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Phytoestrogens and their effects

Alexander V. Sirotkin [a,b,*], Abdel Halim Harrath [b]

[a] Constantine the Philosopher University, Nitra and Research Institute of Animal Production, Lužianky, Slovak Republic
[b] Dept. of Zoology, College of Science, King Saud University, Riyadh, Saudi Arabia

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ABSTRACT

The chemical structure, classification, source, metabolism, physiological and health effects of plant phytoestrogens and mechanisms of their action are reviewed. The available knowledge suggests that phytoestrogens can affect a number of physiological and pathological processes related to reproduction, bone remodeling, skin, cardiovascular, nervous, immune systems and metabolism. Due to these effects, phytoestrogens and phytoestrogen-containing diet can be useful for the prevention and treatment of menopausal symptoms, skin aging, osteoporosis, cancer, cardiovascular, neurodegenerative, immune and metabolic diseases. Possible problems in understanding and application of phytoestrogens (multiple targets and multiple estrogen receptor –dependent and –independent mechanisms of action, the discrepancy between the results of experimental and clinical studies, adequate source of phytoestrogen) have been discussed.

Contents

1. Introduction

Interest of both public and specialists in medicine and functional food production in the physiological role and practical application of plant bioactive compounds has increased dramatically over the last decade. Of particular interest in relation to human health are the class of compounds known as the phytoestrogens, which includes several groups of non-steroidal estrogens that are widely distributed within the plant kingdom. There is a growing body of evidence, that consumption of some these plants or their molecules could be an additive efficient tool to prevent and to treat several dysfunctions and diseases related to aging,

* Corresponding author.
E-mail addresses: sirotkin@cvzv.sk, asirotkin@ukf.sk (A.V. Sirotkin).

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mental processes, metabolism, malignant transformation, cardiovascular diseases and reproduction - breast and prostate cancers, menopausal symptoms, osteoporosis, atherosclerosis and stroke, and neurodegeneration (see Cassidy, 2003; Tuohy, 2003; Branca and Lorenzetti, 2005 for review). Some aspects of phytoestrogen structure, source, metabolism, physiological action, its mechanisms and interrelationships with some disorders are reviewed below.

2. Phytoestrogen classification and structure

On the basis of their chemical structure and in respect to biosynthesis patterns, phytoestrogens may be divided in chalcones, flavonoids (flavones, flavonols, flavanones, isoflavonoids), lignans, stilbenoids, and miscellaneous classes. Particular attention should be given to isoflavonoids, the subgroup of flavonoids which includes amongst others the chemical groups of isoflavones, isoflavanones, pterocarpanes, and coumestans (Dixon, 2004; Michel et al., 2013). The molecular structures of some selected phytoestrogens are present in Fig.1.

3. Phytoestrogen source and metabolism

Phytoestrogens are known to be present in fruits, vegetables, and whole grains commonly consumed by humans. They are abundant in several edible and/or medicinal plants, belonging mostly to the *Leguminosae* family (Dixon, 2004; Michel et al., 2013). Plant extracts with potential estrogenic activities include soy, red clover, kudzu, hops, licorice, rhubarb, yam, and chasteberry (Hajirahimkhan et al., 2013). Isoflavones are found in legumes—mainly soybeans, flaxseed is a major source of lignans, and coumestans are significantly present in clover, alfalfa and soybean sprouts. 8-Prenyl flavonoids are common in vegetables, hop and beer. Dietary phytoestrogens are metabolized by intestinal bacteria, absorbed, conjugated in the liver, circulated in plasma and excreted in urine (Cassidy, 2003). Gut metabolism seems key to the determination of the potency of action; sometimes the biological effect of dietary phytoestrogens is due to mainly with their metabolites generated by gut microflora (Wang, 2002; Branca and Lorenzetti, 2005). For example, the mammalian phytoestrogens enterodiol and enterolactone are produced in the colon by the action of bacteria on the plant precursors matairesinol, secoisolariciresinol, their glycosides, and other precursors in the diet (Wang, 2002). The estrogenic activity of plant phytoestrogens can be enhanced after metabolization to more active compounds such as genistein and daidzein by gut microorganisms (Zhengkang et al., 2006). For instance, the effects of daidzein is variable depending on individuals and to their ability to convert daidzein to more active equol that seems to be restricted to approximately 1/3 of the population (Gil-Izquierdo et al., 2012). Bioavailability of isoflavones requires an initial hydrolysis of the sugar moiety by intestinal beta-glucosidases to allow the following uptake by enterocytes and the flow through the peripheral circulation. Following absorption, isoflavones are then reconjugated mainly to glucuronic and sulfuric acids (Cassidy, 2003; Chiang and Pan, 2013; Vitale et al., 2013).

4. Phytoestrogen mechanisms of action

Phytoestrogens are strikingly similar in chemical structure to the mammalian estrogen, estradiol, and bind to estrogen receptors alpha and beta with a preference for the more recently described estrogen receptor beta (Younes and Honma, 2011; Rietjens et al., 2013; Paterni et al., 2014). These receptors after binding with ligand are able to move from cytoplasm to the nucleus, bind and affect the transcription-control regions of DNA or small RNAs and therefore the expression of specific genes. Furthermore, steroids are able to bind to receptors of cell surface, promote formation of cytoplasmic cyclic nucleotides and related protein kinases, which in turn via transcription factors control the expression of target genes (Sirotkin, 2014; Yanagihara et al., 2014). Therefore, phytoestrogens can potentially affect all the processes regulated by estrogens including induction sex hormone binding globulin and inhibition aromatase (Wang, 2002). Estrogen receptors are present in different tissues – central nervous system (including hypothalamo–hypophysial axis), gonads, reproductive tract, placenta, mammary gland, bones, gastrointestinal tract, lung a.o. This suggests that phytoestrogens may exert tissue specific hormonal effects (Cassidy, 2003; Younes and Honma, 2011; Böttner et al., 2013). The estrogen receptor-specific effects may occur too. For example, estrogen receptors alpha are considered as promoters of cell proliferation, whilst estrogen receptors beta are in charge for promoting mainly cellular apoptosis (Rietjens et al., 2013).

Phytoestrogens besides their ability to bind to estrogen receptors, have other biological effects, which are not mediated with these receptors – activation of serotoninergic receptors (Hajirahimkhan et al., 2013), IGF-1 receptors (Bourque et al., 2012), binding of free radicals (Wang, 2002; Cassidy, 2003; McKay and Blumberg, 2007; Vina et al., 2011; Martinchik and Zubtsov, 2012), inducting DNA methylation (Lim and Song, 2012; Rietjens et al., 2013), affecting tyrosine kinase, cAMP/protein kinase A, cGMP/NO, phosphatidylinositol-3 kinase/Akt and MAP (ERK1,2, p38) kinases (Vina et al., 2011; Bourque et al., 2012; Ming et al., 2013; Yanagihara et al., 2014), transcription

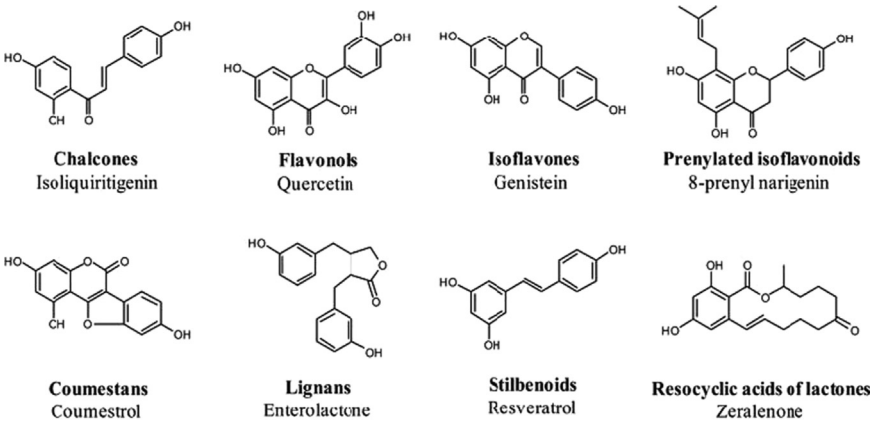

Fig.1. Molecular structure of the most ubiquitous phytoestrogens (from Michel et al., 2013)