

## INFLUENCE OF PROBIOTIC SUPPLEMENTATION ON CLIMACTERIC SYMPTOMS IN MENOPAUSAL WOMEN-A MINI REVIEW

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### ABSTRACT

Menopause (MP) is a natural physiological event of woman's life and is defined as the absence of menstrual periods for at least twelve months and loss of function of ovarian. The common symptoms of MP are irregular vaginal bleeding, hot flushes especially in head and chest, night sweats, insomnia, vaginal and urinary symptoms, cognitive dysfunction, increased cancer risk, osteopenia, high blood pressure, diabetes, and cardiovascular diseases. Microbiome has been associated with several health benefits. Probiotic supplementation helps to enhance the quality of microbiome thereby confers the health benefits to the host system. The microbiome, hormone (estrogen) changes, and probiotic intervention are related to the health status of the female reproductive system. The vaginal microbiome (VM) play a critical role in female reproductive health and MP, which can be greatly influenced by probiotics, and other medicine especially antibiotics and hormone therapy. The role of VM in supporting vaginal health is not clear and debatable. Understanding the role of vaginal *Lactobacillus* could expose the pathogenesis of vaginal dysbiosis, which helps to improve diagnostic and therapeutic strategies for several dysbiosis associated health issues and menopause-related symptoms. Recent studies suggested that the intervention of probiotic preparation with or without nutraceutical formulation (mostly with isoflavones) improve the health status of menopausal women. The mechanism of probiotics mediated health improvement in menopausal women is not yet described clearly. Several controversies are there on the link between probiotic, gut microbiota, vaginal microbiota, and estrogen deficit. The present review summarizes the influence of probiotic supplementation on climacteric symptoms in menopausal women. The literature search was made in Scopus, Google Scholar, PubMed using the keywords "probiotics" and "menopause". The documents were carefully checked for the relevance to the current manuscript, and the selection was made without any restriction in the year of publication.

**Keywords:** Probiotics, Estrogen, Menopause, Vaginal microbiome, Climacteric symptoms

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### INTRODUCTION

Menopause (MP) is a natural physiological event of woman's life and is defined as the absence of menstrual periods for at least twelve months and loss of function of ovarian. MP is not a rapid biological event but is a relatively slow biological process. The age of MP varies (46-52 y) among the people, which greatly depends on the socioeconomic status, personal health care, and food habits. There is no unswerving test to predict the onset of MP. Moreover, MP can't be predictable with the time of initial mensural period. The symptoms and the experience of the perimenopausal transition period differ for each woman [1, 2].

The common symptoms of MP are irregular vaginal bleeding, hot flushes especially in head and chest (about 85% of woman experiencing the hot flushes), night sweats, insomnia, vaginal symptoms (dryness, irritation, dyspareunia, and infections), urinary symptoms (frequent urination, urinary incontinence), cognitive dysfunction, physical changes, restlessness, muscle and joint pain, and MP also associated with increased cancer risk, osteopenia, high blood pressure, diabetes, and cardiovascular diseases. The symptoms are not common to all woman. Some people do not feel any or some of the symptoms during their MP [3-5].

The hormone changes or deficiency is the main cause of MP. Thus, hormone replacement therapy (HRT) is the primary treatment method to nullify or reduce the MP symptoms and to prevent the development of heart diseases and osteoporosis. The mode of administration, dose, and combination of the hormone are the key factors that affect the efficiency of the treatment and help to reduce the adverse side effects. Oral administration therapy was less effective compared to transdermal estrogen therapy [5].

Though HRT has beneficial effects, some of the controversial side effects were reported. The contentious HRT increased the risk of cancer development, thromboembolism, and cardiovascular consequences. There was no general treatment procedure, and HRT

should be customized for each woman [6-8]. Moreover, many women seek alternative treatments other than HRT, when there are several health risks and uncertainty on reported benefits of HRT [6].

The serotonin-norepinephrine reuptake inhibitor and selective serotonin reuptake inhibitor were used to treat the hot flushes. These inhibitors help to improve vasomotor symptoms and sleep quality [9]. The phytoestrogens (PE) are phenolic compounds present in plants with mammalian estrogenic activity. PE binds to estrogen receptors and endorses either agonist or antagonist functions [10].

Probiotics are living microbes when administered in an adequate amount, confers beneficial effects in the host health. Commonly, lactic acid bacteria (LAB) are considered as probiotics, and beneficial impact of the probiotics is highly associated with an individual's health status, age, and lifestyle [11]. Probiotic strains were reported for several health aids and applications [11-23]. Changes in the gut microbiome influence the several physiological and biological process. The microbiome changes during estrogen deficiency, characteristics of MP, critically affects the MP symptoms and facilitates the development of illness like inflammatory diseases. The supplementation of probiotics significantly influences the gut microbiome of an individual [24].

Since the alternative therapies for MP with phytoestrogen and herbal products have been detailed previously by Borrelli and Ernst [25]. The current review narrates the probiotic based alternative treatment for MP and its impact on climacteric symptoms of menopausal women. The literature search was made in Scopus, Google Scholar, PubMed using the keywords "probiotics" and "menopause". The documents were carefully checked for the relevance to the current review, and the selection was made without any restriction in the year of publication.

### Microbiome of women

The microbiome is unique for every individual to some extent. The gut microbiome plays an essential role in almost all biological events

and cognitive functions. Subsequently, microbiome might possibly have a role in making healthy offspring moreover in persuading the general health status of an individual. The microbiome of a woman differs from man. The vaginal microbiome (VM) is influenced by several factors like menses, vaginal discharge, and sperm. VM greatly influences the health status of offspring. *Lactobacillus* spp. (especially *Lactobacillus crispatus*, *L. gasseri*, *L. iners*, and *L. jensenii*) are the dominant bacterial species present in VM of healthy women, and any alteration in the composition of VM leads to several adverse conditions like preterm birth, infertility, inflammatory and high risk of sexually transmitted diseases. Finally, it affects the quality of life [26-28]. *Atopobium*, *Prevotella*, *Peptoniphilus*, *Dialister*, *Megasphaera*, *Gardnerella* are some of the leading non-Lactobacillus microbial community residing in the urogenital tract of women [26].

The role of VM in sustaining vaginal health is not clear and controversial. Understanding the role of vaginal *Lactobacillus* could uncover the pathogenesis of vaginal dysbiosis, which helps to refine diagnostic and therapeutic strategies for several dysbiosis associated health issues and to diminish or manage the menopause-related symptoms [29].

The VM composition differs in post-menopausal women when compared with premenopausal women, particularly the *Lactobacillus* content. The VM is extremely affected by the HRT [30-32]. Menopause decreases a load of *Lactobacillus* in VM, and also affects the diversity of microbes. Age, menstruation, hormone levels, intercourse, other lifestyle habits like smoking, hygiene have an impact on the bacterial community of a woman [33, 34]. The description of the VM in different stages in a woman's life is multifaceted [35].

The dramatic change in VM could be noted at the time of puberty when hormone (estrogen) and glycogen levels increase [36]. The increased level of estrogen and glycogen facilitates or promote the growth of *Lactobacillus*, and it is known that the high level of glycogen is maintained during the fertile period of a woman and further decline in its level during menopause. *Lactobacillus* protects the vaginal area from pathogenic colonization by creating the acidic microenvironment, but an overgrowth of microaerophilic bacteria cause distress, itching, and foul-smelling discharge [37, 38]. Several studies suggested that diversity of *Lactobacillus* spp. and its richness has been decreased during or after menopause [36].

**Probiotics and menopause**

The postmenopausal women with the significantly high Nugent score (between 4 to 6) were screened and selected for the study. The Nugent scoring is an unbiased, semi-quantitative evaluation (microbial content) of vaginal secretion. The subjects were randomly divided into two groups and supplemented with either probiotic (lyophilized *L. reuteri* RC-14 and *L. rhamnosus* GR-1 along with sodium alginate;  $2.5 \times 10^9$  CFU each) or placebo (lactose) for fourteen days. After the intervention, vaginal swabs were collected and further subjected to Nugent scoring. The results showed that about 60% of women who received probiotic supplement had a reduction in their Nugent score from the baseline when compared to that of the placebo group. About three grade reduction was observed among the probiotic group, which indicates the significant improvement in the host health. The results suggested that the oral supplementation of probiotics help to restore the normal flora of the vagina [39].

About 2044 women (40-65 y) were supplemented with a mixture of soybean extract (contains genistein and daidzein; 30 mg each), *L. sporogenes* (500 million spores), 5 µg of vitamin D and 141 mg of calcium for six months and the changes in climacteric symptoms were assessed by questionnaire. The changes were noted by gynecologists and self-assessment. The results suggested that the soybean extract with probiotic supplementation significantly improved the climacteric symptoms and sexuality [40].

A double-blind, randomized, placebo-controlled study was conducted with postmenopausal women with vaginal atrophy symptoms to know the impact of supplementation of Gynoflor® vaginal tablets (a blend of *L. acidophilus* KS400 and estriol 0.03 mg). The supplement was provided for 12 d for initial treatment and 2 tablets per week for 12 w to maintain the effects. Vaginal maturation index (VMI) was changed positively in the treatment group (35.2%) when compared to placebo (9.9%). The study proved that Gynoflor® is effective in reducing vaginal atrophy symptoms and improved the VMI [41].

The ovariectomized mouse was supplemented with *L. reuteri* ATCC PTA 6475 via oral gavage ( $1 \times 10^9$  CFU/ml trice per day) and through drinking water ( $1.5 \times 10^8$  CFU/ml) for four weeks. The probiotic supplementation significantly reduced the bone resorption and osteoclastogenesis. The increase in CD4<sup>+</sup>T-lymphocytes has been reduced and thereby *L. reuteri* directly repressed osteoclastogenesis, and probiotic intervention altered the gut microbiome of the experimental mouse, especially *Clostridiales* was increased in the treated mouse. The results suggested that supplementation of *L. reuteri* suppress the post-menopausal bone loss [42].

Symptomatic postmenopausal women were treated with probiotic (*B. breve* B3 ATCC 15700; 1 trillion CFU) and nutraceutical formula (80 mg of soy isoflavones, 50 mg of *Angelica sinensis* extract, 200 mg of *Morus alba* leaf extract, and 56.25 mg of magnesium) for 4 w or probiotic and placebo or vice versa. The menopause rating scale (MRS) score was reduced, and a significant reduction in triglycerides, LDL, and increase in HDL was observed in the probiotic-treated group. The intervention of probiotic and nutraceutical formula improved the MRS score and risk of cardiovascular diseases [43]. Peri-menopausal women subjects were supplemented with isoflavones and probiotics (34 mg/d isoflavones; probiotic combinations and dosage were not revealed in the study) for 12 w. The hot flush frequency (HFF), hot flush intensity, self-reported HFF, and hot flush severity, plasma lipids and blood pressure were measured. The results suggested that moderate intervention of red clover isoflavone and probiotics significantly reduced the self-reported vasomotor symptoms [44].

Postmenopausal breast cancer patients receiving chemotherapy (with vaginal atrophy and altered microbiota) were treated with probiotics (a mixture of  $1 \times 10^9$  CFU of *L. crispatus* LbV 88,  $1 \times 10^9$  CFU of *L. rhamnosus* LbV 96,  $0.2 \times 10^9$  CFU of *L. ensenii* LbV 116 and  $0.3 \times 10^9$  CFU of *L. gasseri* LbV 150N) twice daily for two weeks. After treatment, changes in the vaginal microbiota and Nugent score were reexamined and compared with baseline. The results suggested that probiotic intervention significantly reduced the Nugent score in the probiotic-treated group when compared to that of the placebo. The vaginal microbiota also altered positively in probiotic-treated women. The study proved that probiotic supplementation helps to regain the normal vaginal flora in women receiving chemotherapy for cancer [45].

**Table 1: The influence of probiotic supplementation on the consequences of menopause**

S. No.	Subjects	Intervention	Dose	Duration	Findings	Ref.
1	Postmenopausal women (72 subjects)	<i>L. rhamnosus</i> GR-1 and <i>L. reuteri</i> RC-14	$2.5 \times 10^9$ CFU each	14 d	Nugent score was reduced, and health status improved significantly.	[39]
2	Women (2044 subjects)	Soy extract (genistein and daidzein; 30 mg each), <i>L. sporogenes</i> , calcium (141 mg) and vitamin D (5 µg).	500 million spores	6 mo	Improved the climacteric symptoms and sexuality	[40]
3	Postmenopausal women with vaginal atrophy	<i>L. acidophilus</i> KS400 and estriol 0.03 mg (Gynoflor®)	-	Single tablet for 12 d followed by	Gynoflor® improved VMI after the 12-day initial therapy, and	[41]

	symptoms			2 tablets per week for 12 w	two tablets weekly was appropriate to prevent the relapse.	
4	Balb/c mice ovariectomized MP model	<i>L. reuteri</i> ATCC PTA 6475	1×10 <sup>9</sup> CFU/ml via oral gavage. 1.5 × 10 <sup>8</sup> CFU/ml in drinking water.	Trice per day for 4 w	Significantly protected mice from bone resorption and loss. Suppressed the CD4+T-lymphocytes increase.	[42]
5	Postmenopausal women (43 subjects)	<i>B. breve</i> B3 ATCC 15700, nutraceutic preparation	1 trillion CFU	4 w	Menopause rating scale score was reduced. Reduced the risk of cardiovascular diseases	[43]
6	Peri-menopausal women (62 subjects)	A mixture of probiotic LAB	34 mg/d isoflavones and probiotics	12 w	Suppressed the self-reported vasomotor symptoms	[44]
7	Postmenopausal breast cancer patients	<i>L. crispatus</i> LbV 88, <i>L. rhamnosus</i> LbV 96, <i>L. ensenii</i> LbV 116 and <i>L. gasseri</i> LbV 150N	2.5 × 10 <sup>9</sup> CFU in total	2 w	Reduction in Nugent score, Improved the vaginal microbiota	[45]

## CONCLUSION

Generally, probiotic supplementation improved the health status of gastrointestinal (GI) system, and it has been proved by several clinical and human studies. Recently, the health benefits of probiotic were beyond the GI and its associated system such as anti-aging, anti-inflammation, improved the cognitive decline, anti-hypertension, anti-hypercholesterolemia, etc. The role of probiotic to manage the postmenopausal disorders and to control the climacteric symptoms is the recent subject of interest for several researchers [46]. The well-planned, placebo-controlled clinical studies on the health benefits of probiotics in menopausal women are very limited (table 1). The reports clearly suggested that the intervention of optimum level of probiotic supplementation along with some nutraceuticals improved the climacteric symptoms and vaginal health status by altering the microbiota. Several studies recommend the isoflavones supplementation to treat symptoms of menopause. The combination of an enzyme producing probiotics such as  $\beta$ -glucosidase producing probiotics with soy extract help to improve the symptoms of menopause via producing bioactive isoflavone aglycones [47]. A study reported that the fermentation of soy milk with *L. acidophilus* does not significantly increase the absorption of Ca in osteopenic post-menopausal women [48]. Some controversial reports stated that the supplementation of soy-isoflavone does not influence the microbiota of menopausal women [49]. The mechanism of probiotics mediated health improvement in menopausal women is not yet explained clearly. The connection between probiotic, gut microbiota, vaginal microbiota, and hormone (estrogen) deficit are the subject of several controversies. Further detailed well-planned intensive studies are required to explore the mysteries between the probiotics and menopause.

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## AUTHORS CONTRIBUTIONS

BSS and PK contributed to conception and design, acquisition, manuscript preparation, and critical revision of the manuscript. CC involved in the review and finalization of the manuscript. All the authors agree with the content of the manuscript.

## CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests

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