Fast dissolving *Agnus castus* fruit extract for the premenstrual syndrome
A controlled clinical trial

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SUMMARY

The aim of the first part of this randomised and controlled clinical study was to evaluate the efficacy and tolerability of a fast acting form of *Agnus castus* fruit extract (*Monoselect Agnus*, MA) administered for 90 days, in comparison with a magnesium supplement, for women with the premenstrual syndrome (PMS).
The aim of the second part of the study was to establish the efficacy of a treatment scheme where MA was given only 7 days before the menstrual cycle for a further 3 months in comparison with the suspended therapy. 82 women were enrolled and randomised in two groups (MA group: 42; Magnesium group: 40). MA (40 mg/tablet) or matching Magnesium (300 mg/tablet) were given, 1 tablet daily, for first 3 consecutive months. For the following 3 months only MA was administered (1 tablet/day for 7 days/month).
Efficacy was evaluated as change from baseline to end point (90th, 120th, 150th and 180th day) as regards to back pain, menstrual pain, breast fullness, headache, asthenia, irritability, appetite modulation and sleep disturbances. As regards to the first part of the study, improvement in the variables was greater in the MA group compared with Magnesium group (P<0.001). With regards to the second part of the study, improvement was greater in the MA group *versus* the non-treated one: results were kept treating patients 7 days/month and a 2-month wash-out cancelled the results obtained in the first 90 days treatment.
During the study, 5 women reported very mild adverse events (2 MA; 3 Magnesium), none of which caused drop-out. The results demonstrate that MA is an effective and well-tolerated treatment for the relief of symptoms of PMS.
Its action is evident after 90 days of continuative treatment and can be kept with a treatment scheme of 7 days/month.

INTRODUCTION

The premenstrual syndrome (PMS) is a complex combination of psychological symptoms, including irritability, aggression, tension, anxiety, and depression, and somatic changes such as fluid retention, breast tenderness, headache, feeling of bloating, and weight increase (**1**). Women are affected irrespective of socioeconomic status, race, or cultural background, and family clusters are well documented (**2**,**3**). The causes of the PMS have not been clearly elucidated (**4**) but have been attributed to hormonal change, neurotransmitters, prostaglandins, diet, drugs, and lifestyle, so causal treatment is difficult (**3**).
Chasteberry (*Vitex agnus-castus*), or monk's pepper, is the fruit of the chaste tree. It is native to eastern Asia and south-western Europe, and is now common in much of the south-eastern United States (**5**). Chasteberry has been used for more than 2,500 years to treat various conditions. In ancient Egypt, Greece, and Rome, it was used for a variety of gynaecologic conditions. In medieval Europe, chasteberry was popular among celibate clergymen for its purported ability to reduce unwanted sexual libido. Over the past 50 years, chasteberry has been used widely in Europe for gynaecologic conditions such as PMS, cyclical breast discomfort, menstrual cycle irregularities, and dysfunctional uterine bleeding (**6**,**7**) The German Commission E approved the use of chasteberry for irregularities of the menstrual

****Monoselect Agnus*** is produced by S.I.I.T., Trezzano S/N, Milan, Italy

cycle, cyclical breast discomfort, and PMS and it is widely prescribed by family physicians and gynaecologists in Germany.
The berry of the chaste tree contains a number of active constituents: flavonoids (casticin, kaempferol, orientin, quercetagetin, and isovitexin), iridoid glycosides (agnuside and aucubin), and essential oils (limonene, cineol, pinene, and sabinene). Chasteberry shows central dopaminergic activity *in vitro* and *in vivo*. This dopaminergic effect inhibits basal- and thyrotropin-releasing hormone–stimulated prolactin release.
Chasteberry's effects are attributed to its indirect effects on various hormones, especially prolactin and progesterone. This hormonal effect appears to be dose-dependent: low doses of extract have resulted in decreased estrogen levels and increased progesterone and prolactin levels, possibly caused by an inhibition of the release of follicle-stimulating hormone (FSH) and stimulation of luteinizing hormone (LH) levels.
Over the past 50 years, about 30 European trials on chasteberry (mostly uncontrolled or unblinded) have reported improvement of menstrual and menstruation-related disorders (**8**-**22**).
Since the nature of the active fraction of the extract, its pharmacokinetics properties, its absorption site and its possible liver first-pass effects are not very well investigated and known, in order not to limit the potential absorption at any level of the actives we evaluated the effects of fast dissolving tablets containing as unique active 40 mg of *Agnus castus* fruit extract (MA).
The study lasted 6 consecutive menstrual cycles and its aim was to verify the MA clinical efficacy and the validity of a possible treatment scheme where the product is administered 7 days/month just before the beginning of the menstrual cycle.

MATERIALS AND METHODS

The study involved either MA (*Vitex agnus castus* fruit extract standardized and titered as 0.5% in agnuside; a product developed in a fast dissolving tablet by using excipients allowing the active to be released within 5 min after swallowing, named *Monoselect Agnus*, containing 40 mg/tablet of active extract, administered once daily) or Magnesium tablets (matched for appearance, size, colour, taste, and smell containing 300 mg/tablet of magnesium oxide).
Both the MA and the Magnesium tablets were developed by Velleja Research, Pontenure (PC), Italy and were manufactured in SIIT, Trezzano S/N, Milano, Italy. MA is currently commercialized by PharmExtracta, Pontenure (PC), Italy.

The study was performed according to current European Union and International Conference on Harmonisation guidelines on Good Clinical Practice and the Declaration of Helsinki and was approved by the ethics committee.

All women were outpatients attending a general medicine clinic (Santa Maria Hospital, Bari, Italia) from April to October 2008. All women were over 18 year of age, had the PMS diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSMIIIR) (**23**) and gave written informed consent before inclusion. Exclusion criteria were participation in other trials, concomitant psychotherapy, pregnancy or breast feeding, inadequate contraception, dementia, alcohol or drug dependence, concomitant serious medical condition, hypersensitivity to *Agnus castus*, fever, pituitary disease, and concomitant use of sex hormones except oral contraceptives for which the doses were kept unchanged.
Baseline assessment was conducted at the start of the therapy and consisted of the combined scores of the following six symptoms relative to previous three cycles: back pain, menstrual pain, breast fullness, headache, asthenia, irritability, appetite modulation and sleep disturbances.
Clinical visits and score evaluation at the end of the third cycle (after 90 days) and for the following 3 months, every month, were mandatory.

Patients were asked also to fill a questionnaire during the first 3 months of the study reporting the following question: 'which is in your opinion the best advantage provided by the treatment after 30 and after 60 days of treatment?'
Possible answers were:
1) physical (back, abdominal, breast, head pain decrease);
2) psychological (irritability, anxiety, sleep disorders, compulsive food approach, asthenia reduction).

At t=0 and for every following clinical visit, PMS scores were rated using a visual analogue scale (VAS), according to the model of Scott-Huskisson, validated for the assessment of the premenstrual syndrome, ranging from 0 (no symptoms) to 10 (unbearable) (**24**,**25**).
A total of 87 women were initially screened, of whom 82 were enrolled and randomised.
The Student's *t* test was used to verify the group homogeneity at baseline.
No difference in the mean values of the three considered parameters was observed (age, cycle length and menses duration, ***Table 1***).
Student's *t* test was also used to compare the results obtained at the end of the treatment *vs* baseline.

RESULTS

Table 1 reports the demographical features of the study populations. Both groups had similar baseline scores. ***Table 2*** shows the results at the end of the first treatment period (90 days). Patients receiving MA had a significant improvement in symptoms compared with those receiving Magnesium in seven of the eight parameters (back pain, menstrual pain, breast fullness, headache, asthenia, irritability and sleep disturbances). As regards to appetite modulation, the low baseline score did not allow a very high significant clinical change.
There were very few adverse events (***Table 3***): mainly acne and urticaria. Each event was reported once and severity was very mild; all events resolved without treatment discontinuation. Their incidence was in any event treatment-unrelated and observable equally in both groups.

Table 4 shows that in those subjects where MA was administered for a further 3 months (7 days/month, just before menstrual cycle), all parameters were significantly lower than the baseline values of subjects where treatment had been discontinued (wash-out); in fact in the subjects where MA treatment had been stopped, scores started rising starting from the following month, and returning to the baseline value within 2 months. The results show that prolonged treatment maintains the improvements.

Table 5 reports the subjective responses of patients described in a questionnaire. The results show that the incidence of patients with beneficial effects after 30 or 60 days of treatment with MA, was significant for breast pain decrease only. Patients treated with Magnesium did not show any relevant effect on the symptoms selected to be reported.

Table 1 *Values (M±SD) of age, cycle length and menses duration of subjects before treatment*

Parameter	***MA*** (n=42)	***Magnesium*** (n=40)
Age (years)	37±9.1	36±8.2
Cycle length (days)	28±1.5	28±1.2
Menses duration	4.7±1.0	4.6±0.9

Table 2 *Clinical effects (M±SD) of MA (40 mg/die; n=42) and Magnesium (300 mg/die; n=40) on PMS symptoms in a 90 days treatment (t0; t90)*

Symptom	***MA***		***Magnesium***	
	t0	*t90*	*t0*	*t90*
Back pain	6.8±1.4	1.4±0.6*	7.2±1.8	5.5±1.5
Menstrual pain	8.4±1.4	2.0±0.4*	8.8±1.4	7.4±2.6
Breast fullness	6.0±1.0	0.4±0.6*	6.2±1.4	5.4±1.8
Headache	8.2±2.8	1.0±0.8*	6.8±1.8	6.4±1.6
Asthenia	5.4±0.5	1.2±0.9*	6.0±1.4	6.4±1.2
Irritability	5.0±1.7	0.4±0.4*	5.8±1.4	5.0±1.1
Appetite modulation	2.0±1.5	0.2±0.2°	2.3±0.4	1.4±0.6
Sleep disturbances	5.8±1.8	1.1±0.5*	5.9±1.9	5.4±0.7

* p<0.01 *vs* baseline and ° p<0.05 *vs* baseline as determined by Student's tT test

Table 3 *Adverse events due to MA or Magnesium treatment*

Treatment	***MA***	***Magnesium***
N°	2	3
Type	acne (1)	acne (2)
	urticaria (1)	urticaria (1)
Withdrawals (N°)	0	0

Table 4 *Clinical effects (M±SD) in subjects treated with MA (40 mg/die; 7 days/month; n=21) vs controls (treatment discontinued) (n=21) on PMS symptoms in a 3 months study subsequent to earlier 90 days treatment with MA*

Symptom	***t120***		***t150***		***t180***	
	MA	Controls	MA	Controls	MA	Controls
Back pain	2.2±0.4*	3.4±1.6	1.2±0.8*	2.5±1.1	1.2±0.8*	3.5±1.5
Menstrual pain	2.4±0.6*	3.0±0.9°	2.8±1.1*	7.4±2.8	2.2±0.5*	8.5±1.4
Breast fullness	1.0±0.6*	3.7±0.9	1.2±1.4*	5.2±1.5	0.8±0.3*	6.5±1.5
Headache	1.2±0.4*	1.0±0.8*	1.0±0.4*	7.4±1.6	2.2±1.0*	7.5±2.4
Asthenia	1.1±0.3*	1.2±0.3*	2.1±0.4*	5.7±1.3	1.2±0.8*	8.4±1.3
Irritability	0.4±0.2*	5.4±1.2	0.8±0.4*	6.0±0.5	0.6±0.4*	5.5±1.1
Appetite modulation	0.4±0.2°	0.8±0.4*	0.3±0.1°	1.4±0.9	0.3±0.1°	2.5±0.2
Sleep disturbances	0.8±0.5*	2.1±0.6	0.9±0.2*	6.6±0.7	0.7±0.4*	5.9±0.9

*p<0.01 *vs* baseline and °p<0.05 *vs* baseline as determined by Student's *t* test

Table 5 *Incidence of symptom improvement at 30 (t30) and 60 (t60) days of treatment from patients' questionnaire*

Symptom	***MA***		***Magnesium***	
	t30	*t60*	*t30*	*t60*
Back pain decrease	2	1	4	5
Abdominal pain decrease	2	2	3	4
Breast pain decrease	23	25	7	5
Head pain decrease	3	2	3	3
Irritability reduction	3	3	4	4
Anxiety reduction	1	2	4	4
Sleep problems reduction	3	2	5	4
Food disorders	2	3	5	6
Asthenia reduction	3	2	5	5

MA: N°42 Magnesium: N°40

DISCUSSION AND CONCLUSIONS

It has been shown that a fast acting *Agnus castus* fruits extract is an effective treatment for women with PMS. Treatment of this condition is a challenge for physicians who most often treat these women (**2**,**8**,**19-22**). Although the condition tends to be mild to moderate, the effects on women can be debilitating and stressing (**3**).

This study was conducted to verify the efficacy of a modified release (fast dissolving) form of a widely used herbal extract (*Vitex Agnus Castus*) in comparison with Magnesium on women with PMS. The choice of Magnesium was based on the fact that the ingredient is commonly used in self-medication for PMS, although conflicting results are reported in the literature.

Such a comparison therefore could provide further proof of efficacy or inefficacy of magnesium when administered as 100% of RDA (300 mg/tab/*die*).

The aim of the study was to establish mainly the clinical role played by MA in PMS and at the same time to find a possible treatment scheme, this being the task of physicians using herbal extracts.

The results show that MA is effective in counteracting PMS symptoms, while Magnesium is not active. If the results analyzed by physicians by the clinical visits carried out at t=0, t=90 and then every 30 days up to t=180 days reports a good efficacy of MA on all the considered parameters without big differences among them, evaluation of the answers given by the subject during the first 3 months of treatment and reported after 30 and 60 days clearly show a particular clinical action played by MA in terms of breast pain reduction. The subjects report seems to highlight a precocious advantage of MA especially for PMS breast complaining.

A discontinuation of the treatment lasting more than one month leads progressively to attenuation and loss of clinical benefits. Moreover, the results clearly show that MA can be administered for prolonged time (7 days/month, before the menstrual cycle, for three months), after reaching beneficial effects.

Special attention was given to the reporting of adverse effects, because herbal treatments are sometimes misguidedly considered to be completely safe. Tolerability of MA was good and the 2 cases of dermatological discomfort were very mild and similar to three cases observed in the magnesium- treated group. Noteworthy, in the second 3 months of treatment (7 days/month) no cases of acne or urticaria, or other discomfort were reported.

In conclusion, MA may be considered to be a well-tolerated and effective treatment for the main symptoms of PMS. MA ought to be considered an option for women whose causal origin for the syndrome has not been established (primary PMS).

Larger studies are however required for a better definition of the dose: in fact 40 mg/day has been used in most studies reported in the literature, although a clinical dose-finding has not been done yet.

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