

# Therapeutic effects of Klimakt-Heel® compared with a phytotherapeutic preparation for the treatment of menopausal symptoms - a randomized study

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## SUMMARY

In dissatisfaction with conventional therapies, many of today's women turn to complementary and alternative medicine for treatment of menopausal symptoms. However, scientific studies on the effectiveness and safety of such therapies are lacking. In a randomized fashion, women with menopausal symptoms were allocated to either the homeopathic preparation Klimakt-Heel® or to the phytotherapeutic medication Femolene Ultra® for 12 weeks. The symptomatic effectiveness of therapy was evaluated as change in Kupperman score, where a lower score indicates less severe symptoms as follows: Severe = 3; Moderate = 2; Mild = 1; Not present = 0. The following symptoms were evaluated: vasomotor/hot flushes, profuse sweating, sleeping problems, nervousness/irritability, depressive moods, feelings of vertigo, inability of concentration, joint pain, headache and heart palpitations. Further, the effects on levels of plasma 17-β estradiol were assessed and tolerability evaluated. At the end of therapy, both treatment groups reported marked reductions in Kupperman scores: from 28.4 at baseline to 13.1 at Week 12 with Klimakt-Heel® and from 26.2 at baseline to 9.8 at Week 12 with Femolene Ultra®.

The response to treatment and the smoothness of therapy over time were greater in the group receiving Klimakt-Heel®. None of the therapies had an appreciable effect on plasma 17-β estradiol levels. Fewer women discontinued treatment with Klimakt-Heel® than Femolene Ultra®, indicating differences in tolerability between the therapies. In conclusion, Klimakt-Heel® is a safe, effective and well tolerated homeopathic remedy for menopausal symptoms and exerts its beneficial action in concordance with the principles of homotoxicology.

## INTRODUCTION

Menopause is a time of physiological as well as psychological changes which can be associated with severe reductions in quality of life. Modern lifestyles and the greater variety of demands posed on women in today's society lead to women suffering from not only the typical symptoms (vasomotor reactions, increased perspiration, sleeping problems, mood changes, headaches, joint pains, urogenital problems, etc.) but also from having to experience these symptoms while combining professional employment with family responsibilities. As today the average age for starting a family is several years higher than that in previous generations, menopausal women are increasingly likely to lead an active, demanding life and to be less inclined to accept losses of versatility and physical abilities.<sup>1</sup> Such demands have been a driving force of therapies to reduce the symptoms associated with menopause and to allow women to lead lives less burdened by menopause-associated restrictions in lifestyle.

However, the realization that traditional medical therapies are not a panacea is growing and the recent debate over hormone replacement therapy<sup>2-4</sup> has further increased awareness of the possible advantages with complementary and alternative medicine (CAM) such as homeopathy and homotoxicology. Such therapies are seeing a steady increase in popularity in many countries<sup>5-9</sup> and surveys of practice patterns consistently show women to use CAM medications more frequently than men.<sup>10,11</sup> Among women, these therapies are frequently used for menopausal symptoms.<sup>12,13</sup> In the US, a recent survey indicated that between 500,000 and one million women use CAM for menopausal symptoms.<sup>14</sup>

This growing popularity of CAM has empowered many women to deal more independently with ailments previously considered part of a woman's condition. However, with this increasing interest and availability of remedies follows a need for clinical studies in the efficacy and safety of alternative medications, conducted with the same stringency as research in conventional therapies. The aim of the current study was to determine the effectiveness of Klimakt-Heel® compared with the phytoestrogen preparation Femolene Ultra® in the treatment of typical climacteric symptoms.

Klimakt-Heel® is a homeopathic product with an established successful record of use in a large number of women and with excellent tolerability. However, controlled clinical research has so far been limited to one study (Kasilewski and Krogulski, manuscript in preparation) which confirmed the good experiences in everyday practice. The constituents of Klimakt-Heel® and their therapeutic effects are listed in Table 1. Femolene Ultra® is a phytotherapeutic product commonly used in countries such as South Africa for treatment of menopausal symptoms.<sup>15</sup> The constituents of Femolene Ultra® are listed in Table 2.

**Table 1:** Constituents of Klimakt-Heel® (1 tablet) and their medical uses

Constituent	Common name where applicable	Medical application
Sanguinaria canadensis D3	Red Puccoon, Bloodroot	Burning sensations, hot flushes, vasomotor disturbances, palpitations, dryness of mucous membranes <sup>24</sup>
Sepia succus D4	Cuttlefish ink	Prolapse, uterine disorders, dyspareunia <sup>21</sup>
Ignatia amara D4	St. Ignatius Bean	Nervous exhaustion, moodiness, migraine <sup>25</sup>
Cedron-simaruba ferroginea D4	Cedron	Neuralgic-type pains, palpitations, urinary incontinence, disturbed sleep <sup>24</sup>
Lachesis muta D12	Bushmaster venom	Hemorrhagic tendencies, palpitations, vasomotor flushes, ovarian dysfunction <sup>21</sup>
Sulphur D4		Local burning, throbbing, congestion, hot flushes, depression <sup>24</sup>
Stannum metallicum D12	Tin	Weakness, bearing-down sensations, uterine prolapse and vaginal pains, anxiety <sup>26</sup>

**Table 2:** Constituents of Femolene Ultra® (2 tablets) and their respective medical uses

Constituent	Common name where applicable	Medical application
Soya isoflavones - 80 mg		Providing estrogenic activity, reducing total estrogen load <sup>27</sup>
Cimicifuga racemosa - 80 mg	Black cohosh	Climacteric symptoms related to estrogen deficiency, vasomotor flushes, irritability, palpitations, depression, anxiety, vaginal atrophy <sup>28</sup>
Dioscorea villosa - 50 mg	Mexican Wild Yam	Potential progestin replacement, osteoporosis <sup>29</sup>
Angelica sinensis - 40 mg	Dong quai	Abnormal bleeding patterns, vasomotor flushes, vaginal dryness <sup>30</sup>
Vitex agnus-castus - 80 mg	Chasteberry	Stimulate the pituitary gland to produce FSH and LH, restore hormonal equilibrium <sup>31</sup>
Gingko biloba - 120 mg	Gingko	Memory difficulties, dizziness, headache, anxiety <sup>29</sup>
Hypericum perforatum - 75 mg	St John's Wort	Neuralgic and rheumatic pain, depression, sleeplessness, anxiety <sup>29</sup>
Folic Acid - 100 mcg		Depression, osteoporosis <sup>30</sup>
Biotin - 50 mcg		General need of strengthening, hair loss <sup>30</sup>
Magnesium - 150 mg	Magnesium carbonate	Nerve and muscle malfunction, heart disease, osteoporosis <sup>30</sup>
Zinc - 5 mg	Zinc gluconate	Immune-system disorders, hormone deficiency <sup>30</sup>
Multi Vitamins • Vitamine A - 2000 mcg • Vitamine B1 - 1.4 mg • Vitamine B2 - 1.6 mg • Vitamine B3 - 10 mg • Vitamine B5 - 5 mg • Vitamine B6 - 5 mg • Vitamine B12 - 2 mcg • Vitamine C - 100 mg • Vitamine D - 5 mcg • Vitamine E - 10 mg		General strengthening

The effects of the treatments were evaluated as change in Kupperman score. This instrument focuses primarily on symptomatic relief, assessed on the basis of a summary of the severity of the climacteric complaints.<sup>16,17</sup> A Kupperman score >35 represents severe symptoms whereas a score of <15 represents favorable therapeutic result or very mild to absent symptoms (Table 3). Other aspects of the study were to establish the action of the two products on hormones, measured on levels of plasma 17-β estradiol, and to conduct a general therapeutic comparison between the two products.

**Table 3:** Kupperman score strata and the corresponding severity of menopausal symptoms

Kupperman score	Severity
>35	Severe
20-35	Moderate
15-20	Mild
<15	Favorable therapeutic result

**Table 4:** Inclusion and exclusion criteria

Inclusion criteria
Female sex
Age 44 - 57 years
Peri-menopausal or menopausal
Currently experiencing menopausal symptoms
Signed patient information and consent form
Exclusion criteria
Currently undergoing hormone replacement therapy
Stopped hormone replacement therapy within 6 weeks of study enrolment
Bilateral ovariectomy or total hysterectomy
Premature failure of ovulation due to autoimmunization, primary germ cell deficiency, a resistance to pituitary gonadotropin, or other reasons
Any process that had impaired blood flow to the ovaries

## METHODS

Participants in this study were recruited from the Gauteng province of South Africa. Patients were recruited both in a community setting and from physicians' practices. Inclusion criteria (Table 4) were female sex, age 44-57 years, menopausal symptoms and written, informed consent to take part. Exclusion criteria were other treatments for menopausal symptoms than those studied, and artificially induced menopause.

Participant meeting inclusion criteria were randomly allocated Klimakt-Heel® or Femolene Ultra® by the researcher. During the trial, participants did not know what treatment they were receiving however, on completion of the trial participants were informed about which treatment they had received. The participants were required to participate in the study for the duration of 12 weeks, unless they experienced side effects. The practical component of the study consisted of an initial consultation and three follow-up consultations for each participant.

At the first consultation, the participant completed the modified Kupperman Menopause Index and blood samples were drawn in order to determine plasma 17β-estradiol levels. Furthermore, the participant received a four-week supply of either Femolene Ultra® or Klimakt-Heel®. Both treatments were administered at the doses recommended by the respective manufacturer for the duration of the study (Klimakt-Heel® was given at a dose of 1 tablet 3 times per day and Femolene was administered at a rate of 1 tablet 2 times per day).

Patients were followed up for a total of 12 weeks, with visits at Weeks 0 (baseline), 4, 8 and 12. At each visit, patients completed a modified Kupperman Menopause Index score card and an index score was calculated. A quantitative assessment of menopausal symptoms was achieved by grading in severity: Severe = 3; Moderate = 2; Mild = 1; Not present = 0. The following symptoms were evaluated: vasomotor/hot flushes, profuse sweating, sleeping problems, nervousness/irritability, depressive moods, feelings of vertigo, inability of concentration, joint pain, headache and heart palpitations. Each symptom was assigned a specific constant, which was higher for the typical climacteric complaints, such as vasomotor flushes, based on the greater significance of such symptoms. Conversely, the rarer the complaint, the lower the multiplication constant. The severity of each symptom was multiplied by the given constant, the resulting values for each symptom were added and the total value gave an indication to the severity of the climacteric syndrome.

In addition, estrogen blood tests were carried out at baseline and at Week 12. At each sampling, 7 ml of blood were drawn and analyzed for 17 $\beta$ -estradiol concentrations (pmol/l) by chemoluminescence test on a Centaur apparatus by an independent laboratory. The level of detection of plasma 17 $\beta$ -estradiol in the assay was 37 pmol/l.

Wilcoxon Rank Sum test, a non-parametric distribution-free test, was used. The sum of rank Kupperman scores together with mean rank were recorded together with average Kupperman score. The Kupperman Menopause Index scores at each time interval (Weeks 0, 4, 8 and 12) for Femolene Ultra<sup>®</sup> and Klimakt-Heel<sup>®</sup> were statistically analyzed. From the Wilcoxon Rank Sum test, the sum of rank scores together with mean rank was recorded. In addition, the number of participants and average Kupperman score was noted. The results for Femolene Ultra<sup>®</sup> and Klimakt-Heel<sup>®</sup> at baseline and at each time point were compared. The statistical change in Kupperman score for Femolene Ultra<sup>®</sup> and Klimakt-Heel<sup>®</sup> from the previous time interval was separately analyzed.

As all women in the study were menopausal, it was not possible to sample and measure estrogen levels at the same point of the menstrual cycle for all participants and estrogen levels were analyzed descriptively.

## RESULTS

### Patients

The trial enrolled a total of 30 participants; 15 of whom were treated with Femolene Ultra<sup>®</sup> and 15 who received Klimakt-Heel<sup>®</sup>. One participant in the Femolene Ultra<sup>®</sup> group withdrew from the study because of recurring migraines. One participant was withdrawn from the Klimakt-Heel<sup>®</sup> group as she was prescribed hormone replacement therapy, one of the exclusion criteria of the research.

The two treatment groups differed slightly at baseline in terms of Kupperman score, with the group receiving Klimakt-Heel<sup>®</sup> scoring slightly higher than the Femolene Ultra<sup>®</sup> group, indicating that patients receiving Klimakt-Heel<sup>®</sup> had somewhat worse menopausal symptoms than those receiving Femolene Ultra<sup>®</sup> (Table 5). Klimakt-Heel<sup>®</sup> patients had an average baseline score of 28.4 compared with 26.2 for patients in the Femolene Ultra<sup>®</sup> group.

### Changes in Kupperman scores with treatment

Both study therapies led to major improvements in menopausal symptoms, reflected in marked reductions in Kupperman scores from baseline to the end of the study. As represented graphically in Figure 1, a gradual reduction in Kupperman scores could be observed in both treatment groups from Week 4 onwards and there was a continuous improvement in Kupperman scores in both treatment groups over time, with an approximate reduction in Kupperman score of 3.3 per four-week period with Klimakt-Heel<sup>®</sup> and 4.1 with Femolene Ultra<sup>®</sup>, respectively. Notably, the Klimakt-Heel<sup>®</sup> group showed a more constant level of reduction during the entire time-course of the study (Figure 1) which was in contrast to patients receiving Femolene Ultra<sup>®</sup>, where the major improvement was seen between baseline and Week 4 (Figure 1a, Figure 1b). If these differences in the first four-week period between treatment groups were accounted for, the average reduction in Kupperman score during the last eight weeks of the study would be 3.5 with Klimakt-Heel<sup>®</sup> versus 2.7 with Femolene Ultra<sup>®</sup>. The absolute reductions in Kupperman score were similar at the end of the study: 16.4 and 15.3 for the Femolene Ultra<sup>®</sup> and Klimakt-Heel<sup>®</sup> patients, respectively. Relative reductions were also similar (63% and 54%, respectively; Table 1).

A statistical analysis showed that the group on Klimakt-Heel<sup>®</sup> experienced a more significant decrease in symptoms with a two-sided  $P \geq |S\text{-mean}|$  value of 0.08. This indicates that 92% of the participants on the Klimakt-Heel<sup>®</sup> experienced an improvement in climacteric symptoms, with an average decrease of 30% in the Kupperman scores. The group on Femolene Ultra<sup>®</sup> also experienced an improvement in symptoms with a Two-sided  $P \geq |S\text{-mean}|$  value of 0.12, which indicates that 88% of the participants had a decrease in symptoms with an average reduction of 32% in Kupperman scores. Thus, more women responded to treatment with Klimakt-Heel<sup>®</sup> than to Femolene Ultra<sup>®</sup> therapy.

### Changes in estrogen levels

The changes from baseline to end of study in 17 $\beta$ -estradiol blood test results are shown in Figure 2. A level of 17 $\beta$ -estradiol <136 pmol/l indicates a post-menopausal state without hormone replacement therapy. Various other higher and lower results indicate various phases of the menstrual cycle.<sup>18</sup> As is evident from the graphs, there was no consistent pattern and no statistically significant changes from baseline in any of the groups. In the Klimakt-Heel<sup>®</sup> group, most subjects appeared to exhibit slight increases in 17 $\beta$ -estradiol, whereas in the Femolene Ultra<sup>®</sup> group, similar number of women showed increases and decreases in 17 $\beta$ -estradiol levels from baseline. None of these differences between the groups was significant, however. The magnitude of the changes in 17 $\beta$ -estradiol levels was very similar in both treatment groups.

### Tolerability

In terms of tolerability, it was notable that more patients (20%) withdrew from treatment with Femolene Ultra<sup>®</sup> than with Klimakt-Heel<sup>®</sup> (15%). This was particularly relevant in light of the fact that patients in the Klimakt-Heel<sup>®</sup> group were on average more afflicted by menopausal symptoms than patients in the Femolene Ultra<sup>®</sup> group.

## DISCUSSION

This randomized, blinded study shows that the homeopathic therapy Klimakt-Heel<sup>®</sup> is an effective and well-tolerated treatment for menopausal symptoms in women aged 44-57 years. The subjects were followed-up for a total of 12 weeks and there were significant improvements in Kupperman score from baseline. The improvements were of similar magnitude to those seen with the phytotherapeutic agent Femolene Ultra<sup>®</sup>, but with more women responding in the Klimakt-Heel<sup>®</sup> group and with better tolerability in terms of discontinuation from treatment.

**Table 5:** Kupperman scores at the beginning and end of the study. The fact that both groups scored <15 at the end of the study is an indication of the effectiveness of the therapies

	Femolene Ultra <sup>®</sup>		Klimakt-Heel <sup>®</sup>	
	Baseline	End of study	Baseline	End of study
Average Kupperman score	26.2	9.8	28.4	13.1
Absolute change		16.4		15.3
Relative change vs baseline		63%		54%

**Figure 1**

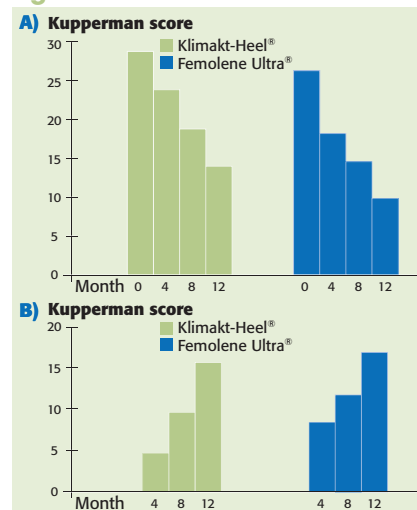


Figure 1. a) Effects of Klimakt-Heel<sup>®</sup> compared with Femolene Ultra<sup>®</sup> treatment on Kupperman score over time of treatment, with measurements taken every four weeks. The gradual improvement over time in both groups is evident, as is the smoother action of Klimakt-Heel<sup>®</sup>. b) Cumulative reductions in Kupperman score over the course of the treatment. As in the overall scores, the smoother action of Klimakt-Heel<sup>®</sup> is evident from the graphs.

**Figure 2**

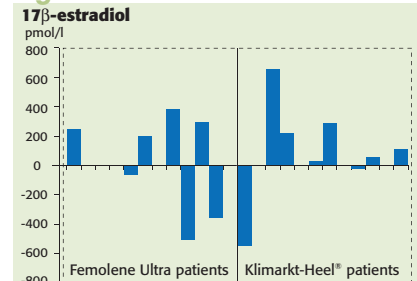


Figure 2. Change in 17 $\beta$ -estradiol levels in women treated with Femolene Ultra<sup>®</sup> (left box) and Klimakt-Heel<sup>®</sup> (right box), respectively. The lack of consistent difference indicates that Klimakt-Heel<sup>®</sup> has no potentially adverse effects on hormone levels and that the homeopathic therapy works in a manner fundamentally different from hormone replacement therapy. The level of detection of plasma 17 $\beta$ -estradiol in the assay was 37 pmol/l.

The two treatment groups were slightly different at baseline: women allocated to the Klimakt-Heel® group had on average higher Kupperman scores than women in the Femolene Ultra® group. These differences indicated that the women receiving Klimakt-Heel® were somewhat more affected by menopausal symptoms and in greater need of effective therapy than women receiving Femolene Ultra®. However, there is no indication that the differences in baseline criteria influenced the effectiveness of the respective therapies and we believe that the conclusion of overall similarity of effectiveness between Klimakt-Heel® and Femolene Ultra® is very sound based on the data collected in the study.

An interesting observation was that whereas patients taking Femolene Ultra® showed greatest improvements in climacteric symptoms during the first four weeks and less improvement during the remainder of the study, patients on Klimakt-Heel® on the other hand showed a smoother, more continuous mode of action with amelioration of symptoms throughout the entire study period (Figure 1). These differences between therapies are in keeping with the current thinking of phytotherapeutic and homeopathic/homotoxicological pharmacodynamics. Homeopathic remedies act on the principle of "like cures like" in obedience to the law of similars: by giving patients a small dose of a substance that produces similar effects to those of the illness.<sup>19</sup> Thus, an initial low effect, or even a worsening of symptoms, is no sign of lack of effect. Such aggravations are expected when treating homeopathically since the drug itself produces symptoms similar to those of the illness.<sup>20</sup> In contrast, phytotherapeutic medication tends to have a quicker initial action, but there is a commonly observed tendency for patients to develop tolerance to the medication (Townsend, W, personal communication). The greater response rates of Klimakt-Heel® at the end of the study are a further sign of the effectiveness of this remedy over the longer time period.

The 17 $\beta$ -estradiol blood results did not show any consistent patterns. Postmenopausal status is typically indicated by estradiol levels <136 pmol/l, with various other higher and lower levels indicating different phases of the menstrual cycle.<sup>18</sup> It would have been desirable to conduct all the 17 $\beta$ -estradiol tests at the same time of the menstrual cycle for all the participants. However, detecting the menstrual phase in a menopausal woman is exceedingly difficult since the menstrual cycle is very irregular during this transition period. All study subjects were menopausal and different subjects may well have been at different stages within their menstrual cycle when the blood tests were performed.

Despite these limitations of the descriptive analysis, the results are a very strong indication that neither Femolene Ultra® nor Klimakt-Heel® increase plasma estrogen levels. These products should thus not be considered to be hormone replacement therapy. This is particularly true for Klimakt-Heel, which in contrast to Femolene Ultra® does not contain phytoestrogens. Phytoestrogens were not detected in the blood tests performed in women taking Femolene Ultra®, but such substances might possibly have been transformed into other estrogen metabolites other than 17 $\beta$ -estradiol. In contrast, Klimakt-Heel® only contains homeopathic ingredients and no estrogens or phytoestrogens. In homeopathy and homotoxicology, a remedy is given which acts in the same way as the reactive mode of the organism and defense mechanisms. Homeopathic therapies stimulate the organism and defense mechanisms and are thus a reactive and stimulatory medicine.<sup>21</sup>

Both therapies were well tolerated and there were few discontinuations, although an indication of differences between treatments was given by the smaller percentage of women who discontinued Klimakt-Heel® therapy compared with Femolene Ultra®. Homeopathic medications in general have a very good tolerability profile<sup>11</sup> and the data on Klimakt-Heel® support the low rates of adverse events and discontinuation (manufacturer's surveys; Kasilewski and Krogulski, manuscript in preparation). The good tolerability of Femolene Ultra® was a reassuring finding, since the potential safety of phytotherapies have been the subject of controversy recently.<sup>22</sup> The current study found no ground for worries about the safety of the phytotherapeutic agent. Good tolerability is an important characteristic of a treatment for menopausal symptoms, since this stage of life lasts for an extended time and active modern women are not willing to settle for suboptimal therapies, either in terms of efficacy or tolerability.

The awareness of the advantages of CAM therapies compared with conventional medical treatments is growing worldwide and the recent worry about possible negative effects of hormone replacement therapy<sup>24</sup> has fuelled the need for safe and well-tolerated alternatives and extensions to common treatments. The demands made by today's society on today's women by extension increase the demand for safe and effective therapies to empower women to lead full-filling lives, which may be a major reason why women turn to practices such as homotoxicology<sup>12,13</sup> and why they do so in greater numbers than men.<sup>10,11</sup> Other therapies of choice are herbal remedies, chiropractic, meditation<sup>15</sup> and dietary supplements and foods containing phytoestrogens.<sup>23</sup> But again, some of these therapies have been associated with safety issues recently<sup>22</sup> and for some there is a lack of clinical studies demonstrating clear evidence of efficacy. The current report adds to the scientific research and reinforces the effectiveness and tolerability of Klimakt-Heel® and Femolene Ultra®. For other phytotherapeutic and homeopathic products in treating menopausal and climacteric symptoms, more research is needed and the conclusions drawn here are only applicable to the treatments studied.

Thus, in conclusion, the homeopathic preparation Klimakt-Heel® appears to be as effective and possibly better tolerated than the phytotherapeutic agent Femolene Ultra® in treating menopausal symptoms in women. This provides further support for the view that Klimakt-Heel® is an appealing treatment option for modern women who need to accommodate the varying demands of active, responsible, lifestyles.

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