

## Phytoestrogens' beneficial effects on cardiovascular system

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### Abstrak

Berbagai bukti yang didapat dari hasil penelitian epidemiologi, uji klinik, dan penelitian ilmu dasar menunjukkan kemungkinan adanya hubungan kausal terbalik antara konsumsi fitoestrogen dan penyakit kardiovaskular. Fitoestrogen adalah bahan alami yang didapat dari tumbuh-tumbuhan, dan mempunyai struktur kimia mirip estrogen, yaitu struktur 2-fenilnaftalen. Fitoestrogen terbagi atas 3 kelas, yaitu isoflavon, lignan, dan coumestan. Kebanyakan fitoestrogen yang terdapat dalam makanan manusia adalah isoflavon, dan lignan. Saripustaka ini merangkum berbagai hal tentang fitoestrogen, terutama isoflavon, mulai dari bahan makanan yang mengandung fitoestrogen dan 'bioavailibility'-nya, sampai berbagai efek fitoestrogen yang menguntungkan sistem kardiovaskular, yaitu pada atherosklerosis, hiperkolesterolemia, elastisitas arteri, dan tekanan darah. (*Med J Indones 2002; 11: 120-3*)

### Abstract

Several lines of evidence, including epidemiological, clinical trial and basic science, suggest the plausibility of a causal, inverse relationship between phytoestrogens and cardiovascular disease. Phytoestrogens are naturally occurring plant compounds that have 2-phenyl-naphthalene-type chemical structures similar to those of estrogens. They are simply divided into three main classes, isoflavones, lignans, and coumestans. The majority of phytoestrogens found in typical human diets are the isoflavones and lignans. This review provides an overview of the potential sources and bio-availability of phytoestrogens particularly isoflavones, and discusses their beneficial effects on cardiovascular system, i.e. on atherosclerosis, hypercholesterolemia, arterial compliance, and blood pressure. (*Med J Indones 2002; 11: 120-3*)

**Keywords:** atherosclerosis, hypercholesterolemia, arterial compliance, blood pressure

Several lines of evidence, including epidemiological, clinical trial and basic science, suggest the plausibility of a causal, inverse relationship between phytoestrogens and cardiovascular disease. The well establish low rates of cardiovascular diseases and the high intakes of dietary phytoestrogens in Asian populations relative to those in other industrialized countries are consistent with the potential protective effect of phytoestrogens.<sup>1-3</sup>

Phytoestrogens are naturally occurring plant compounds that have 2-phenyl-naphthalene-type chemical structures similar to those of estrogens.<sup>1</sup> They are found in many human foodstuffs including beans, grains, green vegetables, fruits, and nuts.<sup>4</sup>

Phytoestrogens are flavonoids broadly grouped into 4 main classes, isoflavones, lignans, coumestans, and resorcylic lactones. The three first mentioned are

found in human diets, while resorcylic lactones are mycotoxins that develop in stored crops. Therefore they are not true phytoestrogens, and phytoestrogens can be simply divided into 3 classes.<sup>5</sup> The majority of phytoestrogens found in typical human diets are the isoflavones and lignans, while the major phytoestrogen consumed by most Asian populations is isoflavones.<sup>1</sup>

This review provides an overview of the potential sources and bio-availability of phytoestrogens particularly isoflavones, and discusses their potential use to prevent cardiovascular diseases.

### POTENTIAL SOURCES OF ISOFLAVONES

The major sources of isoflavones in Asian diet are soy and its products. The primary isoflavones in soybeans are genistein, daidzein, and their respective  $\beta$ -glycosides (genistin and daidzin). In addition, much lower amounts of glycitein and its glycoside (glycitin) are present in soybeans.<sup>6</sup> Humans consume soybeans and their products in many forms, including whole soybeans, tempeh, tofu,

and soy milk. The concentrations of isoflavons in its major sources are showed in Table 1.

Table 1. The potential sources of isoflavons

Source	Concentration ( $\mu\text{g/g}$ )
Soybean	1,176 – 4,215*
Roasted soybean	2,661
Soy flour	2,014
Soy granule	2,404
Textured vegetable proteins	2,261 – 2,295*
Protein isolate	621 – 987*
Tofu	260 – 532*
Tempeh	865
Miso	389 – 647*

Modified from Tham et al, 1998<sup>1</sup>

\* More than one lot were assayed

## BIOAVAILABILITY OF ISOFLAVONE PHYTOESTROGENS

Phytoestrogens in plants are different from that found in humans and animals. To be absorbed they should be fermented/metabolized by gut microflora. In plants, some isoflavons are bound to sugar residue to form glycosides, which are inactive. When the sugar residue is removed, the glycoside form becomes active compounds.<sup>1,6</sup> In plants, both the glycoside and aglycon forms are present.<sup>1</sup> In humans, isoflavone aglycones are absorb faster and in greater amounts than their glycosides.<sup>7</sup> The conversion process from plant isoflavones to human isoflavones detected in blood and urine is showed in Figure 1.

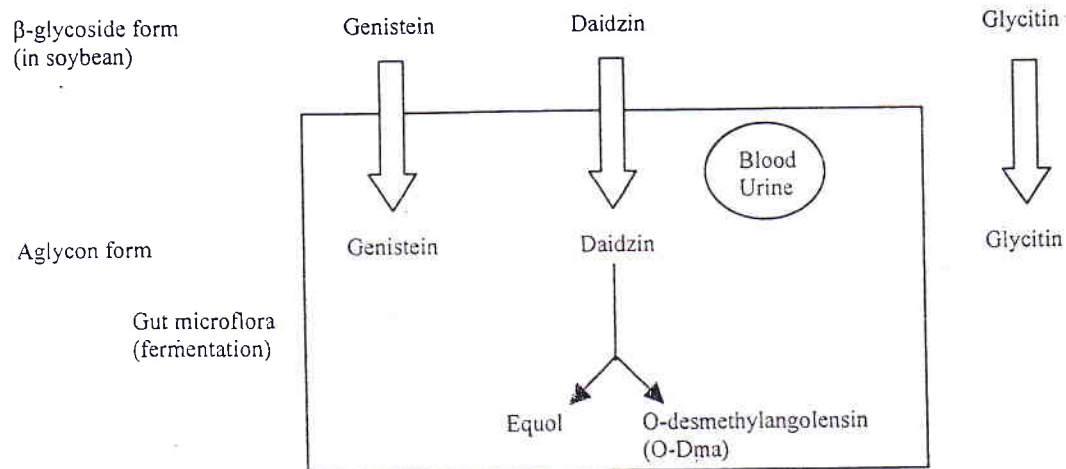


Figure 1. The conversion of plant isoflavones to human isoflavones

Once ingested, several factors influence the bio-availability of isoflavones, i.e. intestinal degradation by colonic microflora and the presence of fiber in the diet, which correlate positively with absorption.<sup>1</sup>

## THE POTENTIAL USE OF PHYTOESTROGENS TO PREVENT CARDIOVASCULAR DISEASES

### Epidemiological studies

Epidemiological studies revealed low rates of cardiovascular diseases among Asian populations whose diets were rich in phytoestrogens, relative to those in Western countries. This evidence suggests a plausible causal inverse relationship between phytoestrogens and cardiovascular disease. However, this association is confounded by other concomitant dietary differences, making it difficult to attribute the low rates of cardiovascular diseases to phytoestrogen intake.<sup>1</sup> Furthermore, the major source of phytoestrogens in Asian diets are soy and its products, that contain cholesterol lowering agents, such as  $\alpha$ -linolenic acid and saponins. Therefore, the low rates of cardiovascular diseases among Asian populations might be attributed to those agents, though the hypocholesterolemic effects of saponins in humans are still speculative.<sup>6</sup>

To assess the potential use of phytoestrogens to prevent cardiovascular diseases, several studies were conducted. Among those studies, a cross sectional study showed that dietary isoflavone intake was associated with reduced cardiovascular disease risk in postmenopausal women. In this study's adjusted

analyses, genistein, daidzein, and total isoflavone intake were each positively associated with HDL cholesterol and inversely associated with post challenge insulin.<sup>8</sup>

### Intervention study

An intervention study suggested a cardioprotective role for supplemental phytoestrogen (isoflavone). In this study, supplementation of 34 mg phytoestrogens for 6 weeks showed improvements in lipid and lipoprotein level, and blood pressure.<sup>9</sup>

### MECHANISMS FOR THE CARDIOVASCULAR PROTECTIVE EFFECTS OF PHYTOESTROGENS

The mechanisms for the cardiovascular protective effect of phytoestrogens are shown by several studies.

#### Phytoestrogens' effect on atherosclerosis

A study showed that isoflavone phytoestrogens reduced lipid peroxidation *in vivo* and increased the resistance of low-density lipoprotein (LDL) to oxidation. Isoflavones (genistein, daidzein and equol) were also shown as antioxidants *in vitro*. These facts may be a significant mechanism in reducing the risk of atherosclerosis and cardiovascular disease.<sup>10</sup>

Furthermore, various studies have suggested that genistein acts as a protein tyrosine kinase inhibitor. An increase in tyrosine phosphorylation at tyrosine residues of platelet proteins is associated with thrombin-induced platelet's activation. Therefore, genistein as a tyrosine kinase inhibitor is thought to be responsible for a reduction in the deposition and aggregation of platelets, and a decrease in the progression of atherosclerosis. This thought is however opposed by other workers who observed that concentrations of genistein up to

100 µg/mL had no significant effect on thrombin-induced platelet activation. On the other hand those workers demonstrated that daidzein, which has no inhibitory activity for tyrosine kinase, and also genistein were able to suppress platelet responses elicited by both collagen and thromboxane A<sub>2</sub>.<sup>11</sup>

However, the thought that genistein and daidzein could suppress platelet activation was opposed by a clinical trial involving 60 g/day of a soy protein isolate beverage powder for 28 days, that showed a dramatic rise in plasma isoflavone concentrations, detected no significant effect on platelet aggregation.<sup>12</sup> Therefore, more studies will need to be conducted to clarify the exact mechanism by which phytoestrogens affect various platelet responses.<sup>1</sup>

#### Phytoestrogens' hypocholesterolemic effect

Several human clinical trials with phytoestrogens have reported inconsistent serum lipid effects,<sup>1</sup> with a bigger tendency to favorable effects. The dose needed to get a hypocholesterolemic effect is shown in Table 2.

The mechanisms for the hypocholesterolemic effect of soy phytoestrogens are supposed to be due to the up-regulation of LDL receptors and/or inhibition of endogenous cholesterol synthesis.<sup>13</sup> This may be of particular significance for hyperlipidemics. Lignans may also affect cholesterol homeostasis, as they have been shown to inhibit the activity of cholesterol-7α-hydroxylase, the rate-limiting enzyme in the formation of primary bile acids from cholesterol.<sup>1</sup>

#### Phytoestrogens' effects on arteries

Soy phytoestrogens favorably influence coronary reactivity. In a study on the effect of phytoestrogens (genistein, phloretin, biochanin A and zearalanone) on isolated rabbit coronary artery rings showed that genistein, phloretin and biochanin A induced

Table 2. The dosage needed to get beneficial effect in various condition

Subject	Phytoestrogens	Dose/duration	Improvement
Perimenopausal women	Phytoestrogens in soy protein	34 mg in single dose or split into 2 doses for 6 weeks	Lipid and lipoprotein level, blood pressure <sup>8</sup>
Healthy, normo-cholesterolemic, premenopausal women	Conjugated isoflavones in soy product	45 mg/day	Total cholesterol <sup>1</sup>



significant gender-independent relaxation in rings with and without endothelium. This study demonstrated that phytoestrogens induce endothelium-independent relaxation of coronary arteries.<sup>14,15</sup> A placebo-controlled crossover trial tested the effects of phytoestrogens in the form of soy-isoflavones in peri- and post-menopausal women, and found that the systemic arterial compliance (arterial elasticity) was significantly improved in those taking soy-isoflavones.<sup>16</sup> Phytoestrogens also inhibit the progression of atherosclerosis in the coronary, iliac and common carotid arteries. The cardiovascular benefits of soy phytoestrogens appear to be equal for males and females.<sup>14</sup>

In another study on human aortic smooth muscle cells (SMC), phytoestrogens may confer protective effects on the cardiovascular system by inhibiting vascular remodeling and neointima formation.

In conclusion, phytoestrogens are strongly believed to have a potential role in the reduction of cardiovascular disease. The mechanisms of actions might be through blood pressure reduction, inhibition of lipid peroxidation and platelet aggregation, thus preventing atherosclerosis, increasing arterial compliance and/or hypocholesterolemic effect.

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