RESEARCH PAPER

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Advantage of soybean isoflavone as antiandrogen on acne vulgaris

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Background: Acne vulgaris (AV) is the commonest skin disorder, whereas soybean isoflavone had been proved as antiandrogen that is it can inhibit the enzyme 3ß-hydroxysteroid dehydrogenase,17ß-hydroxysteroid dehydrogenase and 5α-reductase. The purpose of this study is to prove the advantage of soybean isoflavone as antiandrogen on AV. **Methods**: this study is a clinical study using randomized pretest-posttest control group design. This study is a study with 40 samples randomized into 2 groups, i.e. placebo group and 160 mgs of isoflavone group, the duration is 12 weeks, conducted a double-blind manner. The dependent variabel is total of AV lesion, whereas the intermediate variable is DHT that will be examined using ELISA. Defferential test and multivariate analysis were performed on dependent, independent and intermediate variables. **Results**: This study found that the difference in mean of total AV lesion before treatment was not significant (p: 0.099), whereas after treatment it differed significantly (p: 0.000), with significant delta difference (p: 0.000). Difference of mean DHT level before treatment was not significant (p: 0.574), whereas after treatment it differed significantly (p: 0.000), with significant delta difference (p: 0.000). Delta of DHT (p: 0.003) (r: 0.736) had significant influence on delta of total AV lesion ($P < 0.05$). **Conclusion**: This study concludes that supplementation with 160 mgs/day of soybean isoflavone can reduce total AV lesion as a result of decreased DHT level.

Introduction

Acne vulgaris (AV) is the commonest skin disorder, almost 80% of adolescents and young adults had ever suffer from AV.[1–3] Pathogenesis of AV had not been known clearly, but several studies had proved that dihydrotestosterone (DHT) was the most influential androgen in AV, mainly in women, there are correlation between DHT and amount of AV lesion in women.[4,5]

Soybean isoflavone has active components i.e., genistein, daidzein and glycitein.[7–11] The consumption of soybean isoflavone in Asian countries is 4 times higher as compared with western countries, mean of daily consumption in Asian countries is 24–45 mgs.[11–13] The role of soybean isoflavone in androgen metabolism is to restrict the enzyme 3ß-hydroxysteroid dehydrogenase (3ß-HSD), 17ß-hydroxysteroid dehydrogenase (17ß-HSD) and the enzyme 5α-reductase.[14]

The association between consumption of soybean isoflavone and AV is not known yet, so a study on the influence of supplementation of soybean isoflavone on women with AV by investigating androgen hormone that has association with the amount of AV lesion, then formulate the problem of whether supplementation of oral soybean isoflavone has influence on amount of lesion and DHT hormone in women with AV?

The purpose of this study is to prove that supplementation of oral soybean isoflavone has influence on the reduction of amount of AV lesion and DHT hormone, and that there are association between the 2. This study can be of advantage in giving contribution to science and technology, and to increase the quality of healthcare service, and as a scientific contribution for the benefit of society. The major hypothesis of this study is that supplementation of oral soybean isoflavone has influence on AV, whereas the minor hypothesis is that supplementation of 160 mgs of soybean isoflavone for 12 weeks will cause a difference in the amount of AV lesion and DHT level in person with AV and that there are association between the 2.

Methods of Study

The study design is true experimental clinical study using randomized pretest-posttest control group design. This study used dosage of 160 mgs soybean isoflavone for treatment group and 0 mg for placebo group for 12 weeks, and the sample consisted of 40 persons that is randomized into 2 groups i.e. control group and treatment group and in order to restrict drop out then a follow up was performed using schedule of assessment visit

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Table 1 Amount and percentage of study subject based on age, education, occupation, and marital status between control group and 160-mgs-isoflavone group

Variables	Group			
	Control		160-mgs of Isoflavone	
	n	%	n	%
Age (years)	24.65 ± 4.977	24.05 ± 5.155		
Education				
Lower high school	1	5.0	2	10.0
Upper high school	18	90.0	18	90.0
university graduates	1	5.0	0	0.0
Occupation				
(University) Student	7	35.0	10	50.0
Worker	11	55.0	9	45.0
Civil Servant/Armed Forces /Police	2	10.0	1	5.0
Marital Status				
Unmarried	12	60.0	15	75.0
Married	8	40.0	5	25.0

guidelines. The sample in this study are women with AV attending medical treatment at KenSaras Hospital, Ungaran city, Central Java, Indonesia, the selection of study subject was performed using consecutive sampling and double blind treatment. The standard medicine used here was 0.025% tretinoin cream and sunscreen of 15 SPF, whereas soybean isoflavone that was used in this study was soybean isoflavone that was produced and standardized by NU Health pharmaceutical industry, California, USA. The inclusion criteria was women with AV of mild-to-severe degree according to Lehmann and was not being in medical treatment, was not suffering from hyperandrogenism, and was willing to give signature for informed consent. The exclusion criteria was allergic to soybean isoflavone. The independent variable was soybean isoflavone of 160 mgs/day dosage, the dependent variable was total amount of AV lesion examined by 2 dermatologist, then calculated interclass correlation coefficient and the coefficient α and acting as intermediate variable was DHT that was investigated based on blood serum of person with AV before treatment and after treatment for 12 weeks using ELISA, whereas the controlled confounding variable were age, body mass index (BMI), average of isoflavone consumption from soybean-stuffed food, stress status was measured using beck depression inventory score (BDI),[15] hyperandrogenism was assessed clinically i.e., whether there was amenorrhea, male voice and hirsutism that were assessed using Ferriman dan Gallwey scale,[16] and the uncontrollable confounding variable were genetic, race, environmental pollutant and chemical substance. Data analyses presented minor hypothesis test to prove the delta difference in variable of mean total AV lesion and Mann Whitney unpaired differential test was performed for DHT level. The confounding factor was controlled in randomization process. The limit of degree of significancy will be stipulated at $P < 0.05$ with 95% confidence interval. This study has been approved by the Ethical Committee of Faculty of Medicine/dr Kariadi General Hospital Semarang, Central Java, Indonesia.

Results of Study

During the time periode of study there were 68 women with AV, after selection there were 40 patients that fulfilled the inclusion kriteria and 28 patients were excluded because 17 patients refused to give their blood, the blood from 5 patients underwent lysis on investigation and they refused to repeat blood collection, 2 patients underwent menometroraghi, and 4 patients were being treated for their acne in other beauty clinics.

As study characteristics it was found that the average age for the entire sample was 24.4 ± 5.01 y and the range was 16 y as the youngest and 34 y as the oldest. Level of education was the following: 3 (7.5% of the sampel) passing lower high school/same level, 36 (90% of sampel) passing upper high school/same level, and one (2.5% of sample) passing university, whereas there was no person that only passing Elementary School. Type of occupation of the sample was the following: 20 workers (50.0% of the sample), 17 students (42.5% of the sample), and 3 Civil Servant/member of armed force/police (7.5% of the sample). The marital status is the following: 27 patients with AV were unmarried (67.5% of the sample) and 13 patients were married (32% of the sample). (**Table 1**).

The menstrual cycle and menarche among the control group and 160-mgs-isoflavone group were in normal range. There were no pregnancy in the study sample and no one used hormonal contraception device. (**Table 2**)

There were no sample with clinical symptoms of hyperandrogenism in the form of signs of hirsutism or male voice, and in the entire sample there was no widespread skin infection, mass in breast, and gynecological disorder in both study group. Mean BMI for the entire sample in this study was 20.1 ± 2.20 and the range was 12.3 as the lowest and 25.3 as the highest, in control group the mean BMI was 20.5 ± 2.60 and for treatment group the mean BMI was 19.7 ± 1.70. For stress status there was no sample with moderate and severe BDI score, but there were 31 normal BDI scores (77.7%) and 9 mild BDI scores (22.5% of

Table 2 Amount and percentage of study subject based on menarche, participation in family planing program, menstrual cycle, and pregnancy between control group and 160-mgs-isoflavone group

Variables	Group			
	Control		160-mgs of isoflavone	
	n	%	n	%
Menarche (years)	12.35	1.565	12.0	0.918
Family Planning Participant (tablet, injection, IUD)				
No	20	100.0	20	100.0
Yes	0	0.0	0	0.0
Time periode of menstrual cycle (days)				
26	0	0.0	1	5.0
27	2	10.0	2	10.0
28	17	85.0	14	70.0
29	1	5.0	3	15.0
Menstrual duration (days)				
4	8	40.0	19	95.0
5	10	50.0	1	5.0
6	2	10.0	0	0.0
Regularity of menstrual cycle				
Regularly	20	100.0	20	100.0
Irregularly	0	0.0	0	0.0
Was being pregnant				
No	20	100.0	20	100.0
Yes	0	0.0	0	0.0

sample). Mean of daily isoflavone amount from soybean-stuffed food i.e. soybean cake, tofu, and soybean milk consumed in the entire sample was 32.3 ± 6.27 mgs, in control group it was 33.5 ± 6.15 mgs and for 160-mgs-isoflavone group it was 31.0 ± 6.30 mgs.

The total lesion of acne vulgaris was the combination of amount of closed comedones, open comedones, papules, pustules, and nodules. The mean total of AV lesion before treatment in control group was 85.0 ± 45.28 and in 160-mgs-isoflavone group was 110.8 ± 47.46. After treatment for 12 weeks the mean total of AV lesion decreased in both groups, i.e., control group decreased to 84.8 ± 47.83, whereas 160-mgs-isoflavone group decreased to 34.0 ± 24.82. The difference or the delta of total AV lesion in group that was given 160-mgs/day soybean isoflavone supplementation was −76.8 ± 28.35, this was greater than the delta of mean total AV lesion in control group i.e. −0.2 ± 10.97. (**Table 3**)

Differential paired t test was performed on the difference in mean total AV lesion before and after treatment in control group and insignificant difference was found ($P > 0.05$), and differential paired Wilcoxon Signed Ranks test was performed on treatment group and significant difference was found ($P < 0.05$). As a result of differential unpaired Mann Whitney test on the delta of total AV lesion between control group and 160-mgs-isoflavone group the value (p: 0.001) was found or significant difference ($P < 0.05$). (**Table 4**)

DHT level before treatment in control group had mean value of 300.1 ± 138.01 pg/ml and in 160-mgs-isoflavone group the value was 315.2 ± 165.07 pg/ml. After treatment for 12 weeks the DHT level in control group increased to 397.5 ± 316.66 pg/ml and the difference or delta of mean DHT level in control group was 97.4 ± 320.72 pg/ml, whereas in 160-mgs-isoflavone group the DHT level decreased to 169.5 ± 62.43 pg/ml and the average difference was −145.6 ± 159.17 pg/ml (**Table 5**)

Differential unpaired *Mann Whitney test* was performed on the difference in mean AV lesion before treatment and the results from the 2 groups did not differ significantly ($P > 0.05$) and differential unpaired *Mann Whitney* test was also performed on the difference in mean AV lesion after treatment and the results from the 2 groups differed significantly ($P < 0.05$). As a result of differential unpaired Mann Whitney test on the difference or delta of DHT level between control group and treatment group the value (p: 0.001) was found or the difference was significant ($P < 0.05$). (**Table 6**)

Table 3 Amount of AV lesion before study, after 12-weeks of treatment, and the delta of both control group and 160-mgs-isoflavone group

Group	n	Mean±SDTotal AV lesion before treatment	Mean±SDTotal AV lesion after treatment	Mean±SD Delta of Lesion
Control	20	85.0 ± 45.28	84.8 ± 47.83	−0.2 ± 10.97
Treatment	20	110.8 ± 47.46	34.0 ± 24.82	−76.8 ± 28.35

Table 4 Difference in delta of total AV lesion between control group and treatment group

Group	delta of total lesion	P
Control	−0.2 ± 10.97	0.000*
Treatment	−76.8 ± 28.35	

Note: *Mann Whitney, P* < 0.05 is significant

Table 6 Difference in delta of DHT level between control group and treatment group

Group	Delta of DHT level	P
Control	97.4 ± 320.72	0.000
Treatment	−1457.6 ± 159.1	

Note: [a]*Mann Whitney, P* < 0.05 or significant.

Spearman correlation test was performed on the influence of decrease in delta of DHT level on delta of total AV lesion and resulted the value (p: 0.001) or significant ($P < 0.05$) and the relation between the 2 was strong (r: 0.736).

Discussion

The study characteristics includes age, level of education, occupation, marital status, participation in family planning program, history of pregnancy, menstrual status, stres status, BMI, history of diseases associated with AV, and mean of soybean-stuffed food consumption, these are factors with direct or indirect association to AV that has been controlled using study methodology design through randomization, restriction through inclusion and exclusion kriteria, and data analysis process, so it was assumed to be distributed evenly in each.

As a result of study for 12 weeks we found difference in delta of total AV lesion in group that was given 160-mgs/day soybean isoflavone supplementation i.e., −76.8 ± 28.35, this was larger than difference in mean total AV lesion in control group i.e. −0.2 ± 10.97. As a result of Mann Whitney differential test on the difference of total AV lesion between 160-mgs-isoflavone group and placebo group the value (p: 0.001) was found or significant difference ($P < 0$ .05), thus the minor hypothesis i.e., supplementation of 160 mgs/day soybean isoflavone for 12 weeks will cause a difference in the decrease of AV lesion in women with AV as compared with control group.

The role of soybean isoflavone in androgen metabolism is to restrict the enzyme 3ß-hydroxysteroid dehydrogenase (3ß-HSD), 17ß-hydroxysteroid dehydrogenase (17ß-HSD) and 5α-reductase.[14] Several study had proved that soybean isoflavone had influence on androgen,[10] whereas the role of androgen hormone in AV was mainly in women, there was correlation between DHT and the amount of AV lesion in women.[4,6] Isoflavone also has antiinflammation effect, several study in menopause women had proved the influence of isoflavone on the decrease of pro-inflammation cytokines. Other study that used soybean isoflavone to reduce AV lesion had never been performed yet, but several studies had proved the advantage of isoflavone of 160-mg dosage, such as study that used high dosage of isoflavone (160 mgs) for 12 weeks in menopause women, here had occured a decrease in the expression of inflammation mediator.[17,18]

The role of soybean isoflavone on DHT level in women with AV was investigated in study, after treatment with 160-mgs soybean isoflavone for 12 weeks in treatment group the DHT level decreased and the average difference was −145.6 ± 159.17 pg/ml, whereas in control group the DHT level increased, and the difference was 97.4 ± 320.72 pl/ml. Differential unpaired Mann Whitney test was performed on the difference in the delta of DHT level between 160-mgs soybean isoflavone group and placebo group and the value (p: 0.001) was found or significant ($P < 0$, 05), by the way the minor hypothesis was proved i.e. that supplementation of 160-mgs/day soybean isoflavone for 12 weeks will cause a difference in the decrease of serum DHT level in women with AV as compared with control group. The role of isoflavone on DHT in this follow-up study is almost in agreement with study in United Kingdom, where the use of soybean isoflavone had decreased the level of testosterone and DHT, but the study was performed on males with prostate hypertrophy,[10] whereas similar study about the association between soybean isoflavone and DHT in patients with AV had never been performed yet. The role of DHT in AV is that it has influence on hypersecretion of sebaceous glands, hyperkeratinization of pilosebaceous ducts, and the formation of microcomedones. DHT hormone is the result of metabolism of testosterone through the activity of enzyme 5α-reduktase type 1. Dihydrotestosterone has influence on sebocyte dan keratinocyte in the infundibulum of pilosebaceous ducts, this causes cellular differentiation, proliferation, lipogenesis, and comedogenesis.[9] Isoflavone influences androgen hormone by restricting enzymes that is involved in androgen metabolism. Several studies both in experimental animals and in human had shown that isoflavone had influence on androgen hormone.[7]

Table 5 DHT level before and after 12-weeks treatment, and the delta of both

Group	N	Mean ± SDDHT level before treatment (pg/ml)	Mean ± SDDHT level after treatment (pg/ml)	Mean ± SDDelta of DHT level (pg/ml)
Control	20	300.1 ± 138.01	397.5 ± 316.66	97.4 ± 320.72
Treatment	20	315.2 ± 165.07	169.5 ± 62.43	−145.6 ± 159.17

Conclusion

Supplementation of oral 160-mgs/day soybean isoflavone for 12 weeks in women with AV that received therapy of 0.025% tretinoin cream and sunscreen of 15 SPF will cause significant decrease on the amount of total AV lesion as a result of decrease in DHT level.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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