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Review

Phytoestrogens and the metabolic syndrome

Alois Jungbauer*, Svjetlana Medjakovic

Christian Doppler Laboratory of Receptor Biotechnology, Department of Biotechnology, University of Natural Resources and Life Sciences Vienna, Vienna, Austria

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ABSTRACT

Phytoestrogens are a diverse class of non-steroidal compounds that have an affinity for estrogen receptors α and β, for the peroxisome proliferator-activated receptor (PPAR) family and for the aryl hydrocarbon receptor. Examples of phytoestrogens include prenylated flavonoids, isoflavones, coumestans and lignans. Many phytoestrogens counteract the cellular derailments that are responsible for the development of metabolic syndrome. Here we propose a mechanism of action which is based on five pillars/principles. First, phytoestrogens are involved in the downregulation of pro-inflammatory cytokines, such as COX-2 and iNOS, by activating PPAR and by inhibiting IκB activation. Second, they increase reverse cholesterol transport, which is mediated by PPARγ. Third, phytoestrogens increase insulin sensitivity, which is mediated *via* PPARα. Fourth, they exert antioxidant effects by activating antioxidant genes through KEAP. Fifth, phytoestrogens increase energy expenditure by affecting AMP-activated kinase signaling cascades, which are responsible for the inhibition of adipogenesis. In addition to these effects, which have been demonstrated *in vivo* and in clinical trials, other effects, such as eNOS activation, may also be important. Some plant extracts from soy, red clover or licorice can be described as panPPAR activators. Fetal programming for metabolic syndrome has been hypothesized; thus, the consumption of dietary phytoestrogens during pregnancy may be relevant. Extracts from soy, red clover or licorice oil have potential as plant-derived medicines that could be used to treat polycystic ovary syndrome, a disease linked to hyperandrogenism and obesity, although clinical trials have not yet been conducted. Phytoestrogens may help prevent metabolic syndrome, although intervention studies will be always be ambiguous, because physical activity and reduced calorie consumption also have a significant impact. Nevertheless, extracts rich in phytoestrogens may be an alternative treatment or may complement conventional treatment for diseases linked with metabolic syndrome.

This article is part of a Special Issue entitled 'Phytoestrogens'.

Contents

1. Introduction

Phytoestrogens are a diverse class of non-steroidal compounds that includes prenylated flavonoids, isoflavones, coumestans and lignans. They are present in many plants [1]. These compounds have an affinity for estrogen receptor α [2,3] and β [4] (ERα,

* Corresponding author. Tel.: +43 1476546226; fax: +43 1476546675.
E-mail address: alois.jungbauer@boku.ac.at (A. Jungbauer).

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Table 1
Phytoestrogens from red clover and soy as ligands for PPARα and γ.

Substance	CAS number	EC_{50} value for PPARγ (μM)	EC_{50} value for PPARα (μM)	Sources
Rosiglitazone		0.211 ± 0.05		
Biochanin A	491-80-5	39.5 ± 6.4	29.5 ± 4.6	Red clover
Genistein	446-72-0	18.7 ± 3.2	26.7 ± 10.3	Red clover, soy
Daidzein	486-66-8	77.0 ± 15.1	Active	Red clover, soy
Formononetin	485-72-3	>333	nd	Red clover
Equol	94105-90-5	93.5 ± 65.7	Active	Daidzein metabolite
ODMA	21255-69-6	20.8 ± 1.9	Active	Daidzein metabolite
6-Hydroxydaidzein	17817-31-1	48.6 ± 2.1	30.0 ± 1.4	Daidzein metabolite
3′-Hydroxygenistein	480-23-29	nd	Not determined	Daidzein metabolite
6′-Hydroxy-ODMA	153409-52-0	27.3 ± 7.6	nd	Daidzein metabolite
Dihydrogenistein	21554-71-2	78.4 ± 13.3	nd	Daidzein metabolite
Dihydrodaidzein	17238-05-0	>1000	nd	Daidzein metabolite

Adapted from Mueller et al. [21,132].
Abbreviations: nd, not detected; EC_{50}, half-maximal effective concentration. 'Active' indicates that a compound showed a signal in the appropriate testing system, but that no receptor saturation could be achieved and no EC_{50} value for PPARα value could be determined.

ERβ) as well as for the peroxisome proliferator-activated receptor (PPAR) family of receptors [5–7] and for the aryl hydrocarbon receptor (AhR) [7–9]. There is increasing evidence that phytoestrogens may ameliorate symptoms of the metabolic syndrome [10–12]. Initially, Adlercreutz et al. [13–15] hypothesized that phytoestrogens play a role in breast cancer. He showed with his colleagues that these compounds and their metabolites are found in urine in increasing concentrations after intake of increasing amounts of phytoestrogen-rich food. Adlercreutz et al. also showed that soy drinks and tofu contain phytoestrogens and, in collaboration with his Japanese colleagues, he showed that the intake of isoflavones correlates with reduced prevalence of breast cancer.

Since these very early findings regarding the health effects of phytoestrogens, their potential roles in health have been studied extensively. It appears that their health impact goes far beyond estrogen-related diseases. In light of current findings we would coin a different term for phytoestrogens. Estrogenic activity is an important biological property of these compounds, but this activity does not explain all of the observed health effects of phytoestrogens. The estrogenic/antiestrogenic activity of these non-steroidal compounds can be explained by their (partial) fit into the ligand binding pocket of the estrogen receptor [16]. However phytoestrogens may also activate PPARα or PPARγ (Table 1). The structures of selected phytoestrogen ligands and their important metabolites are shown in Fig. 1. PPARs are similar to the members of the steroid thyroid receptor family in that they possess the canonical domain architecture shared with other nuclear receptor family members. PPARγ is a class II nuclear receptor that heterodimerizes with the retinoid X receptor (RXR). This receptor is mainly found in adipose tissue, but is also found to a lesser extent in kidney, liver and small intestine and in low levels in muscle. PPARγ controls many genes that are associated with fat and energy metabolism and is involved in the control of inflammation in adipose tissue [17]. PPARα and PPARβ/δ are also involved in energy metabolism [18]. A structure/function analysis of phytoestrogens and the ligand-binding domain is currently not available for the PPAR family, although such an analysis has been published for NFκB [19]; however, the structure/function relationship is not striking. PPAR regulates NFκB, and many phytoestrogens and polyphenols are PPAR agonists or partial antagonists [5,7,20,21]. In addition to binding to ER, AhR and PPARs, phytoestrogens have multiple biological properties that suggest that they have potential for treating metabolic syndrome. Placebo-controlled studies show that arterial stiffness is reduced by phytoestrogens from red clover [22]. In addition, red clover isoflavones induce endothelial nitric oxide synthetase [23] and reduce endothelial expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). ICAM-1 and VCAM-1 play pivotal roles in the development of atherosclerosis and in plaque destabilization [24]. Similar effects have been reported for soy [25]. The effects of isoflavones on cardiovascular disease have been studied by large research consortia funded by the European Union, such as ISOHEART and PHYTOHEALTH. The impact of phytoestrogen-rich nutrition on cardiovascular health is well established. Phytoestrogens have relatively good bioavailability [26], and some are metabolized to more estrogenic active compounds. The most prominent examples are equol and O-desmethyl-angolensin (ODMA), the metabolites from daidzein. Interestingly, equol and ODMA are also potent PPAR ligands [27].

The metabolic syndrome has been defined by different consortia, and the diagnosis of metabolic syndrome has been published in consensus papers. The most recent definitions of the metabolic syndrome were published as the Definition Joint Interim Statement from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) [28] (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf) and as statements by the American Heart Association-National Heart Lung and Blood Institute (AHA-NHLBI) (http://www.theheart.org/article/562835.do) and by the International Diabetes Federation (IDF). In Table 2, which is taken from the NIH website (http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf), the metabolic syndrome is defined by the presence of three of five criteria. The same

Table 2
Definition of metabolic syndrome by the National Cholesterol Education Program.

Clinical identification of the metabolic syndrome – any 3 of the following	
Risk factor	Defining level
Abdominal obesity[a]	Waist circumference[b]
Men	>102 cm (>40 in.)
Women	>88 cm (>35 in.)
Triglycerides	>150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	>130/>85 mmHg
Fasting glucose	>110 mg/dL

From http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf.
[a] Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.
[b] Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94–102 cm (37–39 in.). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.