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A PILOT STUDY: EFFECTS OF ELLAGIC ACIDS CONTAINED-POMEGRANATE EXTRACTS CAPSULES ON POST MENOPAUSE WOMEN

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ABSTRACT

Pomegranate extract, a standardized bioactive polar extract of the peel *Punica granatum*, is preclinically proven to have SERM (Selective Estrogen Receptor Modulator) properties. The current clinical study evaluated the efficacy and safety of Pomegranate extract of postmenopausal women. This was a pilot study to healthy post menopause women using Parallel double blind study design. Post menopause women with normal renal and liver function, 52-60 years of age were include in the study. In the treatment, Pomegranate capsules were given as two 550mg capsules two times daily (it contained ± 12.5 mg of ellagic acid per capsule) for 56 days, throughout study, weekly assessment to evaluate adverse event. Thirty subjects of mean age 55.90 ± 3.7 years were evaluable and 7.18 ± 4.2 years since the last menopause. Pomegranate capsule markedly reduced.

KEYWORDS

Clinical efficacy, Pomegranate capsules, Post menopause women and Ellagic acid.

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INTRODUCTION

Osteoporosis is a disease characterized by reduced bone mass and micro-architecture of changes of bone tissue that result in decreased bone strength and increased bone fragility, so easily broken (Ott, 1990).

One of the risk factors of osteoporosis is a hormonal disorder. Women who enter menopause experienced has reduction of estrogen, so in January – March

general, women over the age of 40 years more of osteoporosis than men. Physiologically, estrogen decline starts from the age of 35 years and over until the age of 65 years, called the climacterium period. Decrease the amount of estrogen in postmenopausal women led to increased bone turnover in which bone resorption is greater than bone formation. This causes a loss of bone mass. In older women, decreased estrogen production causes degenerative changes in multiple organ systems such as the bone, cardiovascular, and nervous system (Baziad A, 2003).

Hormone Replacement Therapy (HRT) is effective in overcoming degenerative changes in menopausal symptoms, but long-term use of estrogen therapy increases the risk of breast and endometrial cancer. Therefore, several attempts were made to develop new HRT has a beneficial effect on bone, cardiovascular and nervous system in postmenopausal women, without any adverse effects on the mammary gland and uterus (Baziad A, 2008).

New nonsteroidal synthetic compounds are selective estrogen receptor modulators (SERMs) have been developed and have an effect on estrogen receptor agonists well as estrogen receptor antagonists in specific tissues. Overall, SERMs have beneficial pharmacological effects in the prevention and treatment of osteoporosis and breast cancer. However, the use of tamoxifen and raloxifene has flaws. For example, these drugs do not reduce vasomotor symptoms (hot flushes and night sweats) due to decreased estrogen levels, and often improve symptoms (Poputsi *et al*, 2005). Therefore, research is done continuously to seek SERMs improve antagonistic effects on the breast and uterus and increase agonist effects on bone, cardiovascular, and central nervous system.

Ellagic acid is a polyphenol derived from plants that interact with estrogen receptors ER α and ER β subtype that shows estrogenic/antiestrogenic activity and can act to protect against cancer, inflammation, heart disease, and osteoporosis. These materials are considered a selective estrogen receptor modulator as modulators (SERMs) and

used as an alternative to hormone therapy for menopausal women (Poputsi *et al.*, 2005).

Clinical effectiveness of pomegranate peel as phytoestrogens especially ellagic acid compounds have not been studied, so in this study, we evaluated pomegranate peel extract effect on postmenopausal women.

METHODOLOGY

Evaluation of Ellagic acids compound by HPLC.

Samples of 1g of pomegranate capsules were diluted by methanol, then bring volume to 100 ppm as final concentration. Then injected to HPLC using eluent water methanol 65:35.

Clinical trial, a parallel double blind randomized design.

Research design

We undertook a 2-group, parallel, double-blind, randomized clinical trial (RCT).

Ethics statement

The protocol and consent form for this study were approved by the institutional health science research ethics committee of Universitas Indonesia, Jakarta. Appointments were scheduled for eligible women, where the risks and benefits of their possible participation were reviewed in detail. The informed consent form was read and signed by them before study inclusion.

Study participants

Between July 2014 and December 2014, we enrolled non-smoking healthy women aged 50 to 70 years post menopause woman. We excluded patients with one or more of the following conditions: supplements of any kind of herbal medicine, consumption of ≥ 2 alcoholic drinks per day, allergy or intolerance to herbal, body mass index (BMI) > 27 , hormone replacement therapy (HRT) or hormonal contraception in the preceding 6 months before the pre-randomization visit Women with systolic blood pressure ≥ 160 mmHg, diastolic blood pressure ≥ 100 mm Hg, or treated with antihypertensive medication (s) were also excluded.

Recruitment and randomization

Women were recruited from the general population of Depok City through Center of Ageing Studies of Universitas Indonesia. Potential study participants in the study contacted the study coordinator who explained the research project to them and verified inclusion and exclusion criteria.

Allocating participants to trial groups

At the randomization visit, participants were randomly assigned to either Placebo or Pomegranate peel extract capsules. The randomization schedule was prepared at the Centre of Ageing Studies Universitas Indonesia.

Intervention

Daily Pomegranate peel extracts capsule \approx 50 mg of ellagic acid. Study participants consumed 2x2 capsules per day for 8 weeks. Serum osteocalcin, lipid profile, liver and kidney function was assessed at baseline and at 0 and 8 weeks.

Baseline

A short questionnaire documenting social and demographic characteristics, alcohol consumption, and medication, was completed by participants. Anthropometric data (body weight, height and body fat percentage) were measured according to a standard protocol. Food habits and flavonoid consumption during the last month were estimated by validated food frequency questionnaire (FFQ).

Follow-up visits

Participants returned to our clinical research facility for follow-up visits at weeks 0 and 8. Blood samples were taken at every visit, in the morning after overnight fasting. Blood pressure was measured at every visit.

Evaluation of side-effects

Digestive and other symptoms (nausea, abdominal pain, constipation, and headache) were documented by questionnaire administered at randomization and at each study visit. Blood lipid profile and glucose were measured at baseline, and at week 8.

RESULTS AND DISCUSSION

Identification and quantification of Ellagic Acids by HPLC

Figure No.1 showed that pomegranate capsules contained Ellagic acids and the concentration per capsule as ellagic acids can be calculated. Ellagic acid standard showed a peak on 1.520 minutes and the capsule showed a peak on 1.531 minutes. To ensure that Ellagic acids standard and ellagic acids contained capsule has same ellagic acids, we mix both of them and subjected to HPLC and found they have one peak on 1.884 minutes. So, we concluded that the capsule that we used in this experiment contained Ellagic acids and the concentration per capsule was 12.5 mg.

Characteristic of volunteer

Table No.1 showed that both groups have similar characteristic on the age, systole and Diastole pressure, Body weight and the height. Then are subjected to Pomegranate extract capsules and can be concluded that population is same.

To evaluate the safety of this capsule, we determined renal function and liver function of the subjects. We evaluated liver function because the liver is the largest organ and as a centre of the metabolism of the body. One indicator of damage of cells in the liver is to take a look at the levels of enzymes found in the body including AST (Aspartate Amino transaminase) and ALT (Alanine transaminase). Both of these enzymes are amino transaminase enzymes in serum whose activity is used to measure the severity of liver diseases. Degeneration of cell and damage of cell showed the high number of these enzymes. After took a pomegranate peel extract capsules for 56 days, showed that AST and ALT as Liver function marker have not changed during experimental time. In addition to liver function tests are also carried out checks for kidney function, namely Urea N, urea and creatinine. Kidneys including vital organs. In general, the function of the kidneys is to excrete waste products such as urea, uric acid, creatinine, and other substances that are toxic, adjust the volume of blood plasma, and the amount of water in the body, keeping the osmotic pressure by

regulating the excretion of salts, i.e. discard number Excessive salt and salt hold if the amount in the body decreases, adjust the pH of plasma and body fluids to excrete urine is alkaline, but can also excrete acidic urine, and functions as a hormone with mengasilkan two kinds of substances, namely rennin and erythropoietin suspected of having endocrine function (Dharmawan, 2009). Renal function can decline if factors such as pre-renal blood flow to the kidneys, obstruction, shock or severe hypovolemia. Kidney function may also be impaired as a result of post-renal factors, such as obstruction of urine flow in the lower urinary tract (Girindra, 1986). The concentration of urea, blood urea nitrogen (BUN), creatinine, ammonia, kidneys is associated with food and beverages consumed. However, the indicator for the detection of kidney damage is blood urea nitrogen, urea and creatinine, as it will increase in the blood. Therefore, examination of blood urea nitrogen, urea and creatinine can be used as an indicator to determine the occurrence of disorders of the kidneys. In the severe renal impairment levels of blood urea nitrogen and creatinine increase (Japaries, 1992).

BUN levels normal range from 13.9 to 28.3 mg/dL and creatinine levels normal normal range is 0.30 to 1.00.

And the same result was shown in Urea N, Ureum and creatinine as a marker for renal function also did not change as well.

The effects of Pomegranate peel extract on lipid profile and body weight were shown in Table No.3. Pomegranate peel extract could increase HDL from 51.28 ± 8.60 mg/dL to 53.28 ± 8.14 mg/dL. But no effect on LDL concentration but could increase Total cholesterol from 185.71 ± 22.52 mg/dL to 188.1 ± 35.75 mg/dL. Pomegranate peel extract also decreased Triglyceride from 88.57 ± 40.74 mg/dL to 85.71 ± 32.37 mg/dL and body weight from 56.75 ± 6.49 to 53.42 ± 5.94 kg.

Lipid content of the blood is correlated with the risk of cardiovascular diseases so then we evaluated blood pressure of postmenopausal women and the result was shown at Table No.4. The systolic and diastolic pressure have tendency to increase in Placebo group and have tendency to decrease in pomegranate group.

Table No.1: Characteristic of Volunteer

S.No	Description	Placebo Group	Pomegranate Group
1	Age (Year)	56.53 ± 4.36	57.56 ± 4.78
2	Sistole (mmHg)	122.81 ± 7.74	121.875 ± 13.27
3	Diastole (mmHg)	78.75 ± 5.00	78.75 ± 6.19
4	Body weight (Kg)	56.75 ± 6.49	53.89 ± 6.04
5	Body Height (Cm)	150.62 ± 5.70	149.36 ± 5.32
6	BMI	24.87 ± 1.99	24.1 ± 2.11

Table No.2: The effects of Pomegranate extract capsules on Liver and Renal Function during experimental time

S.No		Placebo Group		Pomegranate Group	
		Before	After	Before	After
1	AST (U/L)	18.89 ± 3.44	18.8 ± 2.86	19.90 ± 1.52	22.90 ± 7.21
2	ALT (U/L)	15.67 ± 4.27	13.6 ± 2.17	16.0 ± 4.00	19.00 ± 9.26
3	Urea N (mg/dL)	12.67 ± 2.18	10.62 ± 1.67	11.70 ± 4.06	10.80 ± 1.87
4	Ureum (mg/dL)	27.11 ± 4.88	22.87 ± 3.34	25.00 ± 8.29	23.3 ± 3.83
5	Creatinine (mg/dL)	0.65 ± 0.09	0.578 ± 0.10	0.69 ± 0.10	0.634 ± 0.11

Table No.3: The Effects of Pomegranate extract capsules on Lipid Profiles and body weight of Postmenopausal Women

S.No		Placebo Group		Pomegranate Group	
		Before	After	Before	After
1	HDL (mg/dL)	54.07 ± 8.87	53.80 ± 8.58↓	51.28 ± 8.60	53.28 ± 8.14↑
2	LDL (mg/dL)	127.4 ± 39.88	122.9 ± 35.84↓	119.5 ± 23.14	119.2 ± 34.79↓
3	Total Cholesterol (mg/dL)	192.33 ± 36.54	197.1 ± 32.92↑	185.71 ± 22.52	188.1 ± 35.75↓
4	Triglyceride (mg/dL)	88.5 ± 43.17	102.2 ± 36.12↑	88.57 ± 40.74	85.71 ± 32.37↓
5	Body weight (kg)	58.89 ± 4.83	59.55 ± 4.61	53.10 ± 6.92	53.50 ± 7.04

Table No.4: The Effects of Pomegranate Extract Capsules on Cardiovascular Parameter of Postmenopausal Women

S.No		Placebo Group		Pomegranate Group	
		Before	After	Before	After
1	Systole (mmHg)	125.56± 8.82	126.67 ±14.14↑	122.00± 16.19	118.00 ±14.76↓
2	Diastole (mmHg)	80.00 ± 7.07	84.44 ± 8.82↑	79.00 ± 7.38	78.00 ± 9.19↓

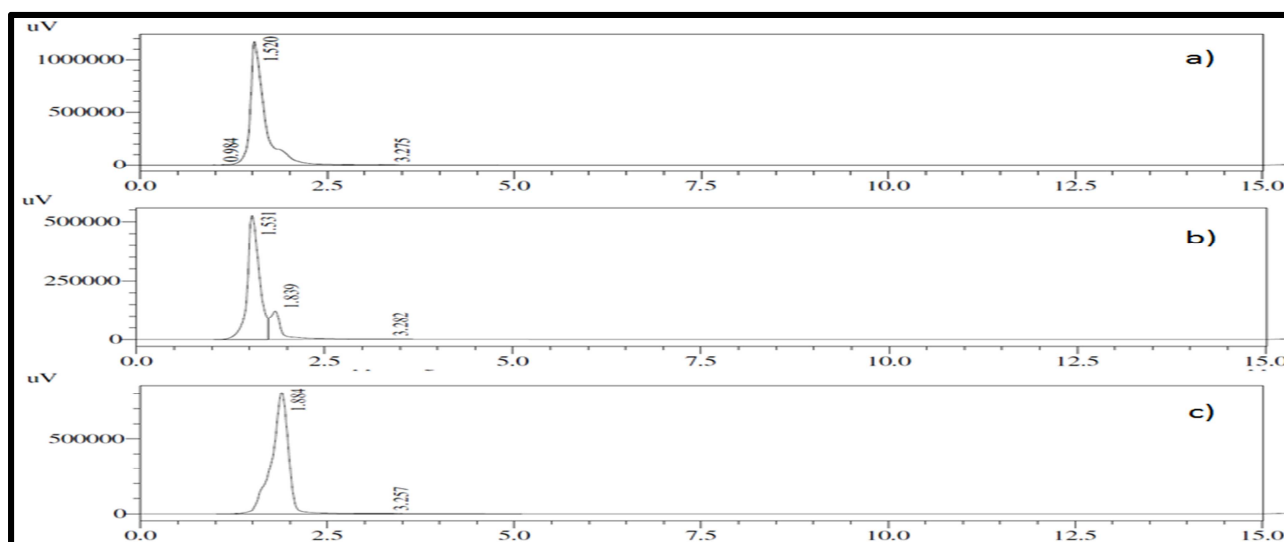


Figure No.1: Chromatogram of Ellagic Acids. Ellagic acids in Pomegranate capsules were identified using Methanol: water (65:35) as eluent, a) standart ellagic acids, b) Pomegranate capsule, c) Mix Standart and capsule

CONCLUSION

Pomegranate peel extract capsules were contained 12.5 mg of Ellagic acid per capsule. Pomegranate peel extract capsules were safe consumed by human. Pomegranate peel extract capsule have tendency to reduced lipid profile, body weight and blood pressure of postmenopausal women.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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