

# Menosan<sup>®</sup> (TABLET)

Helps her glow again!

## Alleviates perimenopausal symptoms

- **Vasomotor symptoms**  
decreases hot flashes and night sweats
- **Physiological symptoms**  
reduces vaginal dryness and pruritus vulvae
- **Psychological symptoms**  
reduces anxiety, depression, mood swings, insomnia, etc.

## Reduces postmenopausal risk of:

- Osteoporosis

**Natural and surgical menopause**

### Dosage

1 tablet twice daily. The treatment period may vary from 12 to 18 months.

Rx **Menosan**  
Helps her glow again!



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# An Open Clinical Evaluation of Menosan Tablets in Menopausal Syndrome: Efficacy and Safety Study

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## ABSTRACT

Menopause is defined as the permanent cessation of menses resulting from reduced ovarian hormone secretion that occurs naturally or is induced by surgery, chemotherapy or radiation. Menopause is caused by the natural declining function of the ovaries, which gradually produce lower and lower levels of the hormones estrogen, progesterone and testosterone. Women in the menopausal transition commonly report a variety of symptoms, including vasomotor symptoms (hot flushes and night sweats), vaginal symptoms, urinary incontinence, disturbed sleep, sexual dysfunction, depression, anxiety, mood swings, memory loss, fatigue, headache, joint pains and weight gain. This study was planned to evaluate the clinical efficacy and safety profile of Menosan tablet in the management of menopausal syndrome. Forty postmenopausal women (both natural and surgical) were included in the study. Clinical symptoms of the patients were evaluated on entry and at monthly intervals for the first three months and followed up at six and 12 months. The severity score for clinical symptoms was assessed using a grading scale of 0 to 3 where 0: Nil, 1: Mild, 2: Moderate and 3: Severe. The patients were administered Menosan at a dosage of two tablets, twice-daily for a period of 12 months. In addition, hormonal assay [follicle stimulating hormone (FSH) and estrogen] and cholesterol levels were estimated at entry and at the end of the study (12 months). Significant improvements in symptoms such as hot flushes, excessive sweating, dryness of vagina and anxiety was observed in patients from the third month onward and continued to show further improvement till the end of the study (12 months). Backache, heaviness of body, palpitation and irritability, significantly improved from the sixth month onward till the end of the study. Insomnia improved significantly from the second month onward till the end of the study. All the seven patients who presented with mood swings at entry showed a significant improvement with a significance of  $p < 0.0114$ . Effect of Menosan on the hormonal assay showed that FSH decreased from  $53.59 \pm 25.32$  IU/l to  $47.43 \pm 21.09$  IU/l with a significance of  $p < 0.046$ . Cholesterol decreased from  $190.1 \pm 41.75$  mg% to  $184.3 \pm 39.05$  mg%. A clear trend toward improvement of estrogen levels was also observed but was not significant. All the patients completed the study and the compliance to the study was good. Therefore, it can be concluded that Menosan is clinically effective and safe in the management of postmenopausal syndrome, for both short- and long-term use.

**Key words:** Menopause, Menosan

Menopause is defined as the permanent cessation of menses resulting from reduced ovarian hormone secretion that occurs naturally or is induced by surgery, chemotherapy or radiation. Natural menopause is recognized after 12 months of amenorrhea that is not associated with a pathologic cause. The average age of menopause in the United States is 51 years, and can vary between 40 and 58 years.<sup>1</sup> Stages and nomenclature of the menopausal transition were defined by experts in 2001 at the Stages of Reproductive Aging Workshop (STRAW).<sup>2</sup> These stages can also be described by the following terms:

- Premenopause: The time upto the beginning of the perimenopause; can also be defined as the time upto the last menstrual period.
- Perimenopause: The time around menopause during which menstrual cycle and endocrine changes are occurring but 12 months of amenorrhea has not yet occurred.

- Postmenopause: Begins at the time of the last menstrual period, although not recognized until after 12 months of amenorrhea.

Menopause is caused by the natural declining function of the ovaries, which gradually produce lower levels of the hormones - estrogen, progesterone and testosterone. This causes a decline in the total serum levels of these hormones in females. Decreasing estrogen levels may cause many long-term health problems, such as osteoporosis and heart disease after menopause.

The symptoms of menopause can be grouped as follows:<sup>3,4</sup> Vasomotor, genital and urinary, psychological and other general clinical features. Vasomotor features constitute hot flushes, night sweats, insomnia, palpitations and paresthesia. Genital and urinary features include dyspareunia; dryness and atrophy of the vagina; atrophy of the vulva; pale, thin and almost translucent vulval skin; atrophy of the cervix; ceasing of glandular activities, accompanied with diminished mucous secretion and decrease in size and atrophy of the uterus. Psychological features include anxiety, headache, irritability, depression and mood swings.

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General features include other clinical symptoms such as backache, pain in the joints and muscles, fatigue, dryness of skin, brittleness of hair, weight gain and osteoporosis. A hot flush is a sudden feeling of warmth that is generally most intense over the face, neck and chest. The duration is variable but averages about four minutes. It is often accompanied with sweating that can be profuse and followed by a chill. The prevalence of hot flushes is maximal in the late menopausal transition, occurring in about 65% of the women.<sup>5</sup>

Postmenopausal women with vaginal symptoms generally have decreased vaginal blood flow and secretions, hyalinization of collagen, fragmentation of elastin and proliferation of vaginal connective tissue. Vaginal fluid, which is acidic before menopause, becomes more neutral, facilitating the proliferation of enteric organisms associated with urinary tract infection.

Osteoporosis or diffused osteopenia is a condition of reduced bone mass resulting from a relatively long period of negative imbalance in remodeling process. A rate of demineralization from 2% to 5% in a year occurs at menopause and has been documented with other causes of severe estrogen deficiency. The principal laboratory test used for diagnosing menopause is the serum follicle stimulating hormone (FSH) level. As ovarian function declines, the serum FSH level rises. Alternative approaches are now viewed as safer and more individualized. There is substantial interest in natural alternatives to hormone replacement therapy (HRT). In particular, phytoestrogens have received attention as potential dietary sources of exogenous estrogens for postmenopausal women.<sup>6-8</sup> Along with lifestyle modification, herbal remedies can be taken to combat menopausal symptoms, as they do not cause any adverse effects. Menosan, a polyherbal formulation with anti-inflammatory, antihypertensive, sedative, tranquilizing, hematinic and rejuvenating properties, is used in the treatment of geriatric problems and has no adverse effects on breast, endometrium and total cholesterol. The present study is an open clinical trial conducted to evaluate the efficacy of Menosan in relieving the symptoms of menopause.

### **Objective of the Study**

The primary objectives were to evaluate the efficacy of Menosan tablet in the management of symptomatic

menopausal women. The secondary objectives included evaluation of the effect of Menosan on serum FSH and estrogen levels and lipid profile and to report adverse effects if any and compliance to the drug.

### **Material and Methods**

#### **Inclusion Criteria**

Postmenopausal (both natural and surgical) women aged above 40 years presenting with postmenopausal symptoms and who were willing to give consent to participate in the study and comply with the study procedures were included in the study.

#### **Exclusion Criteria**

Patients on hormone or any other drug therapy during the previous three months that could affect the variables being studied; had participated in any clinical trial or were on any investigational products during the last four weeks and patients with known or suspected malignancy; significant hepatic, renal, cardiac, metabolic or endocrinal diseases; and abnormal uterine bleeding were excluded from the study.

#### **Study Procedure**

All the patients were subjected to a routine evaluation (including medical history, systemic examination, pelvic examination, Pap smear, routine hematological and biochemical laboratory tests, hormonal assays of serum FSH, estradiol and total cholesterol levels) at entry and at the end of the trial (12 months). They were administered Menosan at a dosage of two tablets, twice-daily for a period of 12 months and were instructed to report any relief in the symptoms or any side effects of the drug. A detailed history of menopausal symptoms was taken and following symptoms were evaluated at monthly intervals for the first three months and followed up at six and 12 months: Vasomotor - hot flushes; psychological - insomnia, irritability and depression; and others - vaginal dryness, vaginal pain, irritation, urinary symptoms, muscle and joint pain, etc. The severity score for the clinical symptoms was assessed using a grading scale of 0 to 3 where, 0: Nil, 1: Mild, 2: Moderate and 3: Severe. All adverse events, either reported or observed by patients, were recorded with information about severity, date of onset, duration and action taken regarding the study drug were enquired and documented in the Case report form.

## Primary and Secondary Outcome Measures

Clinical recovery from the symptoms of menopause was defined as the primary outcome measure, whereas clinical safety and toxicity profile of Menosan tablets were defined as the secondary outcome measure.

## Statistical Analysis

Statistical analysis was performed using GraphPad Prism version 4.01, for Windows (GraphPad Software, San Diego, California, USA) by repeated measures of ANOVA (Freidman test) followed by Dunnett's multiple comparison posthoc test to calculate the level of significance for the relief of clinical symptoms, except for mood swings, which was analyzed using Fisher's exact test. Hormonal assays and cholesterol levels were analyzed using paired Student's 't' test. The minimum level of significance was fixed at  $p < 0.05$ .

## Results

Among the 40 patients included in the study, majority (54%) belonged to the age group of 40-49 years (Table 1). Only 16.2% patients had menopause for more than five years; the maximum number of cases had menopause for 0 to 2 years (Table 2). Of the 40 patients included in the trial, 22 had natural menopause while 15 had surgical menopause (Table 3). Clinical response to Menosan tablet is summarized in

**Table 1.** Age of the Patients

Age (y)	Number of patients	Age-wise distribution (%)
<40	4	10.8
40-49	20	54.0
50-59	12	32.4
>60	1	2.7

**Table 2.** Duration of Menopause

Duration (y)	Number of patients	Percentage
0-2	14	37.8
2-3	10	27.02
3-4	7	18.9
4-5	0	0
>5	6	16.2

**Table 3.** Type of Menopause

Type	Number of patients	Percentage
Natural	22	59.45
Surgical	15	40.45
<b>Total</b>	<b>37</b>	<b>100</b>

Table 4. Improvement in hot flushes was observed in patients from the third month onward with significant improvements at the 6th and 12th months of the study ( $p < 0.001$ ). Excessive sweating and dryness of vagina improved from the third month onward ( $p < 0.01$ ) till the end of the study ( $p < 0.001$ ). Backache, heaviness of body and irritability significantly improved from the sixth month onward till the end of the study ( $p < 0.001$ ). Anxiety was significantly reduced in patients from the third month onward ( $p < 0.05$ ) till the end of the study ( $p < 0.001$ ). Palpitation was also reduced significantly ( $p < 0.01$ ) from the sixth month till the end of the study. Insomnia improved significantly from the second month ( $p < 0.05$ ) onward with further improvements at 3rd, 6th and 12th months ( $p < 0.001$ ). All the seven patients who presented with mood swings responded well with a significance of  $p < 0.0114$  (Table 5). Effect of Menosan on hormone levels is given in Table 6. FSH decreased from  $53.59 \pm 25.32$  IU/l to  $47.43 \pm 21.09$  IU/l with a significance of  $p < 0.046$ . Cholesterol decreased from  $190.1 \pm 41.75$  mg% to  $184.3 \pm 39.05$  mg%. A clear trend toward improvement of estrogen levels was also observed but was not significant. All the patients completed the study with good study compliance (Table 6). One patient reported improvement in her facial pigmentation (chloasma). A total of 30 of the 37 patients (81%) experienced a sense of well being at the end of 12 months. Side effects of the drug were not reported except in one patient who developed skin rashes after two months of treatment, but disappeared later on continuation of the treatment.

## Discussion

Management of menopausal syndrome remains a major health concern throughout the world. Several types of hormone therapies are available for the management of menopausal symptoms but they have various side effects. Of all the alternative treatment modalities available, phytoestrogens seem to offer the potential for the prevention and treatment of postmenopausal syndrome, including protection against osteoporosis, cardiovascular accidents, and cardiovascular diseases. Phytoestrogens are natural 'selective estrogen receptor modulators' (SERMs) having a diphenolic ring in their structure similar to human estrogens. They bind to the estrogen receptors, acting either as 'partial agonists' or 'antagonists,' depending on the levels of endogenous estrogens.<sup>9,10</sup> Phytoestrogens exhibit estrogenic activity in the order of  $10^{-2}$  to  $10^{-3}$  to that

**Table 4.** Clinical Response to Menosan Treatment (Mean ± SD)

Symptoms	1st month	2nd month	3rd month	6th month	12th month
<b>Vasomotor symptoms</b>					
Hot flushes	1.82 ± 0.80	1.12 ± 0.72 NS	0.83 ± 0.70 p < 0.001	0.35 ± 0.76 p < 0.001	0.26 ± 0.75 p < 0.001
Excessive sweating	1.64 ± 0.79	1.04 ± 0.85 NS	0.79 ± 0.83 p < 0.01	0.37 ± 0.81 p < 0.001	0.33 ± 0.81 p < 0.001
Palpitation	1.071 ± 0.45	0.50 ± 0.40 NS	0.42 ± 0.34 NS	0.00 ± 0.00 p < 0.01	0.00 ± 0.00 p < 0.01
Insomnia	1.25 ± 0.51	0.60 ± 0.36 p < 0.05	0.41 ± 0.35 p < 0.001	0.12 ± 0.26 p < 0.001	0.10 ± 0.25 p < 0.001
<b>Psychological symptoms</b>					
Anxiety	1.52 ± 0.51	0.82 ± 0.61	0.67 ± 0.52 p < 0.05	0.14 ± 0.34 p < 0.001	0.12 ± 0.33 p < 0.001
Irritability	1.09 ± 0.30	0.68 ± 0.56	0.50 ± 0.31	0.18 ± 0.34 p < 0.001	0.14 ± 0.32 p < 0.001
<b>Urogenital symptoms</b>					
Dryness of vagina	1.3 ± 0.48	0.50 ± 0.45	0.15 ± 0.32 p < 0.01	0.076 ± 0.28 p < 0.001	0.077 ± 0.28 p < 0.001
<b>General symptoms</b>					
Backache	1.41 ± 0.59	0.93 ± 0.47 NS	0.75 ± 0.40 NS	0.13 ± 0.35 p < 0.001	0.09 ± 0.29 p < 0.001
Heaviness of body	1.23 ± 0.49	0.80 ± 0.62 NS	0.73 ± 0.53 NS	0.16 ± 0.52 p < 0.001	0.13 ± 0.52 p < 0.001

Statistical analysis was done using repeated measures of ANOVA by Friedman test followed by Dunnet's multiple comparison posthoc test.

**Table 5.** Clinical Response to Menosan Treatment (Mean ± SD)

Symptoms	Present	Absent	Significance
Mood swing			
Pretreatment	7	30	p < 0.0114
Post-treatment	0	37	

Statistical analysis was done using Fisher's exact test.

**Table 6.** Effect of Menosan on Follicle Stimulating Hormone, Estrogen and Cholesterol Levels (Mean ± SD)

Investigations	Initial	After 3 months
FSH (IU/l)	53.59 ± 25.32	47.43 ± 21.09 (p < 0.046)
Estrogen (pg/ml)	37.22 ± 16.04	40.23 ± 19.72 NS
Cholesterol (mg%)	190.1 ± 41.75	184.3 ± 39.05 (p < 0.013)

Statistical analysis was done using paired 't' test.

of 17β-estradiol,<sup>11-13</sup> but may be present in the body in concentrations 100-fold higher than endogenous estrogens.<sup>14-16</sup> Phytoestrogens have a higher binding affinity for α-estrogenic receptors than for β-estrogenic receptors.<sup>17-19</sup> It is also well-documented that, in Asia, only 10% to 20% of women experience postmenopausal syndrome compared with 70% to 80% of women in the Western countries; the possible reason for this may be the high consumption of soya, which is a rich source of phytoestrogens, among Asian women.<sup>20-24</sup> Evidence

for the potential benefits of phytoestrogens with regard to bone metabolism can be obtained from a number of studies on ipriflavone (7-isopropoxyisoflavone, an isoflavone derivative), which has been shown to be effective in promoting bone mass and preventing bone loss.<sup>25-27</sup> The phytoestrogens present in Menosan may help in preventing the osteoclastic bone resorption occurring in postmenopausal women.<sup>28</sup> Hormone-related cancers of the breast, ovary and endometrium have been reported to vary by 5 to 20 folds among different populations, and migrant studies indicate that this difference is largely attributable to environmental factors rather than genetics.<sup>29,30</sup> The highest rates of these cancers are typically observed in populations with Western lifestyles that include relatively high fat, meat-based, low fiber diets; whereas the lowest rates are typically observed in Asian populations with Eastern lifestyles that include plant-based diets with high phytoestrogen content.<sup>31</sup>

Menosan, a polyherbal formulation, is a rich source of phytoestrogens. It is recommended for the management of postmenopausal syndrome and contains extracts of *Asparagus racemosus* and *Saraca indica* and the powders of *Centella asiatica*, *Terminalia chebula*, *Glycyrrhiza glabra*, *Sida cordifolia*, *Kukkutandatvak* bhasma

and Zaharmohara bhasma, processed in *Terminalia arjuna*, *Bombax malabaricum* and *Chlorophytum arundinaceum*.

The principal active compound of *G. glabra* is glycyrrhizin (glycyrrhizic or glycyrrhizinic acid - a triterpene glycoside). The other active compounds are isoflavonoid derivatives (isoflavonol, kumatakenin, licoricone, glabrol), glabridin, hisglabridin A, hisglabridin B, 4'-O-methylglabridin, 3'-hydroxy-4'-O-methylglabridin, chalcones and coumarins, which have potent antioxidant activities. Shihata and Elghamry and Van Hulle reported that the administration of *G. glabra* to immature, ovariectomized mice exhibited estrogenic activity.<sup>32,33</sup> *A. racemosus*, a good source of phytoestrogens especially isoflavones and the other active compounds, are steroidal saponins (shatavarins I-IV). Shatavarin I is the major glycoside with 3-glucose and rhamnose moieties attached to sarsasapogenin, whereas shatavarin IV contains isoflavones (8-methoxy-5,6,4'-trihydroxyisoflavone-glucopyranoside),<sup>34-36</sup> asparagine (a polycyclic alkaloid), racemosol (a cyclic hydrocarbon 9,10-dihydrophenanthrene) and polysaccharides. Thatte et al reported that *A. racemosus* acts as an immunomodulator and was also capable of producing leukocytosis, neutrophilia and increased phagocytic activity of macrophages.<sup>37,38</sup> Furthermore, *A. racemosus* was able to prevent myelosuppression by reducing cyclophosphamide-induced leukopenia.<sup>39</sup> Rao documented that *A. racemosus* inhibited drug-induced mammary carcinogenesis, drug-induced suppression of chemotactic activity and production of interleukin-1 and tumor necrosis factor- $\alpha$ .<sup>40</sup>

The active ingredients of *T. arjuna* are glycosides (arjunetin, arjunosides I-IV), flavones, tannins, oligomeric proanthocyanidins, acids (arjunic acid and terminic acid) and minerals. *T. arjuna*, a potent antioxidant agent (comparable to vitamin E) present in Menosan, has a significant hypocholesterolemic effect.<sup>41</sup> *T. arjuna* exhibits anti-ischemic properties, which are beneficial in patients with ischemic heart disease. Gupta et al reported that *T. arjuna*, a potent hypolipidemic agent, induced partial inhibition of atheroma.<sup>42</sup> Arjunolic acid in *T. arjuna* has been shown to prevent the decrease in the levels of superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin,  $\alpha$ -tocopherol, reduced glutathione, ascorbic acid, lipid peroxide and hence enhances cardioprotection. In a study conducted among patients with angina pectoris, congestive cardiac

failure and left ventricular hypertrophy, significant improvement in left ventricular ejection fraction and reduction in left ventricular mass was documented, and patients with ischemic cardiomyopathy showed significant symptomatic relief in coronary heart failure from NYHA class III to NYHA class I.<sup>43</sup>

Epidemiological studies have implicated postmenopausal estrogen deficiency for increase in the lower urinary tract symptoms. Various ingredients of Menosan are reported to possess potent antimicrobial activities. *T. chebula* is shown to have a significant activity against a wide range of Gram-positive and Gram-negative bacteria.<sup>44,45</sup> *T. arjuna* is reported to possess a significant antibacterial activity against *Escherichia coli*, *Klebsiella aerogenes*, *Proteus vulgaris* and *Pseudomonas aeruginosa*.<sup>46</sup> *S. indica* also possesses potent antimicrobial activity.<sup>47</sup> *A. racemosus*, due to its active ingredient 9,10-dihydrophenanthrene, shows considerable *in vitro* antibacterial efficacy against *E. coli*, *Bacillus subtilis* and *Staphylococcus aureus*.<sup>48</sup>

Menopause is frequently associated with psychological symptoms such as mood swings, anxiety, depression, irritability and insomnia. *C. asiatica*, an ingredient of Menosan, has anxiolytic and sedative effects. In a previous study, *C. asiatica* was reported to produce a marked increase in the time spent in the open arms of the plus maze. In another study, the effect of triterpenes from *C. asiatica* on the immobility time in forced swimming test and estimation of amino acids concentration in mice brain tissue revealed a potent antidepressant activity. Some studies have documented the 'adaptogenic' and immunostimulatory effect of *A. racemosus*. (Plant adaptogens are defined as 'smooth pro-stressors,' which reduce the reactivity of host defense systems and decrease the damaging effects of various stressors due to increased basal level of chemomediators involved in the stress response). This adaptogenic effect helps the postmenopausal women to adapt to the changes in the neurotransmitter levels, which is responsible for the resultant postmenopausal anxiety and depression.<sup>49-52</sup>

Dietary phytoestrogens has been found to be antiatherogenic, and the proposed mechanisms for the hypocholesterolemic effect of phytoestrogens are: The up-regulation of LDL receptors and/or the inhibition of endogenous cholesterol synthesis.<sup>53,54</sup> Phytoestrogens stimulate the clearance of cholesterol, probably by up-regulating LDL receptors and thereby increasing LDL receptor activity.<sup>55</sup> Lignans also affect cholesterol

homeostasis, as they have been shown to inhibit the activity of cholesterol-7- $\alpha$  hydroxylase, the rate-limiting enzyme in the formation of primary bile acids from cholesterol.<sup>56</sup> Menosan is also a good source of calcium as it contains Kukkutandatvak bhasma, which is a rich source of natural organic calcium, resulting in healthy bone formation and improvement in bone mineral density, which helps prevent postmenopausal symptoms.

The herbs present in Menosan *A. racemosus*, *G. glabra*, *C. asiatica*, *T. chebula*, *S. cordifolia* and *S. indica* improve hormonal utilization and provide an overall hormonal balance. The symptoms of irritability and fatigue were relieved due to the synergistic effect of *Withania somnifera*, *C. asiatica* and *A. racemosus* as they possess rejuvenating properties. Depression was relieved by the mood elevating properties of *C. asiatica*, *A. racemosus* and *G. glabra*. Bone and joint pain was relieved by the analgesic and anti-inflammatory properties of *G. glabra* and *T. cordifolia*. There was a small reduction in weight gain because of the weight reducing properties of *W. somnifera*, *C. asiatica*, *Adhatoda vasica* and *Boerhaavia diffusa*. The symptoms of insomnia and headache were relieved by the rejuvenating, analgesic, anxiolytic and sedative properties of *C. asiatica*, *A. racemosus*, *G. glabra*, *A. vasica* and *T. cordifolia*.

## Conclusion

This study observed a significant reduction in vasomotor, urogenital and psychological symptoms in patients receiving Menosan. The study also observed a near normalization of hormonal levels. There were no clinically significant adverse reactions and the overall compliance to the treatment was excellent. Therefore, it can be concluded that Menosan is clinically effective and safe in the management of postmenopausal syndrome, for both short- and long-term use.

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