

Effect of daily supplementation of soy isoflavones on hot flashes and night sweats in African menopausal women

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ABSTRACT

The aim of this study was to evaluate the effectiveness of a pharmaceutical grade isoflavone supplement (Inoclim[®]) 40 mg per capsule of soy extract rich in daidzin and genistin) on the number of hot flashes and night sweats in menopausal African women. This open, prospective, multicenter study involved 140 menopausal women with climacteric symptoms (*i.e.*, a minimum of five hot flashes and/or moderate to severe night sweats per day). These patients received a daily 40-mg supplement of soy isoflavone contained in an Inoclim[®] capsule (Laboratoire Innotech International, France). The dose was increased to two capsules per day when there were more than five hot flashes or when the women could not sleep because of night sweats. The patients were followed up over a 4-month period and data were analyzed using EPI-Info[™] version 3.5.1. The outcome measure was fewer hot flashes and night sweats. The mean daily number of episodes of hot flashes was 5.7 at baseline and 1.8 at week 16, corresponding to a decrease of 68.4% ($n = 93$ patients at baseline and $n = 66$ at 16 weeks). The mean number of daily episodes of night sweats was 3.7 at baseline and 0.8 at week 16, corresponding to a decrease of 78.4% ($n = 127$ patients in the first week and $n = 73$ at 16 weeks). Over 80% of patients took a single one 40 mg capsule per day. The percentage of patients who

adhered to the prescription was more than 95% during the 4-month follow-up period. These results confirm the effectiveness of a pharmaceutical grade isoflavone supplement (40 mg, rich in genistin and daidzin) on vasomotor symptoms in menopausal women.

KEYWORDS

Menopause; Climacteric Disorders; Hot Flashes; Night Sweats; Soy Isoflavones; Genistin, Daidzin; Genistein; Daidzein; Inoclim

1. INTRODUCTION

The most common symptoms associated with menopause include vasomotor instability, decreased libido, vaginal dryness, insomnia, and bone or joint disorders. Hot flashes are a vasomotor response to estrogen deficiency, which generally appears up to five years after the end of menstruation, and lasts for at least one year [1]. Hot flashes and sweating are estimated to affect 80% of the female population in Western countries. However, this prevalence is lower in Southeast Asian populations [2]. With regard to African women, few studies are available in the relevant literature, and those that exist mainly reflect a lack of information on menopause (e.g., symptoms and available treatments) [3-7]. The prevalence of climacteric disorders varies according to studies from 57% to 85%, and their management remains inadequate [4-6]. In addition, the age of menopause onset seems to be slightly hi-

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gher for African women compared to the rest of the world (between 48 and 49 years on average).

Menopausal women often consider hot flashes to be the most difficult symptom to tolerate. These vasomotor-related effects can greatly impact the quality of life [8]. Hormone replacement therapy (HRT) remains the most effective treatment for vasomotor instability during menopause [9]. Nevertheless, treatment approaches must be personalized by evaluating the risk/benefit balance for each patient and taking into account certain risk factors, including breast cancer, coronary events, stroke, and thromboembolism. Indeed, several studies have suggested that long-term HRT increases the risk of breast cancer, ovarian cancer, endometrial cancer, and stroke [9]. This explains the high demand for non-hormonal treatments for menopausal disorders [10]. Isoflavones are substances that have an affinity for estrogen receptors, although they are chemically non-steroidal [11,12]. Their safety in humans has already been demonstrated in previous studies [13]. However, findings related to their effects on menopausal symptoms have been at times contradictory due to the variety of isoflavones and standardization of doses. The two main soy isoflavones are daidzin and genistin. They are transformed within the intestinal tract into biologically active compounds, daidzein and genistein. The chemical structure of genistein and daidzein is similar to that of 17β -estradiol, which allows them to bind estrogen receptors, but with a relatively low affinity [14]. The Inoclim[®] formulation (Laboratoire Innotech International, France), which contains 40 mg of soy isoflavones, has not been evaluated in the context of climacteric disorders. Therefore, the goal of this study was to evaluate the effect of Inoclim[®] on hot flashes and night sweats in menopausal African women.

2. METHODS

This was a prospective, open, and multicenter study carried out on menopausal women with hot flashes and/or night sweats. During the 16-week study, the patients received a daily supplement of one Inoclim[®] capsule (Laboratoire Innotech International, France), which contained 40 mg of soy isoflavones. In some cases, the dose was increased to two capsules per day, when deemed necessary by the investigator.

To be included in the study, patients had to be menopausal for at least one year and to experience at least five episodes of hot flashes per day and/or moderate to severe night sweats every day. Exclusion criteria were women with ongoing hormonal treatment (*i.e.*, taken in the last six weeks) or a history of hormone-dependent cancer (*i.e.*, breast, uterus, ovarian).

A total of 270 patients were included in 10 countries (Benin, Burkina Faso, Cameroon, Congo-Brazzaville, Ivory Coast, Gabon, Guinea, Mali, Mauritius, and Togo).

During the selection or inclusion visit, patients were informed of the study both orally and in writing. Also, a general and gynecological clinical examination was performed. Appointments were scheduled at the end of every month for four months (*i.e.*, three follow-up visits and one end-of-trial visit). Each patient recorded information regarding hot flashes and night sweats in an individual journal. Additionally, every patient signed an informed consent form before the beginning of the study, which was carried out in accordance with the latest version of the Helsinki Declaration on recommendations for biomedical research.

Evaluation criteria included the number of hot flashes and daily episodes of night sweats during the study. The data collected on hot flashes and night sweats were daily, but were grouped per week for analysis. We entered data into spread sheets and analyzed using EPI-Info[™] version 3.5.1. We calculated mean number of hot flashes and/or daily night sweats during the 16 weeks of the study and represented these graphically using Excel spread sheet. Only women who finished the study were included in the effectiveness analysis.

3. RESULTS

Altogether, 241 patients were included in the study. The mean age was 51 years old (range: 38 - 66 years). Among them, 9.2% had a personal history of cardiovascular disease. At the end of the four-month study period, the complete files (observation notebook and patient follow-up journal) for 140 patients were analyzed. The other patients were lost to follow-up due to unusable files or because they had chosen to discontinue treatment.

In accordance with the study protocol, patients who were not followed up for at least three months were not included in the final analysis of treatment effectiveness. A progressive decrease in the number of hot flashes and night sweats was observed during the 16 weeks of follow-up (**Figure 1**). Overall, the mean number of hot flashes and/or night sweats went from 9.4 at baseline to 2.6 after four months of treatment, which is an overall decrease of 72.3%. Since not all patients experienced hot flashes and night sweats simultaneously, the data for each symptom could be analyzed separately. The mean number of daily hot flashes was 5.7 at baseline ($n = 93$ patients) and 1.8 at week 16 ($n = 66$), which is a decrease of 68.4%. The mean number of daily night sweats was 3.7 at baseline ($n = 127$ patients) and 0.8 at 16 weeks ($n = 73$), which constitutes a decrease of 78.4%.

The percentage of patients who adhered to the prescriptions was greater than 95% during the four months of follow-up, with more than 80% of patients remaining on one capsule per day.

The product was well tolerated. In fact, discontinua-

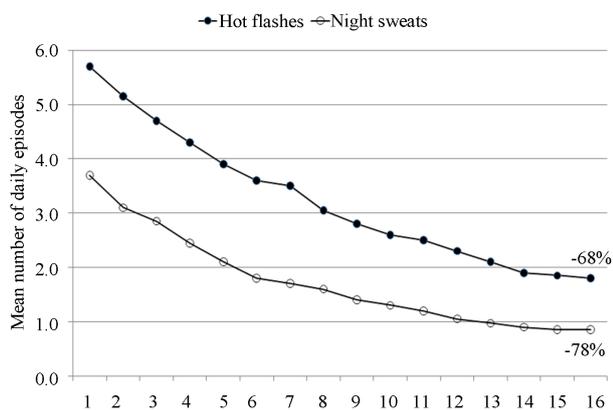


Figure 1. Mean number of hot flashes and/or daily night sweats during the 16 weeks of the study (n = 140).

tions due to adverse effects were rare, occurring in five patients at the one-month follow-up visit (palpitations, dizziness, high blood pressure, skin allergy) and in two patients at the two-month follow-up (stomach pain, psychiatric disorders). The contribution of Inoclim[®] treatment to these adverse effects was not evaluated.

4. DISCUSSION

Our study was carried out with pharmaceutical grade soy extract, which was rich in daidzin and genistein. During the four months of the study, we observed a gradual decrease in hot flashes (68.4% at 16 weeks) and night sweats (78.4% at 16 weeks). Notably, the daily dose was adhered to by more than 95% of women throughout the study. In addition, more than 80% of the patients received only one capsule per day of isoflavone-rich soy extract (40 mg/day) and did not feel the need to increase the daily dose. Mixed results have been reported in clinical studies that examined the effects of dietary intake of soy or isoflavone supplements on hot flashes [15-29]. These inconsistent findings could be explained by the diversity of products studied, the origin of the extracts, the composition/dosage of isoflavones (particularly daidzein), the number of hot flashes at baseline, and individual metabolism (e.g., equol production) [30-34]. According to The North American Menopause Society, treatment of vasomotor symptoms using isoflavones can be achieved with an initial dose of 50 mg/day for at least 12 weeks [34]. Here, we demonstrated that a 40-mg daily dose with Inoclim[®] was sufficient to reduce climacteric disorders for 80% of patients. However, this study had some limitations. Besides being an open study, problems related to completing the study documents (*i.e.*, non-standardized completion, difficulty in maintaining regular follow-up) made analysis of the results complex. Nevertheless, our findings have contributed essential data to the limited information that exists regarding menopausal women in Africa, which has mostly come from prospective, open,

and/or descriptive studies [3-7]. We propose that a future comparative study should be carried out, involving placebo control, a robust protocol, and a coherent follow-up that incorporates usual management of African patients.

Our results are consistent with studies that have been carried out in other regions. Indeed, Taku's meta-analysis, which included 36 comparative studies vs. placebo, showed a statistically significant decrease of 20.6% in the frequency of hot flashes ($p < 0.00001$), as well as a 26.2% reduction in their severity ($p = 0.001$), using a mean dose of isoflavones of 54 mg/day for six weeks to 12 months [24]. Furthermore, Upmalis *et al.* compared the efficacy of 50 mg of genistin plus daidzin to placebo in a randomized, double-blind study [25]. After six weeks, the number of daily night sweats had decreased by 60% in the genistin plus daidzin group and by 25% in the placebo group ($p < 0.04$). The severity of hot flashes had also decreased after 12 weeks by 27% in the genistin plus daidzin group and by 19% in the placebo group ($p = 0.01$). Another randomized, double-blind study by Crisafulli *et al.* compared HRT (1 mg/day of 17β -estradiol and 0.5 mg of norethisterone acetate) to 54 mg/day of genistein and to placebo [26]. As expected, it was observed that HRT, which remains the standard therapy for climacteric disorders, reduced the number of hot flashes by 92% after 12 months of treatment, whereas the placebo led to only a 19% reduction. The effect of genistein, which led to a 55% decrease in hot flashes, confirmed the efficacy of isoflavones ($p < 0.01$ vs. placebo). Notably, there was a 50% decrease in hot flashes after the third month of treatment with genistein. In Cheng's randomized, double-blind study against placebo, a 57% reduction ($p < 0.01$) in hot flashes was observed after three months of treatment with isoflavones (60 mg/day) [27]. Additionally, D'Anna's randomized, double-blind study against placebo led to decreased hot flashes following one month of genistein treatment (54 mg/day) and reached a peak effect after 12 months (56.4% reduction; $p < 0.001$) [28]. Finally, a 51% decrease ($p = 0.049$) in the number of hot flashes was observed following genistein treatment (30 mg/day for 12 weeks) in Evans's randomized, double-blind, multicenter study [29].

Taken together, a four-month treatment with Inoclim[®] was well tolerated by menopausal patients in our study. However, the contribution of this supplement to potential adverse effects was not evaluated. Nevertheless, the fact that isoflavones were well tolerated seems to confirm previous comparative, double-blind studies indicating no differences in the frequency of adverse events between isoflavone-treated and placebo groups [35-41].

5. CONCLUSIONS

These results confirm the efficacy of a pharmaceutical grade isoflavone supplement (Inoclim[®], 40 mg), which is

rich in genistin and daidzin, on vasomotor disorders in menopausal African patients. Specifically, we found that Inoclim[®] treatment led to a significant decrease in the number of hot flashes and night sweats while displaying very good long-term tolerance.

6. LIMITATIONS

This study was based on two climacteric symptoms whereas about forty of such symptoms have been described. It was not randomized and controlled using a placebo thus findings may not be conclusive. Some participants received two capsules but analyses were not based on the number of capsules received. As it was a longitudinal symptom-based trial, the biochemistry of plasma estrogens should be combined with such analyses in future trials

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