nontoxic ingredient with no adverse effects reported.

Menopause is a natural part of aging that is often associated with symptoms of discomfort in middle-aged women. Appropriate care and management of health during and after menopause is important for maintaining a woman's quality of life. The reduction in estrogen after reaching middle age is a major cause of physiological and psychological changes related to menopausal symptoms, including hot flashes and vaginal dryness.[5,6,7] These symptoms can be at least comparatively reduced by local or systemic administration of exogenous estrogens using hormone replacement therapy (HRT). However, in some women, HRT may cause side effects or increased risk for other issues. Therefore, alternative and safe natural approaches, including dietary interventions, have been investigated for the alleviation and management of menopausal symptoms.

A team of Korean researchers spent 15 years screening a multitude of natural substances for their potential to support menopausal women's health, however most of these substances failed to meet sufficient safety and efficacy standards. Finally, the botanical extract combination that is now MS-10® was identified as a safe, natural substance to provide menopausal symptom relief.

MS-10® Botanical Raw Materials

Korean Thistle (*Cirsium japonicum var. Maackii* (Maxim.) Matsum.) is a perennial plant of the Compositae family that grows in mountainous regions and fields in Korea, Japan, and China. The Latin name for Korean Thistle is Herba Cirsii, and it has been used as an herbal preparation in traditional Eastern medicine for centuries. Thyme (*Thymus vulgaris* L.) is a semi-shrub species of flowering plant in the mint family Lamiaceae, native to southern Europe. It's small, grey-green leaves are highly aromatic and commonly used for culinary and herbal purposes.

Bulk Ingredient Characteristics and Applications

MS-10® is extracted via a proprietary process and is a free-flowing, yellowish to light brown powder that is shelf stable for up to 3 years when stored at room temperature. It is water-soluble and heat-stable and can be used as a formulation ingredient in various dietary supplement applications. **Serving forms include tablets, capsules, gel tabs, gummies, beverages, films and powdered mixes**. The recommended serving size is **300 mg.**

REGULATORY SUMMARY

MS-10® Regulatory Status as a Dietary Ingredient in the United States

MS-10® is the first and only dietary ingredient complex of its kind to successfully file a **New Dietary Ingredient Notification with the US FDA (NDIN #1119).** In response, the FDA issued a "letter of acknowledgement without objection" in 2019. FDA reviewed the ingredient's identity, purity and limit on contaminant specifications, manufacturing process, historical consumption and a suite of toxicology data and had no objection to "a reasonable expectation of safety" established for MS-10® in order for it to be marketed and sold as a dietary ingredient in the United States.

MS-10® Regulatory Status as a Dietary Ingredient in Korea (Country of Origin)

MS-10® received certification from the **Ministry of Food & Drug Safety of Korea** (MFDS) as a Health Functional Food Ingredient with an authorized health claim (Certification No. MFDS FSD – 2020-23, Health claim: **May help with menopausal women's health**). MFDS is the FDA-equivalent regulatory body in Korea and prior to granting the certification, the agency evaluated the safety and efficacy of the dietary ingredient. The agency states that only the party that's been granted the certification can make health claims regarding the efficacy and performance of the product.

MS-10® Regulatory Status as a Natural Health Product in Canada

MS-10® received certification from **Health Canada** as a Natural Health Product with an authorized health claim (NPN no. 80121629 (2022. 10)), **Health claim: "Clinically shown to help relieve symptoms of menopause such as facial flushing, night sweats, sleep disturbances and nervousness.** Helps promote/maintain/support sexual health in menopausal women. **Clinically shown to help promote/maintain/support sexual health in menopausal women**. Helps support emotional aspects of sexual health in women. **Helps to reduce cortisol levels, a biomarker of physical stress.** Clinically shown to help reduce menopausal symptoms including hot flashes, night sweats, low energy, difficulty sleeping, difficulty concentrating, irritability/nervousness, muscle and joints discomfort, headaches, paresthesia (tingling, burning sensation of the skin), vertigo and vaginal dryness. **MS-10 helps to provide menopausal symptom relief."**

MS-10® Regulatory Status in India

The federal government of India established the Food Safety and Standards Authority of India (FSSAI) which governs foods, functional foods, and dietary supplements. The main objective of FSSAI is to set science-based standards for articles of food and regulate the manufacture, processing, distribution, sale, and importation of foods to ensure their safety for human consumption. MS-10® was approved under the Food Safety and Standards Regulations, 2017 as "non-specified food and food ingredients" (File number: 52/Std/PA/FSSAI/2021 on 30.05.2022).

HUMAN CLINICAL TRIALS –

Alleviation of Menopausal Symptoms

Human Clinical Study – "A Complex of *Cirsium japonicum var. maackii (Maxim.) Matisum*. and *Thymus vulgaris* L. Improves Menopausal Symptoms and Supports Healthy Aging in Women." [1]

In this study, researchers evaluated the efficacy and safety of MS-10® in regards to menopausal symptoms in addition to monitoring the levels of various key markers in the body related to bone, vascular and hormonal health. A double-blind, randomized, placebo-controlled clinical trial was performed in 71 pre-, peri-, and post-menopausal women over the age of 45, for 12 weeks (with endpoint monitoring also occurring at 4 weeks) at a dose of 300 mg of MS-10® a day.

For the efficacy evaluation, the Kupperman Index (KI) and Menopause-Specific Quality of Life (MenQoL) questionnaires were used to assess the severity of menopausal symptoms, and the Psychological Well-Being Index (PWI) was used to assess the mental health status of the subjects.

The bone health evaluation monitored levels of serum osteocalcin, bone-specific alkaline phosphatase (BSALP), and C-telopeptide of type I collagen (CTx) and urinary levels of deoxypyridinoline (deoxyPYD) and N-telopeptide of type I collagen (NTx).

Additionally, insulin-like growth factor-1 (IGF-1), a hormone linked to healthy aging, and cortisol, the "stress hormone" were monitored, and endolethin-1 (ET-1) was measured as a marker for vascular health.

For the safety evaluation, adverse events were monitored and levels of sex hormones, such as estradiol (E2), progesterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH), were measured in addition to body weight, and blood pressure. In order to monitor potential liver injury, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were also measured.

Results.

Alleviation of Menopausal Symptoms

The menopause-specific quality of life (MENQOL) questionnaire was used to assess the physical and mental health and the quality of life of menopausal women before and after MS-10® intake. The questions in the MENQOL test are categorized into four aspects of health –vasomotor, psychosocial, physical, and sexual health.

A total of 12 individual menopausal symptom scores were assessed using Kupperman's Index (KI), an internationally accepted and well-documented method for recording the severity of climacteric symptoms.

Every one of the 12 individual symptoms (hot flashes, paresthesia (tingling sensation), sleep difficulties, nervousness, melancholia, vertigo, fatigue, joint discomfort, headache, palpitations, formication (skin crawling), and vaginal dryness) were significantly reduced in the MS-10® group compared with those in the control ($p < 0.05$). The study found that **MS-10® effectively improved the overall KI scores from baseline by approximately 48% after 12 weeks** (Fig. 1).

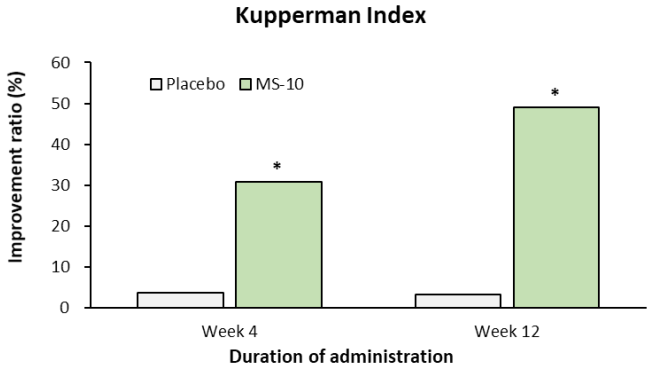


Figure 1. Improved Kupperman Index (KI) scores following administration of 300 mg/day of MS-10® for 12 weeks. Improvement ratio in KI scores are represented as % from baseline. Both 4- and 12-weeks KI total score results significantly improved in the MS-10® group compared with the placebo group. (*P < 0.05, t-test).

In addition, the **quality of life parameters evaluated by the (MenQoL) questionnaire indicated an overall improvement of 36%,** as well as improvement in each of the four sub-categories: vasomotor, psychosocial, physical, and sexual symptoms. In the placebo group, there were no significant changes (Fig 2).

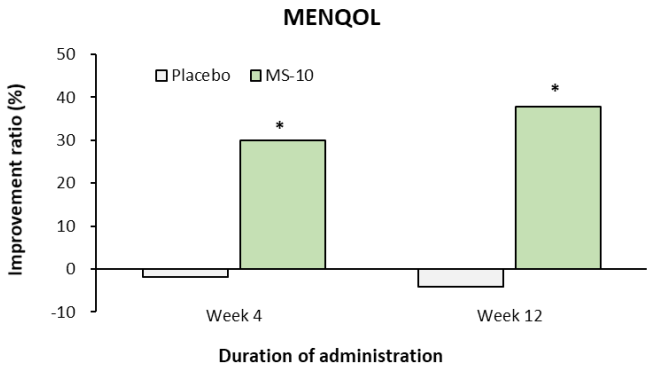


Figure 2. Improved MenQoL (Menopause-specific Quality of Life) scores following administration of 300 mg/day for MS-10® for 12 weeks. Improvement ratio in MenQoL scores are represented as % from baseline. (*P < 0.05, t-test).

Bone Health

The results demonstrated that the five bone-generation and resorption markers in serum (osteocalcin, BSALP, and CTx levels) and urine (deoxyPYD and NTx) significantly improved, suggesting that **MS-10® may help maintain bone health during menopause.** These results are consistent with the self-reported improvement in muscle and joint discomfort as per the KI and MenQol scores.

Reduction in Blood Cortisol Levels

Common symptoms in menopausal women include stress, fatigue, irritation, and sleep difficulties. Cortisol, known as the "stress hormone", plays a role in these psychosocial symptoms. [8,9]

The cortisol levels in MS-10® group dropped from 7.03 ± 0.46 ng/dl (week 0) to 5.94 ± 0.47 ng/dl (week 12) ($p < 0.05$), which indicated an approximately **16% reduction or improvement in the stress hormone levels** (Fig. 3). The control group exhibited no reduction in cortisol levels.

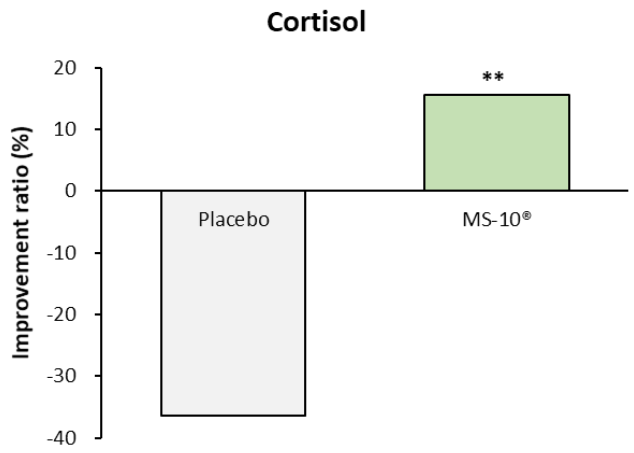


Figure 3. Improved Cortisol level in serum following administration of 300 mg/day MS-10® for 12 weeks. Improvement ratio of Cortisol levels are represented as % from baseline. (*P < 0.05, t-test).

Consistent with the reduction in cortisol, the Psychological Well-Being Index (PWI) score also saw a significant reduction from 49.51 ± 3.38 (0 week) to 38.80 ± 3.17 (week 12) ($p < 0.05$) in the MS-10® group, while no difference was seen in the placebo group ($p < 0.05$) (Fig. 4).

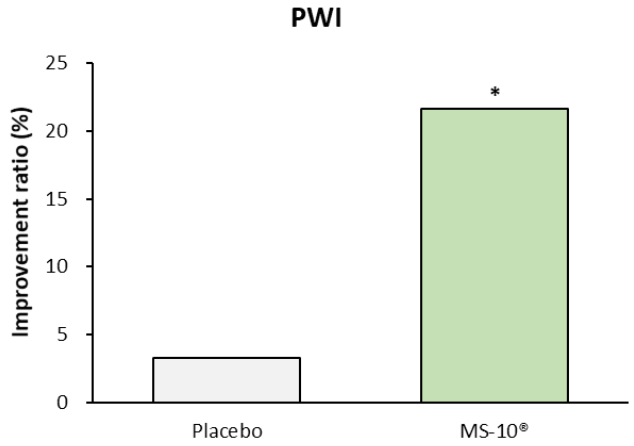


Figure 4. Improved PWI scores following administration of 300 mg/day MS-10® for 12 weeks. Improvement ratio of PWI scores are represented as % from baseline. (*P < 0.05, t-test).

Decreased ET-1 Levels Suggest Vascular Health Support

Decline in blood vessel health is an important issue in menopausal women, which may result in a variety of symptoms such as hot flashes and facial flushing. [10] Endolethin-1 (ET-1) is a peptide produced by vascular endothelial cells (inner cellular lining of arteries, veins and capillaries) with potent vasoconstrictor activity. Elevated levels of ET-1 can be a marker for poor vascular health, therefore, well-controlled down regulation of ET-1 may be a factor for promoting healthy vascular function. [11]

In the MS-10® group, the ET-1 serum levels decreased from 1.43 ± 0.06 pg/ml (0 week) to 1.21 ± 0.05 pg/ml (12 week), while there was no change in the placebo group. **These results indicate an approximately 15% improvement in serum ET-1 levels** (Fig. 5). Consistently, the MenQoL scores in the vascular symptoms sub-category also demonstrated improvement.

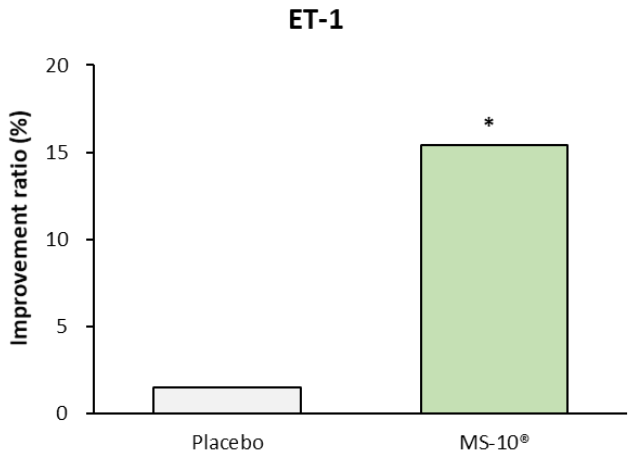


Figure 5. Improved Endothelin-1 (ET-1) level in serum following administration of 300 mg/day for 12 weeks. Improvement ratio of ET-1 level is represented as % from baseline. (*P < 0.05, t-test).

Safety Evaluation

To ensure the safety of MS-10®, female sex hormones E2, LH, FSH, and progesterone were evaluated. There were no significant changes in the levels of female sex hormones in the MS-10® group compared to those in the placebo control. Consistently, no significant changes were detected in the AST, ALT, creatine, bilirubin levels, blood pressure, and body weight of the MS-10® group compared with those of the placebo group ($p>0.05$). **The researchers concluded these results support the safety profile of MS-10®.**

Human Clinical Study – "The Natural Substance MS-10® Improves and Prevents Menopausal Symptoms, Including Colpoxerosis, in Clinical Research." [2]

To determine the effect that MS-10® supplementation had on climacteric symptoms, a 12-week, randomized, double blind, placebo-controlled clinical study was conducted in 30 middle-aged women.

Volunteers were randomly distributed into one of three groups and were given 300 mg of MS-10® daily, 500 mg of MS-10® daily, or placebo. Menopausal symptoms were evaluated using the Kupperman's Index (KI) and a vaginal dryness questionnaire before and after the 12-week study period.

Results. ***Decreased KI Scores Indicate Improved Menopausal Symptoms***

There was no significant difference in the KI scores of the placebo group. However, KI scores declined from 25 to 20 in the 300 mg/day MS-10®-treated group and from 24.7 to 15 in the 500 mg/day MS-10-treated group. **These results indicate that MS-10® improved menopausal symptoms dose-dependently by as much as 20% (300 mg/ day) and 40% (500 mg/day) from baseline** (Fig. 6). Moreover, 300 and 500 mg/day MS-10® effectively improved the vaginal dryness score by about 15% and 25%, respectively (Fig. 7).

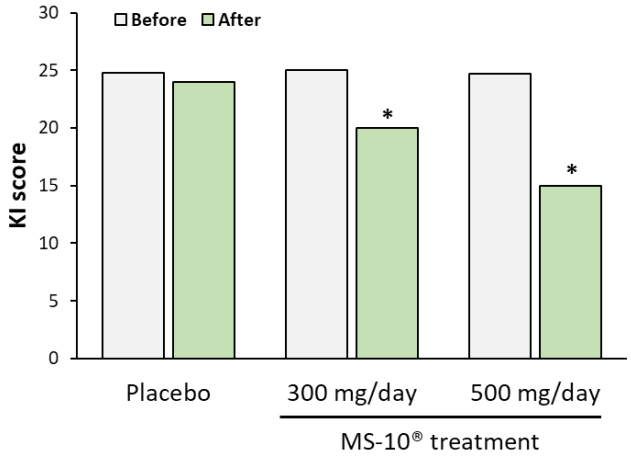


Figure 6. Improved Kupperman's Index (KI) scores following administration of 500 and 300 mg/day of MS-10, (*P <0 .05).

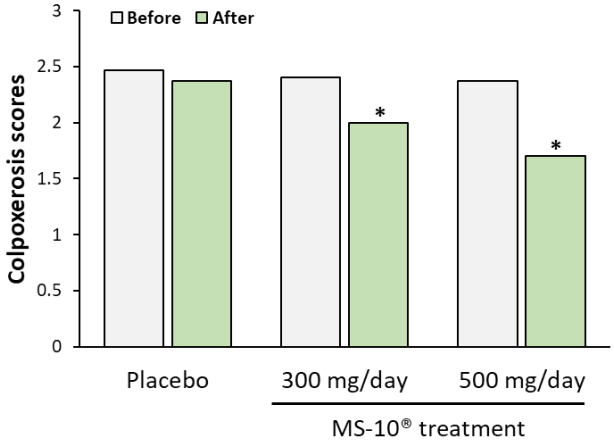


Figure 7. Improved colpoxerosis (vaginal dryness) scores following administration of 500 and 300 mg/day of MS-10®, (*P <0 .05).

Human Clinical Study – "Natural Substance MS-10 Improves Women's Health via Regulation of Estrogen Receptor." [3]

A 12-week randomized, double-blind, placebo-controlled clinical study was carried out in 62 middle-aged women (55.4± 1.5 years of age). Subjects were randomly assigned to receive either 500 mg/day of MS-10® or placebo. Clinical menopausal symptoms were evaluated using the Kupperman's Index (KI).

Results. ***Significant Improvement in Vaginal Dryness Scores***

In the MS-10® treatment group, the total KI score decreased significantly by about 18% whereas there was no decrease in the placebo group. **Vaginal dryness, a common symptom of menopause, significantly improved by about 21% after ingestion of MS-10®** in contrast to the placebo group which had no significant improvement (Fig. 8).

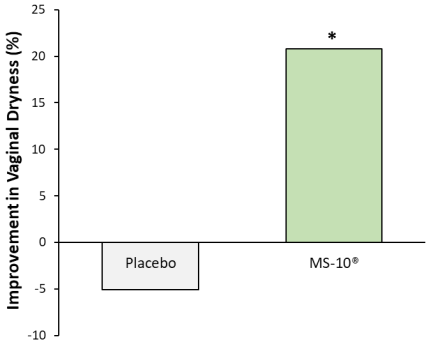


Figure 8. Improvement in vaginal dryness symptom following administration of 500 mg/day of MS-10® or placebo. Percent improvement in vaginal dryness scores presented as a mean. Significantly different values from placebo are indicated with an obelisk († p<0.05, Mann-Whitney Rank Sum Test).

Increased Serum IGF-1 Concentrations

In addition, blood samples were taken before and after the study period to measure serum IGF-1 levels. IGF-1 is a hormone growth factor that plays various roles in the body. In particular, IGF-1 plays a significant role in direct maintenance and protection of central nervous system cell activity of estrogen [12], and it has been reported that IGF-1 produced from osteoblasts (bone cells) plays a diverse role in bone health - from bone formation directly to bone regeneration, reconstitution, and growth. [13] Cellular studies have also shown that increased IGF-1 can inhibit cellular

aging [14], and that IGF-1 may exert beneficial effects on the vascular aging process.[15]

The serum **IGF-1 concentration significantly increased by about 10% in the MS-10® group** whereas there was no significant change in the placebo group. (Fig. 9)

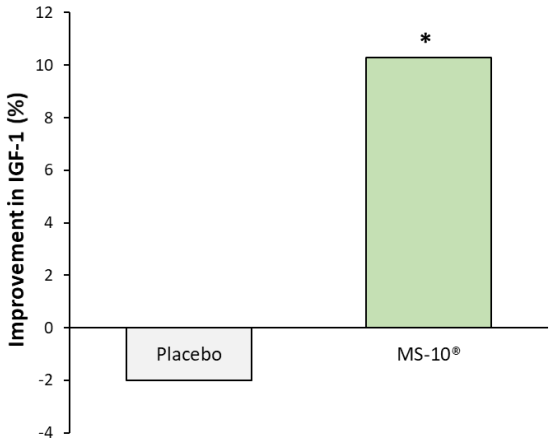


Figure 9. Improvement in insulin-like growth factor-1 (IGF-1) following administration of 500 mg/day of MS-10® or placebo. The % improvement from baseline is presented as a mean. Significantly different values from placebo are indicated with an obelisk (†P<0.05, two-sample, *t*-test).

Human Clinical Study – "The effects of MS-10 dietary supplement, mixture of Korean thistle and thyme extracts, on bone health, and symptoms in menopausal women." [4]

This 12-week, randomized, placebo-controlled study examined the effects that MS-10® supplementation had on bone health of menopausal women by measuring ossification-related markers and serum osteocalcin levels, in addition to evaluating menopausal symptoms via the Menopausal-Specific Quality of Life (MENQOL) questionnaire.

The mean age of the 142 female study participants was 54.85 ± 0.72. Study subjects were given 500 mg/day MS-10® (n=71) or placebo (n=71). The MENQOL questionnaire was used to assess the physical and mental health and the quality of life of menopausal women before and after MS-10® intake. The questions in the MENQOL test are categorized into four aspects of health –vasomotor, psychosocial, physical, and sexual health. The overall MENQOL scores, as well as the scores in each individual category, were evaluated. In addition, capillary blood samples were collected before and after the treatment with MS-10® or placebo to determine the levels of bone specific alkaline phosphatase (BSALP) and osteocalcin.

Vasomotor nerve symptoms occur when abnormalities in the nerves cause the blood vessels to expand or contract. These symptoms include facial flushing, night sweats, and excessive sweating. Psychosocial symptoms include life dissatisfaction, irritability, low work performance, interpersonal intolerance, and avoidance of interpersonal relationships. Physical symptoms of menopause include gastrointestinal symptoms, fatigue, sleep disturbance, loss of endurance, dry skin, weight gain, growth of facial hair, loss of skin elasticity, swelling, and urinary symptoms such as urinary incontinence. Sexual symptoms include loss of libido, vaginal dryness, and avoidance of intimacy.

Results.

Significant Improvement in MENQOL Scores

The average overall MENQOL score of women in the placebo group was 103.0 at baseline and 102.0 after 12 weeks; thus, there was no significant change or improvement in the placebo group (P=0.204). However, in the MS-10® group, the MENQOL score improved significantly, from 104.0 before MS-10® treatment to 87.8 after treatment (P < 0.001). **In other words, MS-10® intake resulted in an approximately 15.1% reduction in the overall MENQOL score, which reflects improvement in the severity of menopausal symptoms as a whole (P < 0.001).** The vasomotor, psychosocial, physical, and sexual health categories for the MS-10® treatment group all demonstrated significant improvements in their scores, **with the sexual health category showing an improvement of 18.8%.**

Improved Bone Heath Indicators.

The BSALP and osteocalcin levels of the MS-10® group decreased significantly, with no significant change in the placebo group (Figs. 10 and 11). High levels of osteocalcin in the blood can point to bone loss and predict low bone density and fracture risk in aging populations. In addition, researchers found that higher levels of osteocalcin in the blood were linked to lower bone mineral density and osteoporosis in four studies with a total of 417 postmenopausal women. [16, 17, 18, 19] Animal studies suggest that this is because the breakdown of bone tissue then releases osteocalcin from the bones and thus raises its circulating levels in the blood. [20]

Thus, the study researchers concluded that decreases in BSALP activity and osteocalcin levels in the MS-10® group may be indicative of improved bone health.

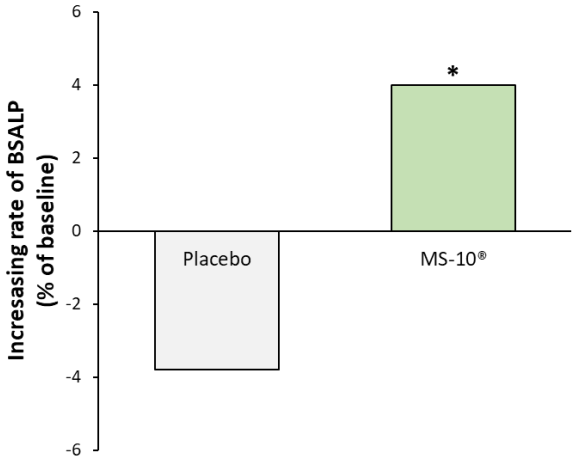


Figure 10. MS-10® administration improves bone-specific ALP (BSALP). The rate of improvement over baseline of circulating levels of BSALP before and after treatment of 500 mg/day of MS-10® for 12 weeks († p<0.05, two-sample *t*-test).

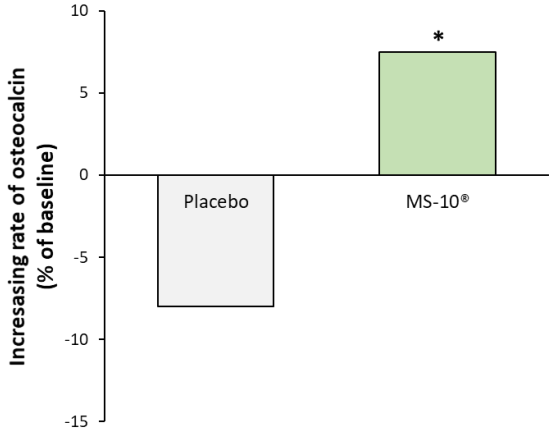


Figure 11. MS-10® administration improves osteocalcin levels. The rate of improvement of concentration of osteocalcin in the blood before and after treatment of 500 mg/day of MS-10® for 12 weeks († p<0.05, two-sample *t*-test).

PROPOSED MECHANISMS OF ACTION

Mechanism of Action: Enhances Estrogen Receptors in Postmenopausal Conditions

Cell Proliferation Assay [2]

MCF-7 cells are estrogen receptor-positive human cells that serve as a model for the study of estrogen, whereby estrogen stimulates the cells to proliferate and grow.

To evaluate the effects of MS-10®, as well as each of its components individually (Korean thistle extract and thyme extract) on cell proliferation, estrogen receptor-expressing MCF-7 cells were treated with various concentrations of estrogen, MS-10®, Korean thistle extract or thyme extract. Cell viability was assessed using the Alamar Blue proliferation assay.

The dose-dependent effects of estrogen (0.001– 1000 nM) on cell proliferation were investigated. Cell proliferation increased dose-dependently by treatment with estrogen up to a concentration of 10 nM and gradually decreased at higher concentrations. It was established that a low estrogen concentration of around 0.1 nM represented physiological menopausal conditions and a concentration of about 1 nM represented premenopausal conditions in humans. Physiological concentrations of estrogen increased cell viability, whereas abnormally high doses of estrogen inhibited the cell growth.

In the presence of MS-10® (50 µg/mL) and low concentrations of estrogen (lower than 1 nM), cell proliferation increased compared to the control and individual components. Interestingly, in the presence of MS-10®, cell proliferation decreased at very high concentrations of estrogen (higher than 10 nM). These results showed that MS-10® enhanced the physiological role of estrogen when its concentration was low to normal, which represents the postmenopausal to premenopausal conditions in the body. The reduction in cell proliferation by MS- 10® treatment when the concentration of estrogen was very high demonstrates that MS-10® prevented the over-proliferation of cells induced by abnormally elevated concentrations of estrogen, such as what arises when estrogen therapy is administered, indicating that it may perform a balancing or stabilizing role over estrogen receptor activity.

Thus, the researchers found that under a low concentration of estrogen, which represents postmenopausal physiological conditions, **MS-10® had beneficial effects on estrogen receptor-expressing MCF-7 cells by enhancing estrogen activity.**

Preclinical Model for Menopause [3]

In this animal study, the researchers used ovariectomized (OVX) Sprague-Dawley female rats as a preclinical model for menopause. OVX is a well-known experimental model of menopausal symptoms and mimics estrogen deficiency in females. Menopausal conditions were created by removing one ovary in each experimental animal and suturing the excision site. The control group was sutured without removal of the ovary. The rats were divided into three groups: the OVX group administered 50 mg/kg/d of MS-10®, the OVX group administered the placebo (saline) and the control group administered saline. At the end of the study period, stained cross-sections of the uteruses were analyzed by western blot for estrogen receptor expression.

The researchers found that estrogen receptor expression decreased in the OVX rats, however **those in the OVX group that consumed MS-10® daily had 2.8-fold higher estrogen receptor expression than animals not receiving MS-10®.**

In other words, the estrogen receptor expression improved overall in animal models that were consuming MS-10®, and estrogen receptor-expressing cells in the endometrium and epithelium lining significantly increased in the OVX menopausal animals that consumed MS-10® (Fig. 12).

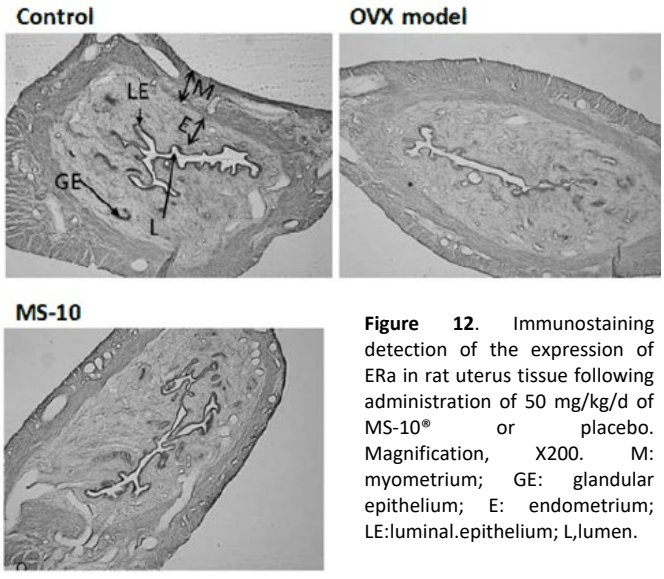


Figure 12. Immunostaining detection of the expression of ERa in rat uterus tissue following administration of 50 mg/kg/d of MS-10® or placebo. Magnification, X200. M: myometrium; GE: glandular epithelium; E: endometrium; LE:luminal.epithelium; L,lumen.

The authors concluded that **MS-10® effectively activated estrogen receptors** in the animal model of the study. These results are in line with the results to the MCF-7 cell proliferation assay described above, **indicating that when estrogen is in low concentration, the estrogen receptor expression may be enhanced in the presence of MS-10®.** Furthermore, after discontinuing use of MS-10® for 1 week, it was found that these effects were reversible and returned to baseline.

Conclusion

The results of various *in vivo, in vitro* and human clinical trials indicate the potential for MS-10® to be a safe and efficacious natural substance for alleviating menopausal symptoms.

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** These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.*

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