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EFFECT OF FLAX SEED IN POST-MENOPAUSAL SYMPTOM REDUCTION IN COMPARISON TO MEDICAL TREATMENT:

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Abstract:
Background: Menopause is a natural phenomenon that women must undergo usually after the age of 50. Most of the female population faces post-menopausal symptoms for which they are usually prescribed hormone replacement therapy. However, side effects of allopathic treatment are common.

Objective: The present study focuses on assessing the impact of flax seeds on post-menopausal symptoms and comparing it with the standard allopathic treatment that is usually prescribed.

Method: The study comprises 120 patients who were enrolled in the gynaecology department of tertiary care hospital. They were randomly divided into 4 groups each comprising 30 patients. Group 1 was labelled as control, Group II was given Selective Serotonin Reuptake Inhibitors, and Group III was treated with Hormone replacement therapy whereas Group IV was administered Flax seeds. Baseline and 3 months post-treatment blood levels of FSH and estradiol were done. Dexa scan was also performed. SPSS 26 was used for analyzing the data.

Results: The results showed a highly significant effect of flax seeds in reducing the post-menopausal symptoms compared to the control group. The effects were comparable with the HRT therapy.
Conclusion: Our study concluded that Flax seeds could be used in post-menopausal women to reduce their symptoms and they would be as efficacious as other allopathic therapies.

Key words: menopause, Flax seed, SSRI.

Introduction

When a woman has not had menstruated in 12 months and can no longer conceive naturally, the condition is referred to as menopause. It frequently appears amid the ages of 45 and 55, but it can appear at some time before or beyond that (Monteleone et al., 2018).

About four years before the last menstrual period, most women begin to experience menopause symptoms. Symptoms might remain for up to four years after a woman has had her last menstruation. Significant symptoms include hot flashes, weight gain, vaginal dryness, sleep problems, mood swings, and slow metabolism (Vellanki and Hou, 2018). After menopause, women get higher risks of cardiovascular diseases because when oestrogen levels drop due to menopause, levels of LDL cholesterol rise while levels of HDL cholesterol fall, causing fat and cholesterol to form up in the arteries, aggregate the danger of heart attack and stroke (Kittnar, 2020).
Estrogenic supports the lubrication, flexibility, and thickness of the vaginal canal. Low oestrogen levels can induce vaginal wall weakening, dryness, and irritation. This is mentioned as vaginal atrophy, which many women face after menopause (Naumova and Castelo-Branco, 2018). Osteoporosis is also a significant risk after menopause because the decline in oestrogen during the menopausal transition period causes bone resumption than production, resulting in osteoporosis (Khosla and Pacifici, 2021).
These risks and symptoms need to be treated for the better health of women because if they are left untreated, they may cause depression in women, which is also a considerable situation. The treatment includes many therapies, but most important are SSRIs (selective serotonin reuptake inhibitors), and HRT (hormone replacement therapy), which includes administration of hormones so that their lack may not cause any disturbance in the body (Erbil, 2018).

These treatments have many benefits and have fewer side effects that may cause severe other health problems in the long term. Nature has created many benefits in all dietary products, which can be authenticated by research. Flax seeds are one of nature's greatest gifts, containing many beneficial constituents for humans (Puri et al., 2012).

Flaxseed is the most common oilseed crop, and it is farmed for medicinal and nutritional uses in many parts of the world. It has been utilised for oil and fibre for millennia. Flaxseed is often used in functional foods because of its nutritional and medicinal properties-Flaxseed, often known as linseed, in the Linaceae family. Flax is developed in many portions of the world, including India, Argentina, America, China, and Canada. Canada is the world's largest flaxseed exporter, accounting for 75 percent of worldwide flaxseed trade and producing 40 percent of the world's flaxseed (Marpalle et al., 2015). Flaxseed is a nutrient booster that helps improve the nutritional value of food. According to one study, adding roasted flaxseed to bread increased calorie content, reduced glycaemic index, and increased antioxidant activity (Tan et al., 2015). All parts of the herb can be used raw or in processed form. Flax stems provide the highest quality fibre, both strong and long-lasting. Flax seeds are high in oil, which contain omega-3 fatty acids, proteins, and lignans. 40–45 percent lipids, 20–25 percent protein, 20–25 percent fibre, and 1% lignans make up flaxseed (Kaur et al., 2019). It possesses antioxidant and anti-carcinogenic properties. It is digested in the colon by bacterial flora, which produces mammalian lignans, protecting humans against breast and prostate cancer (Tirgar et al., 2017). Flaxseed proteins have anti-inflammatory properties. Because they are high in arginine and glutamine, they are suitable for the heart. Flaxseed proteins also act as a fungicide against plant and human infections (Ho et al., 2007).

As of the existence of mucilage in the outer layers of the seed, flaxseed stands out among the oilseeds. Mucilage from flaxseed provides a variety of health benefits and potential functional characteristics. The viscosity of intestinal contents is increased by flaxseed mucilage, which delays stomach emptying and nutritional absorption. Flaxseeds have also been found to have trypsin inhibitors (Kajla et al., 2015).

Menopause is a natural female condition that must be treated with care to better women's physical and mental health. The present study has been designed to evaluate the effect of flax seed on menopausal symptoms and comparison of it with commonly used allopathic medicine.

Materials and Method:

Study Design and Settings

This study is Randomized control clinical trial & conducted in the Department of Obstetrics & Gynaecology Jinnah Postgraduate Medical College (JPMC). All cases were taken from the general population visiting the Gynae and obstetric department JPMC.

In this study, a total of hundred and twenty (120) patients were enrolled. They have been divided into four groups, with 30 patients in each group. i.e. Control group, Hormonal replacement Therapy Group, Selective serotonin receptors inhibitors group, and Flax seed group. The study was conducted for a duration of 12 weeks. The patients were selected from the outpatient department (OPD) after they fulfilled the inclusion criteria. After explaining the details of this study to every patient enrolled informed consent was obtained. Those who did not agree were not included in the study.

Detail of all female patients age (40-69), economic status, marital status, height (in cm), weight (in kg), body mass index (BMI), Blood pressure measurements, Greene climacteric scale calculation by asking -Psychological symptoms, Somatic symptoms, Vasomotor symptoms were obtained. In addition to all initial laboratory workups, FSH levels, estradiol levels, Dexa scan of the head of the femur; left hip, and spine by calculating T scoring were also measured.

The following are the criteria for Inclusion and for exclusion:

Post-menopausal women with hot flushes of 40-69 of age. Criteria for menopause,
FSH 40 ml IU/ml., Estradiol ‹ 20pg/ml (69.34pmol/l).
14 bothersome hot flashes/week. Amenorrhea for last 12 consecutive months. Exclusion include.If they had any sign of active cancer.Any chronic cardiac, hepatic & renal disease.Patients on chemotherapy or radiotherapy.

Minimization of Bias

Bias was minimized by the inclusion of a patient's investigation from the same hospital in Follow-up visit as it has been done from initial visit.

Parameters

Serum Follicle stimulating Hormone Levels

Serum FSH were done as baseline investigation before treatment of hot Flashes from specific medication and after 12 week of treatment.

After menopause - 25.8 to 134.8 mIU/mL (25.8 to 134.8 IU/L)

Estradiol levels Serum estradiol levels were done at baseline for confirmation of menopause and after giving specific treatment of all groups after 12week treatment.

In postmenopausal females, normal estradiol levels are **0 to 30 pg/ml.**

Dexa scanning

- Dexa scan of head of femur, left hip and spine by calculating T score. BMD was measured at the femoral neck by DXA with a LUNAR DPX-L densitometer (GE-LUNAR, Madison, WI). In those subjects in whom BMD had been measured more than once before a hip fracture, the most recent DXA scan before the event was used for analysis. All clinical data were taken from the appropriate BMD visit.
- A T score of -1 to +1 is considered normal bone density. A T score of -1 to -2.5 indicates osteopenia (low bone density). A T score of -2.5 or lower is bone density low enough to be categorized as osteoporosis.
- A T-score shows bone density is higher or lower than the bone density of a healthy 30-year old adult. A healthcare provider looks at the lowest T-score to diagnosis osteoporosis.

Greene Climacteric Scale scoring. (GCS).
The Greene Scale provides a concise measure of menopause symptoms. It can be used to assess changes in different symptoms, before and after menopause treatment. Three main areas are measured: a) Psychological b) Somatic c) Vasomotor
The scoring scheme is simple, i.e., the score increases point by point with increasing severity of subjectively perceived symptoms in each of the 11 items (severity 0 [no complaints] ... 4 scoring points [very severe symptoms].

Ethical Approval: The study was approved by the IRP of the JPMC and given number NO.F2-81-IRB/2020-GENL/4345/JPMC

Incorporating the Data , itsStatistical Analysis:
Data was stored and analysed using IBM-SPSS version 23.0, Counts with percentages were reported for baseline qualitative data sets, Mean with Standard deviation for quantitative data sets were given. The one-way ANOVA was used to compare the mean scores across groups at baseline and after the 12^{th} week of study, whereas Paired sample t-test was used to compare these scores from baseline to 12^{th} week within groups. P-values less than 0.05 were considered statistically significant.

Results:
Table -1 showed that the % of married females in control, SSRI, HRT, and flax seed were 60%, 43.3%, 36.7 % and 43.4 % respectively. The percentage of unmarried female was 13.3% for Control and SSRI group, whereas it was 10% for HRT and Flax seed group. There were 26.7%, 43.4%, 53.3% and 46.7% widows in control, SRI, HRT, and flax seed group respectively. The mean age of control samples was 64.30 years, in SSRI samples it was 67.7 years, in HRT samples it was 64.9 years, whereas for Flax seed samples it was 65.60 (SD=±4.90) years. Pearson Chi Square test did not give any significant association of Marital status with studied groups (p=0.68). Similarly One-way ANOVA did not give any significant difference between the mean age of groups.
Table-2 reported at baseline the mean Estradiol of control, SSRI, HRT and Flax seed samples was 23.89 pg/ml, 23.80 pg/ml, 24.17 pg/ml and 24.67 pg/ml respectively. Similarly, the FSH values at baseline for Group I-IV were 53.50 mIU/ml, 54.83 mIU/ml, 54.43 mIU/ml and 52.50 mIU/ml respectively. At baseline the mean Hot Flashes of control samples was 2.70 units, SSRI group was 2.43 units, HRT group was 2.63 units and in Flax Seed group was 2.63 units. One way ANOVA gave an insignificant mean difference for Estradiol, FSH and hot flashes. At baseline the T score SD in control group was -2.42 units, in SSRI was -2.49 units, in HRT group was -2.54 units and in Flax Seed group was -2.50 units. One way ANOVA gives an insignificant mean difference for baseline T scores SD across groups with p-0.20.
Table-3 gives the mean comparison of Estradiol, FSH and Hot Flashes after 12^{th} week across groups. One way ANOVA gives a significant mean difference for Estradiol at 12^{th} week across studied groups with <0.01. in post hoc analysis using Tukey's test a significant mean difference was observed for SSRI vs. HRT and HRT vs. control group ($p<0.01$). The mean difference was insignificant for FSH at 12^{th} week across studied groups with p=0.78. There was a significant difference for Hot flashes across studied groups with $p<0.01$. In post hoc analysis using Tukey's test a significant mean difference was observed for SSRI vs. control, HRT and Flax Seed ($p<0.01$). A significant mean difference was observed for T scores SD across groups after 12 weeks with $p<0.01$. The post hoc analysis showed a significant mean differences for control vs. SSRI, HRT, Flax Seed ($p<0.01$) and HRT vs. SSRI group ($p<0.01$).
Table-4 gives the mean comparison of Estradiol from baseline to 12^{th} week in each study group, results showed there were no change observed for Estradiol from Baseline to 12^{th} week in Control and SSRI group, however significant mean changes in Estradiol from baseline to 12^{th} week were observed in HRT and Flax Seed group with $p<0.01$. Table-5 gives the mean comparison of FSH from baseline to 12^{th} week in each study group, results showed there were no change observed for FSH from Baseline to 12^{th} week in all groups. Table 6 gives the mean comparison of Hot Flashes from

baseline to 12th week in each study group, results showed there were no change observed for Hot Flashes from Baseline to 12th week in Control, HRT and Flax seed groups, however significant mean changes were observed in SSRI group with p<0.01. Table 7 gives the mean comparison of T scores SD from baseline to 12th week in each study group, results showed significant mean changes were observed in T scores SD from baseline to 12th week in SSRI, HRT Flax Seed group with p<0.01, and insignificant mean changes in control group.

Table 1: Baseline Characteristics of Studied Samples (n=120)

Characteristic	Controls (n=30)		SSRI (n=30)		HRT (n=30)		FLAX SEED (n=30)		p-value
	n	%	n	%	n	%	n	%	
Marital Status									
Married	18	60.0	13	43.3	11	36.7	13	43.3	0.68
Un-married	4	13.3	4	13.3	3	10.0	3	10.0	
Widow	8	26.7	13	43.3	16	53.3	14	46.7	
Age (Years)									
Mean (±SD)	64.30	±8.35	67.67	±4.81	64.90	±8.16	65.60	±4.90	0.57

Table 2: Mean Comparison of Post-Menopausal Symptoms at Baseline

	Group I Control	Group II SSRI	Group III HRT	Group IV Flax Seed	
	Mean±SD	Mean±SD	Mean±SD	Mean ±SD	P value
Baseline Estradiol (pg/ml)	23.89±2.27	23.99 ±2.19	24.17 ±1.82	24.67± 1.92	0.20
Baseline FSH (mIU/ml)	53.50 ±4.97	54.83 ±4.54	54.43 ±6.91	52.50± 5.03	0.54
Baseline Hot Flashes	2.70±0.46	2.43 ±0.50	2.63±0.49	2.63± 0.49	0.29
Baseline T Scores SD	-2.42±0.30	-2.49±0.11	-2.54 ±0.19	-2.50±0.19	0.20

Table 3: Mean Comparison of Post-Menopausal Symptoms after 12th Week

	Control	SSRI	HRT	Flax Seed	P Value
	Mean ±SD	Mean±SD	Mean ±SD	Mean ±SD	
Estradiol (pg/ml)	23.13±2.27	23.80±2.19	37.53 ±1.66	37.57 ±1.68	<0.01*
FSH (mIU/ml)	53.50±4.97	54.83 ±4.02	53.63 ±5.03	53.57 ±4.99	0.78
Hot Flashes	2.70±0.47	1.77 ±0.43	2.70 ±0.47	2.70 ±0.47	<0.01*
T Scores SD	-2.41±0.29	-1.50 ±0.18	-0.16 ±0.90	-0.29 ±0.18	<0.01*
*p<0.05 was considered significant using One Way ANOVA					

Table 4: Mean comparison of Estradiol between Groups

Group	Baseline Estradiol (pg/ml)		After 12th Week Estradiol (pg/ml)		p-value
	Mean	SD	Mean	SD	
Control	23.89	2.27	23.13	2.27	NS
SSRI	23.99	2.19	23.80	2.19	NS
HRT	24.17	1.82	37.53	1.66	<0.01*
FLAX SEED	24.77	1.92	37.57	1.68	<0.01*
*p<0.05 was considered statistically significant using Paired Sample t-test N.S: non-significant					

Table 5: Mean comparison of FSH between Groups

Group	Baseline FSH (mIU/ml)		After 12th Week FSH (mIU/ml)		p-value
	Mean	SD	Mean	SD	
Control	53.50	4.97	53.50	4.97	NS
SSRI	54.83	4.54	54.83	4.02	0.99 (NS)
HRT	54.43	6.91	53.63	5.03	0.49 (NS)
FLAX SEED	52.50	5.03	53.57	4.99	0.31 (NS)
*p<0.05 was considered statistically significant using Paired Sample t-test N.S not significant					

Table 6: Mean comparison of Hot Flashes between Groups

Group	Baseline Hot Flashes		After 12th Week Hot Flashes		p-value
	Mean	SD	Mean	SD	
Control	2.70	0.47	2.70	0.46	N.S
SSRI	2.43	0.50	1.77	0.43	<0.01*
HRT	2.63	0.49	2.70	0.47	0.32
FLAX SEED	2.63	0.49	2.70	0.47	0.32
*p<0.05 was considered statistically significant using Paired Sample t-test N.S: Non-significant					

Table 7: Mean comparison of T Scores SD between Groups

Group	Baseline T Scores SD		After 12th Week T Scores SD		p-value
	Mean	SD	Mean	SD	
Control	-2.42	0.30	-2.41	0.29	0.57
SSRI	-2.49	0.11	-1.50	0.18	<0.01*
HRT	-2.54	0.19	-0.16	0.90	<0.01*
FLAX SEED	-2.50	0.19	-0.29	0.18	<0.01*
*p<0.05 was considered statistically significant using Paired Sample t-test					

Discussion

Menopause is a natural biological process. The change from a woman's reproductive to non-reproductive phase is menopause. Hormonal changes, especially during perimenopause and post-menopause, can cause discomfort and have health effects. Nevertheless, the symptoms, such as hot flashes and emotional symptoms of menopause, may disrupt sleep, lower energy, or affect emotional health (Monteleone et al., 2018). There are many valuable treatments available, from lifestyle adjustments to hormone therapy.

The main cause of hot flashes after menopause is lower levels of oestrogens, which are responsible for the production of serotonin and endorphins, and after menopause, serotonin levels drop by 50%, corresponding to lower oestrogen levels. The decrease in Serotonin levels causes increase in norepinephrine levels thus disrupting the hypothalamic thermostat (Bansal and Aggarwal, 2019).

Estradiol is an essential hormone after menopause because it is prevented from osteoporosis. Estradiol levels restored on time can prevent oestrogen-dependent bone loss and significantly reduce the risk of fracture. According to studies, 2 mg of Estradiol taken orally is an acceptable dose; 1 mg would suffice if accompanied by a high calcium intake in the diet. Without oestrogen, a high calcium diet is ineffective in preventing the rapid loss of bone that happens in the years following menopause (Ettinger, 1988).

The current study is conducted to evaluate the different treatments for the symptoms of menopause, such as SSRIs, Hormone replacement therapy, and a dietary flaxseed product. The comparison showed remarkable results in SSRIs, HRT, and flaxseed. SSRIs are anti-depressant drugs that are prescribed for the reduction of hot flashes and also for the maintenance of estradiol and FSH (Barton et al., 2003). The mechanism of action of SSRIs for reducing hot flashes is still not precise. However, it is one of the neuroendocrine pathways, including neurotransmitters like serotonin or norepinephrine, which are thought to be responsible for altering thermoregulation and reducing hot flashes (Stubbs et al., 2017). HRT is considered a gold treatment for hot flashes, as oestrogen and progesterone are considered vital components in treating the symptoms of menopause, but it has many severe risks, such as breast cancer, ovarian cancer, and cardiovascular diseases (Fantasia and Sutherland, 2014).

Hormone replacement therapy showed almost 80% results in overcoming the symptoms of menopause. In addition lack of estradiol and progesterone also causes impaired cognition and

memory loss in elderly age, which is also a paramount concern and need to treat, for which hormone replacement therapy is a good option (Pinkerton, 2020).

The treatment with SSRIs showed many side effects such as nausea, vomiting, GI upset, insomnia, somnolence, and sedation on an early basis while in long term use, SSRIs may cause sexual dysfunction and weight gain, so the menopausal treatment with SSRIs may cause other health issues (Hirschfeld, 2003).

Flaxseed is one dietary remedy that has shown potential in alleviating hot flashes. Flaxseed is an annual plant grown in temperate and tropical climates. The seeds and the oil extracted from the seeds are the plant's major components with physiologic abilities (Muir and Westcott, 2003). The ironic source of lignans, one of three primary classes of phytoestrogens, Secoisolariciresinol (SDG), the essential fatty acid alpha-linolenic acid (a physiologic precursor of omega-three fatty acids), and fibre are the main lignans found in flaxseed. Lignans have oestrogen agonist and antagonist features, as well as antioxidant potentials. Flaxseed and its lignans may have significant oestrogen receptor anti-estrogenic properties (Lewis et al., 2006). Lignans are converted to enterodiol and enterolactone by colonic bacteria, and these metabolites are thought to have vital physiologic features such as inhibiting aromatase, 5 alpha-reductase, and 17 beta-hydroxysteroid activity (Pruthi et al., 2012). This conversion of lignans into estradiol and enterolactone may increase estradiol levels in the body and FSH, as our results have indicated.

Our results indicated that flaxseeds have significant results in reducing hot flashes and maintaining estradiol levels. Flaxseeds are dietary product and easy to take in daily life with very fewer side effects as compare to other therapies such as SSRIs and HRT.

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