

## Minireview - Benefit of Isoflavone for Geriatrics

IGP Suka Aryana, RA Tuty Kuswardhani

Geriatric Division, Department of Internal Medicine

Faculty of Medicine, Udayana University/ Sanglah Central Public Hospital Denpasar, Bali, Indonesia.

suka\_aryana@unud.ac.id

*\*Corresponding Author:* IGP Suka Aryana, Geriatric Division, Department of Internal Medicine, Udayana University, Bali, Indonesia.

### Abstract

*Isoflavone is a cheap, easily found diet that possible to be consumed on regular basis. Many epidemiological studies and animal experiments as well as clinical trial studies have proved the beneficial effects of isoflavones. However, no large meta-analysis study available to prove significantly. Isoflavones are believed to have the effect of decreasing the menopausal symptoms, prevent osteoporosis, prevent cardiovascular event, and even prevent breast and prostate cancer. Isoflavones mechanism of action including numerous pathways to reach the effects, but still being a challenge to be investigated further. Isoflavones are expected to replace HRT in the future that have been shown to have a very high risk of malignancy. Further clinical studies in larger scale and also biomolecular research are needed to prove the isoflavones benefit for the elderly population.*

### INTRODUCTION

Isoflavone is a plant-derived natural ingredient belonging to phytoestrogens. Isoflavone is now being a potential alternative therapy for patients with clinical conditions associated with hormonal disorder such as cancer, menopause, cardiovascular disease and osteoporosis. Research data have shown many clinical benefits of isoflavone, especially in animal studies and some clinical studies in human, but clinical studies of both large and long-term studies are needed to prove them.<sup>1,2</sup>

The chemical structure of isoflavone is very similar to mammalian estrogens. Phenolic ring is an important element that will bind to estrogen receptor. Due to the similarity of these structures isoflavone can bind to estrogen receptor (ER). Differences in isoflavon bind to ER will affect the differences of biological activity of isoflavone in individuals.<sup>3</sup>

The effects of in vivo isoflavone are more difficult to predict because of the influence by the pathway into the body, isoflavone metabolism form, bioavailability, half-life, time and exposure levels, intrinsic estrogen and hormonal factors affecting the activity of isoflavone. All of these factors should be considered in

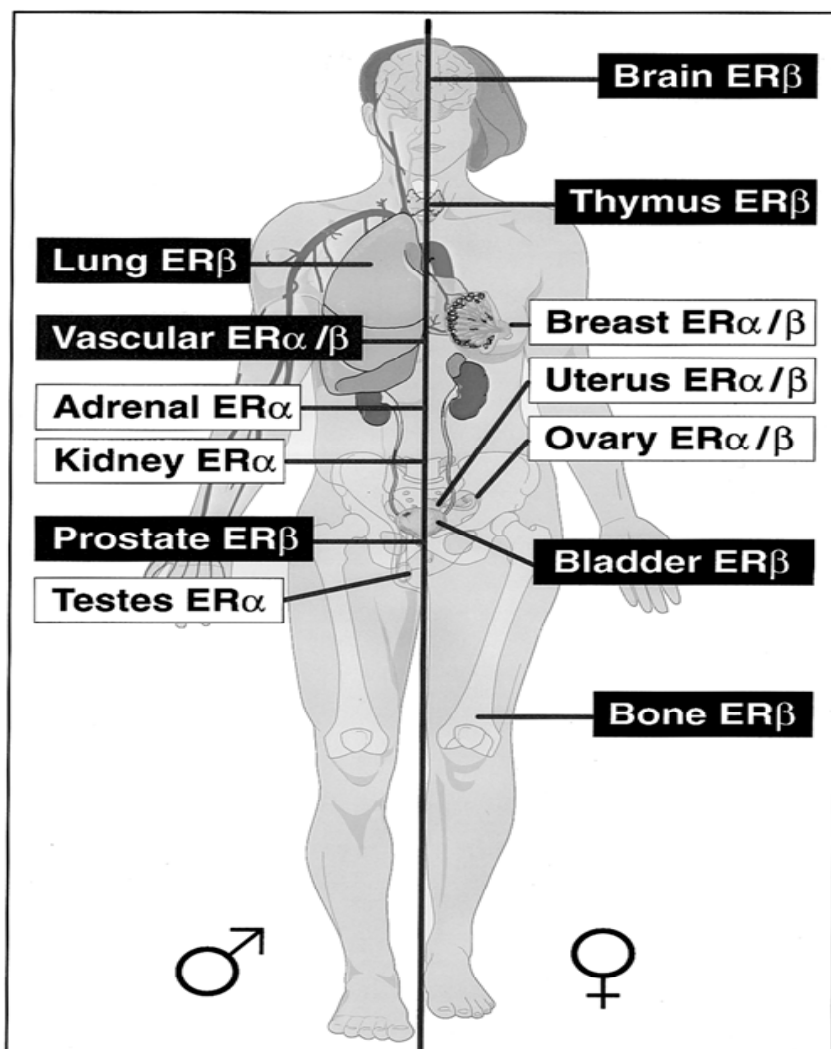
designing studies to examine the effect of isoflavone. The discovery of a second estrogen receptor by Kuiper named "ER $\alpha$ " is different from the previous type. Both ER $\alpha$  and ER $\beta$  receptors play a role in regulation and activity in the body. ER $\beta$  receptors are present in the brain, bone, bladder and vascular epithelium in which all of these tissues are very responsive to hormonal therapy.<sup>2,4</sup>

### ISOFLAVONE SOURCES

Isoflavone mostly found in soybean and other products made from soybean. The substances that are the source of isoflavone are nuts. Isoflavone mainly formed due to glucosidation process in plants that is water soluble. The content of isoflavone in various types of food with soybean raw materials of about 0,1-0,3 mg/g. Some supplement products with concentrate extract from soybean are widely produced. But the clinical effects of isoflavone supplements have not fully evaluated. Megadoses usage of isoflavone is still being a concern because of the side effects that possibly happen that occur as well as the use of other supplements. The intake of protein containing isoflavone is sourced from foods such as nuts especially soybean and soy products (milk, tempeh, tofu). In western countries, isoflavone intake only ranges 1 mg/day where as in Asia such as

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China and Japan that consume a lot of soybeans, soy products, or in vegetarian ranging from 20-50 mg/ day. This distinction is more obvious between the urban and rural population.<sup>5-7</sup>



**Figure 1.** Different receptor location of ER $\alpha$  and ER $\beta$  in male and female<sup>3</sup>

**Table 1.** Type of food and content of isoflavone and its calories<sup>7</sup>

Food	Serving	Soy protein (g)	Isoflavone content (mg)	Kcal
Soy Burger	1 patty	8	7	100
Soy nuts	1 oz	12	38	150
Soy Milk	1 c	8	24	100
Texturized Vegetable Protein (TVP)	¼ c	14	27	50
Tofu	3 oz	9	33	45
Soy Protein Bar	1 bar	6	10-15	180
Soy Breakfast Patty	2 patties	16	4	160
Soy Flour	¼ c	12	33	90
Soy Beans, Boiled	½ c	7	47	190
Tempeh	½ c	18	36	200
Soy Nut Butter	2 Tbs.	8	0	160

## ABSORPTION AND METABOLISM

The isoflavone active ingredients is strongly influenced by the bioavailability process of dietary intake, absorption, metabolism, and biological activity after being bound to receptors. In the gastrointestinal tract, the metabolism and bioavailability is strongly influenced by the microflora. Isoflavone of soybeans after being eaten will undergo hydrolysis process by glucosidase enzyme and produce aglycones, daidzein, genistein and glucitein. This substances will absorb and metabolised specifically to form equol and

p-ethylphenol. Metabolism that occur is also strongly affected by diet components. High carbohydrate diet will improve the fermentation process so that more equol produced. Biological activity of equol is higher than its daidzein precursor. The use of radical antibiotics will kill the microflora so that it will lower the isoflavone level drastically. The half-life of daidzein and genistein is about 7,9 hours. Plasma concentration can reach 50-800 ng/mL when consuming isoflavone around 50 mg/day. Regular consumption to obtain isoflavone levels range from 40-80 pg/mL.<sup>6,7</sup>

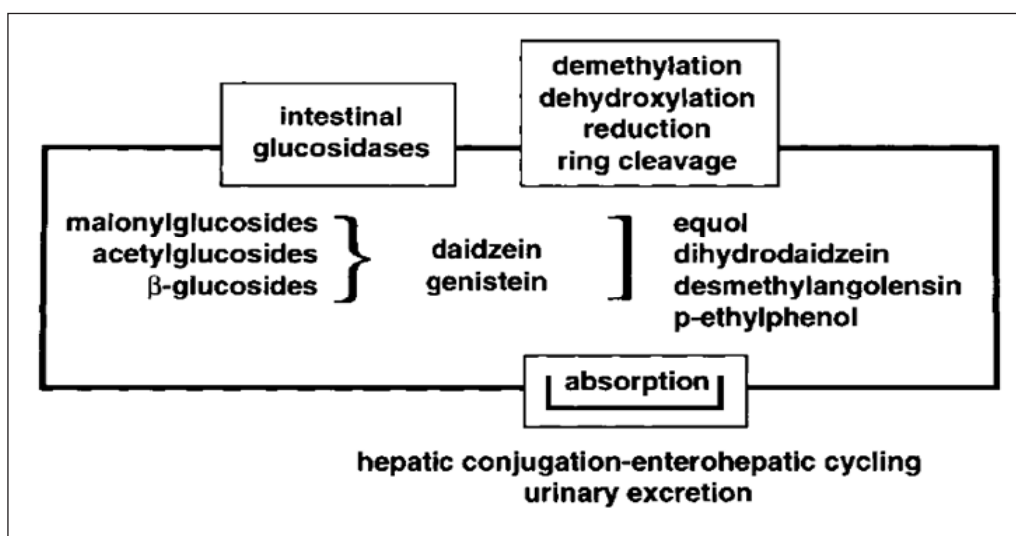


Figure 2. Metabolism process of isoflavone from soy intake in the gastrointestinal tract.<sup>7</sup>

## CLINICAL EFFECTS OF ISOFLAVONE

Studies on isoflavones are still much needed to clearly understand the pharmacokinetics and dynamics of isoflavones. Optimal doses of isoflavone being studied in premenopausal women, given aglycones 50 mg/day was obtain an hormonal effects compared with 25 mg/day doses. Besides of doses, length of administration is also greatly affect the desired hormonal effects. Epidemiological and clinical trials suggest that estrogen therapy in the postmenopausal women giving protective effects of the cardiovascular, prevent osteoporosis, improve cognitive function and reduce menopausal symptoms. But, this hormone replacement therapy (HRT) is increasing the risk of breast cancer. This prompted researcher to know the protective effect of high isoflavone diet as in the vegetarian group which turned out to be much milder postmenopausal symptoms. Isoflavone potentially became the substitute of HRT as

a source of external estrogens that also decrease the incidence of osteoporosis, breast cancer and the other postmenopausal symptoms.<sup>8-10</sup>

The isoflavone mechanism of actions is very diverse and provides many opportunities for further investigation. From various studies that have been done, it can be concluded that isoflavone have mechanism of action including:<sup>10</sup>

1. Bind to estrogen receptors
2. Inhibit the reactive oxygen species (ROS) production
3. Trigger the destruction of DNA strand so that apoptosis can perform easily
4. Inhibit the angiogenesis
5. Inhibit the production of thrombin and platelet aggregation
6. Increase the LDL receptor activity

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Based on this mechanism of action, isoflavone will have the desired clinical effects. The interesting thing is isoflavone has estrogenic and antiestrogenic effects. This effect was investigated because of the effect in vivo studies were different with the in vitro studies. It is suspected that isoflavones will have antiestrogenic effect if estrogen level in the body are still high and will have an estrogenic effect when the estrogen levels are low or in postmenopausal period. This remains a controversy.<sup>11</sup>

### EFFECT IN MENOPAUSE

Studies conducted in Europe, Malaysia, and China found the incidence of hot flushes 70-80%, 57% and 18%. After being given a diet with soy content (fitoestrogen/isoflavone) for 12 weeks found symptoms reduction for 40-55% while in control decreased for 20-35%. The effect on vaginal epithelium and histological outcome was not significant. This inconsistent results is probably because of the optimum isoflavone intake has not been measured. Measurement of isoflavone levels also shows varying results that indicate the isoflavone metabolism in every sample is very individual.<sup>11</sup>

### CARDIOVASCULAR EFFECT

Mortality due to cardiovascular disease in men and women is similar and in postmenopausal women more death are attributable to cardiovascular disease. Estrogen deficiency is associated with impaired lipoprotein metabolism resulting in dyslipidemia. The cardioprotective effect on HRT (estrogen) is because of the lipid profile improvements such as decreased LDL cholesterol and increased HDL cholesterol. This directly contribute on vascular wall in the process of atherosclerosis. The mechanism of isoflavone to improve dyslipidemia is multimechanism. Isoflavone can improve the secretion of synthesis and bile excretion that play a role in cholesterol homeostasis in gastrointestinal tracts and its hepatic cycle. Isoflavone also activate the LDL receptor to increase the uptake of cholesterol. Another mechanism is the effect of estrogen can directly improve lipid profile.<sup>7-9</sup>

Isoflavones have an antioxidant effect that can decrease the amount of oxidated LDL so it can act as cardioprotector. Isoflavone can also increase the reactivity of coronary blood vessel thereby causing the coronary vasodilatation resulting in blood flow to heart muscle. Another mechanism on endotel is that

genistein can inhibit the coagulation process through inhibition on platelet derived growth factor and thrombin formation. This may also due to genistein effect on inhibiting the tyrosine kinase, which is a central enzyme of inflammation process and thrombin formation.<sup>9</sup>

### OSTEOPOROSIS

Ipriflavone is a syntetic form of isoflavone whose estrogen activity is mild but the structure is similar to daidzein and genistein. Giving 600 mg/day of ipriflavone prevents osteoporosis and increase the bone formation. Low doses of genistein can prevent the osteoporosis process but the high doses did not work. Genistein not only affect the tyrosine kinase but also in growth factor and sitokin that plays an important role in osteoclas activity. Isoflavone can prevent the osteoclast formation so that there is no bone destruction and decreasing the calcium excretion in urine and isoflavone also help in the absorption of calcium in gut.<sup>10</sup>

### BREAST AND PROSTATE CANCER

There is no differences in the bioavailability or metabolism of isoflavone between women and men. The hypocholesterol effect also found in several studies but Cassidy found that 60 g/day of isoflavone diet did not get the desired effect either on the cholesterol improvement or platelet aggregation. The anti-cancer effects of isoflavones are based on epidemiological studies in which Asian countries with high isoflavone consumption have a low incidence of breasts and prostate cancer compared with countries in Europe and America. Isoflavone inhibit the tyrosine kinase protein that triggers the occurrence of cancer cells.<sup>9,11</sup>

### CONCLUSION

Isoflavone have many epidemiological studies and animal experiments as well as clinical trial studies have proved the beneficial effects. However, no large meta-analysis study available to prove significantly. Isoflavones are believed to have the effect of decreasing the menopausal symptoms, prevent osteoporosis, prevent cardiovascular event, and even prevent breast and prostate cancer. Mechanism of action isoflavone including numerous pathways, but still being a challenge to be investigated further including in elderly population.

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