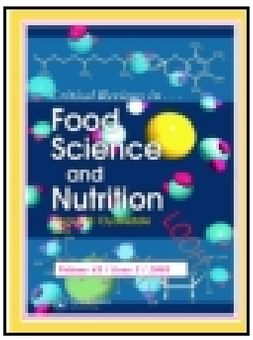

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REVIEW

Bacterial metabolism as responsible of beneficial effects of phytoestrogens on human health

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ABSTRACT

Phytoestrogens (PE) are compounds found in plants such as soy (isoflavones), flax seeds and cereals (lignans) and pomegranates (ellagitannins). PE have shown estrogenic/antiestrogenic, antioxidant, anti-inflammatory, antineoplastic and apoptotic activities. The human studies are showing promising although inconsistent results about the beneficial effects of PE on ameliorating the menopausal symptoms or reducing the risk of certain cancers, cardiovascular disease or diabetes. The effects of PE on the organism are mediated by the intestinal microbiota, which transforms them into bioactive PE such as genistein, equol, enterolignans and certain urolithins. In this work, we review the most recent findings about the bacteria able to metabolize PE, together with the latest studies on the effects of PE on health. In addition, we describe the possible factors hindering the demonstration of the beneficial effect of PE on health, evincing the importance of measuring the actual circulating PE in order to encompass the variability of PE metabolism due to the intestinal microbiota. With this in mind, we also explore an approach to ensure the access to bioactive PE.

KEYWORDS

Isoflavones; enterolignans; urolithins; intestinal microbiota; menopause; cancer

Introduction

The lower incidence of menopausal symptoms, osteoporosis and breast cancer in the Asian population compared to the Western population has been associated with a diet rich in soy, and in particular, with its content in isoflavones (Qin et al. 2006; Watanabe, Uesugi, and Kikuchi 2002). Since the appearance of the first scientific article about the benefits of soy in health (Adlercreutz et al. 1992), more research is developed every year about the benefits of isoflavones and other phytoestrogens (PE) in human health and especially in women after menopause.

PE are plant polyphenols with similar structure to 17β-estradiol, which confers them weak estrogenic and antiestrogenic activity (Farooq 2015). Five different families of phenolic compounds are considered PE, isoflavones, lignans, ellagitannins, stilbenes and coumestans. PE are present in foods commonly consumed such as soy, cherry, pomegranate, strawberries, flax seed and sunflower seeds (Dixon 2004; Landete 2011). Among the benefits attributed to PE are the reduction of menopause symptoms, such as hot flushes and osteoporosis, and the decreased risks of breast and prostate cancer, cardiovascular disease, metabolic syndrome and type 2 diabetes (Rietjens, Louisse, and Beekmann 2017). However, controversies in the use of PE have arisen due to their endocrine disruptor nature. This downside could be surpassed by sufficient evidence in the beneficial effects of PE, unfortunately inconsistencies on the beneficial effects have come out in many studies (de Cremoux et al. 2010). Several factors can be interfering in the demonstration of the effectivity of PE considering that their effects depend on the composition and dosage of PE used, the age and health status of the individuals, and the action of the gut microbiota metabolizing the PE. This last factor is of paramount importance in explaining the inter-individual variability observed when applying PE treatments.

After ingestion, isoflavones, lignans and ellagitannins, undergo metabolic modifications by the action of intestinal microbiota, which lead to the formation of a series of derived PE (Landete et al. 2016). Plant isoflavones are transformed in first place into the aglycones genistein and daidzein, which can be transformed later into equol and *O*-desmethylangolensin (*O*-DMA) (Figure 1). Lignans are metabolized into enterolactone and enterodiol, known as enterolignans. On their part, ellagitannins undergo a series of transformations ending in urolithin A, urolithin B and isourolithin A. These microbial-derived compounds have increased bioavailability and bioactivity, having higher estrogenic/antiestrogenic, antioxidant, anti-inflammatory, antineoplastic and/or apoptotic activities than their precursors (Espín et al. 2013; Landete 2012; Vitale et al. 2013).

In the present work, we review the mechanism of action and health impact of PE, and discuss about the factors hindering the demonstration of PE effects. Given the importance of bacterial metabolim when studying the PE

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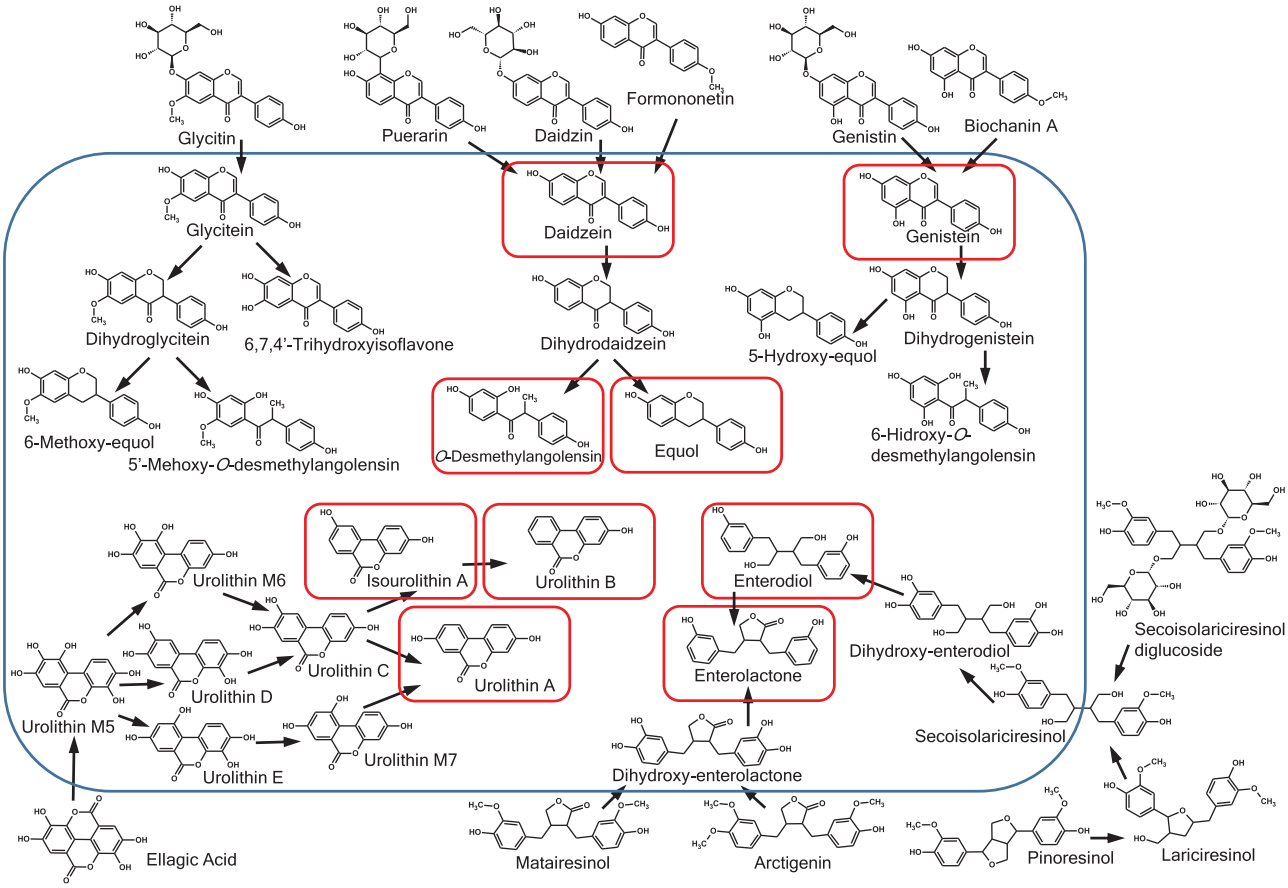

Figure 1. Microbial metabolism of phytoestrogens. The big square surrounds the compounds produced by intestinal bacteria. Compounds highlighted by a small square are those mainly investigated for their bioactivity and potential beneficial effects on health.

effectivity, the list of bacteria involved in PE transformation is updated, and the potential application of these bacteria in functional products is addressed.

PE modes of action

Many of the potential benefits of PE are due to their similarity with estradiol, which gives them the capacity to bind to the estrogen receptors (ER), although PE have less estrogenic potency than estradiol. Thus, depending of the levels of circulating estradiol in the organism, PE can exert either estrogenic or anti-estrogenic activity. The ER act as transcription factors, regulating different metabolic routes involved in cell proliferation, differentiation and survival (Lecomte et al. 2017). Isoflavones are the best studied PE in terms of estrogenic activity, and among them, genistein and equol have shown the highest affinity for ER, with higher affinity for ERβ than for ERα (Rietjens, Louisse, and Beekmann 2017; Vitale et al. 2013). This is of interest because the expression of both ER is different in each organ and tissue and because, while ERα is involved in cell proliferation and mediate the estradiol physiological effects, ERβ may counteract the ERα action and is associated with antiproliferative and anti-inflammatory activity (Ko et al. 2018; Poluzzi et al. 2014). Thus, the ERα/ERβ ratio determines the effect that PE exert through the interaction with those receptors (Sotoca et al. 2008). As for enterolignans, they have less affinity for ER than many isoflavones and act as weak estrogens after menopause, while they can have an antagonistic role when estradiol is present (Carreau et al. 2008). The estrogenic activity of urolithins A and B has been described as weaker than that of other PE, although there are few studies about it (Larrosa et al. 2006; Tomás-Barberán et al. 2017).

Besides their estrogenic/antiestrogenic activity, some PE also have an important antioxidant activity. Genistein, equol, and enterolignans are potent antioxidants (Cassidy 2005; Kitts et al. 1999; Kladna et al. 2016) with activity against DNA damage and lipid peroxidation, which gives them a potential preventive effect against atherosclerosis (Tikkanen et al. 1998). Moreover, the antioxidant activity of enterolignans has been suggested to contribute to the reduction of hypercholesterolemia, hyperglycemia, and atherosclerosis (Prasad 2000). Also ellagitannins and ellagic acid possess high antioxidant activity, although their possible effects would be limited to the gastrointestinal tract, since they are not absorbed (García-Muñoz and Vaillant 2014).

Other ER-independent mechanisms of action of PE include signaling control in cell division and growth, and gene expression. Genistein is an inhibitor of protein tyrosine kinase, which is key in several metabolic pathways such as the signal transduction inducing carcinogenesis (Ko 2014),

the platelet activation involved in atherosclerosis (González Cañete and Durán Agüero 2014) and the glucose uptake (Ha et al. 2012). Genistein also exert epigenetic actions, including the reduction of DNA methylation and the acetylation of histones, which cause the activation of certain tumor suppressor genes (Lecomte et al. 2017), which could lead to positive effects on reducing the development of cancer. Equol, enterolignans, isourolithin A and urolithins A and B have anti-inflammatory effects and antiproliferative and apoptosis-inducing activities that gives them a potential role in cancer chemoprotection (DeLuca, García-Villatoro, and Allred 2018; García-Muñoz and Vaillant 2014; González-Sarrías et al. 2017; Kasimsetty et al. 2010; Kiyama 2016; Yang et al. 2016). Moreover, isoflavones and enterolignans have been suggested to lowering the C-reactive protein (CRP), an inflammation marker involved in the developing of cancer and cardiovascular disease (Reger et al. 2017).

Evidences of PE effects on human health

The interest about the beneficial effect of PE on health has been focused mainly on isoflavones and lignans, since they are the predominant PE in the diet of Asian and Western populations respectively. Given their estrogenic nature, many studies have been carried out in menopausal related symptoms and breast cancer. Nevertheless, seen the multiple activities of PE, other targets like cardiovascular disease and diabetes have been also addressed.

Effects of PE on menopause symptoms

During menopause, the declining of ovarian function and subsequent decrease in estrogen level cause several physical and mental conditions that impair the quality of women's life. As a consequence of the estrogenic activity of PE, there has been great interest in studying their potential for the treatment of climacteric symptoms and menopause related diseases (Poluzzi et al. 2014). PE could provide benefits to postmenopausal women as an alternative to hormone replacement therapy (HRT) to avoid its side effects (Wuttke et al. 2002).

The relief of hot flushes is one of the main properties attributed to isoflavone compsumtion during perimenopause (Nie et al. 2017). Several meta-analyses have studied the effect of isoflavones on vasomotor symptoms with not conclusive results, since there are studies reporting the reduction of hot flushes (Chen, Lin, and Liu 2015; Taku et al. 2012) while others did not find enough evidence due to the high heterogeneity of the studies (Bolaños, Del Castillo, and Francia 2010; Lethaby et al. 2013). As for lignans, the studies testing the effect of flax seed intake on vasomotor symptoms did not find evidence of a better performance compared with placebo (Chen, Lin, and Liu 2015).

The research on the association of isoflavones and bone mineral density is in a similar state, with inconclusive or even negative results due to varying effects (Abdi et al. 2016; Greendale et al. 2015; Salari Sharif, Nikfar, and Abdollahi 2011). In the same way, the existing studies regarding the beneficial effect of isoflavones on some aspects of cognitive function in postmenopausal women do not show enough evidence (Soni et al. 2016; Thaung-Zaw, Howe, and Wong 2017). On the contrary, lignan intake seems to have some positive effect on cognitive function (Nooyens et al. 2015; Rietjens, Louisse, and Beekmann 2017).

Effects of PE on cancer risk

PE can influence cell proliferation, apoptosis and angiogenesis through various mechanisms, which confer them anticarcinogenic potential (Lecomte et al. 2017; Virk-Baker, Nagy, and Barnes 2010). Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among women. Thus, the influence of PE on breast cancer has been addressed by many studies, finding inverse correlations of isoflavones and lignans with the risk of developing breast cancer (Goodman et al. 2009; Zaineddin et al. 2012). Published meta-analysis have suggested that the beneficial effect of isoflavone intake may be limited to Asian population, which has a high consumption of soy (Xie et al. 2013b). A review of studies measuring isoflavone biomarkers has associated high circulating genistein and daidzein with low risk of breast cancer (Rienks, Barbaresko, and Nothlings 2017). Regarding the lignans, enterolactone levels in blood or urine have been linked to low risk of breast cancer, although meta-analysis associated that low risk only with high lignan intake (Buck et al. 2010; Velentzis et al. 2009).

The association of PE with prevention of prostate cancer has been also tackled by several studies with unequal outcomes. Some review studies have described association of circulating genistein, daidzein, and enterolactone with a reduced risk of this cancer (He et al. 2015; Rienks, Barbaresko, and Nothlings 2017). On the contrary, other study found high circulating equol to have protective effect, while the rest of PE were not associated with prostate cancer risk (Pérez-Cornago et al. 2018).

Moreover, the relation of PE with gastric, colorectal, lung and endometrial cancers has been studied, although the results are not conclusive (Grosso et al. 2017). On their part, urolithins effects on cancer are promising on the light of *in vitro* experiments, but there is a lack of *in vivo* human evidence (Tomás-Barberán et al. 2017).

Effects of PE on cardiovascular health

Cardiovascular disease is the leading cause of death globally and its risk increases after menopause. The studies addressing the effects of PE on cardiovascular disease have shown an association between their intake and a lower cardiovascular risk (de Kleijn et al. 2002). Both isoflavones and lignans have obtained positive results in improving blood lipid profile and endothelial function, and hence they could act positively in the early steps of atherosclerosis, especially after menopause (Cano, García-Pérez, and Tarín 2010; Peterson et al. 2010). There are also evidences suggesting a protective effect of equol, *O*-DMA and enterolignans on cardiovascular

risk (Frankenfeld 2017). However, other studies have not found enough evidence for those associations (Rienks, Barbaresko, and Nothlings 2017; van der Schouw et al. 2005; Yeung and Yu 2003). Hence, the effect of PE on cardiovascular disease is not well stablished and more research is needed on the subject (Rietjens, Louisse, and Beekmann 2017).

Effects of PE on diabetes

Diabetes is increasing globally, with higher incidence in post-menopausal women. Maintaining a healthy diet, together with regular exercise have shown to prevent type 2 diabetes, which is the predominant type of diabetes. There is emerging evidence suggesting that PE may influence on the glycemic metabolism, having beneficial effects for the prevention and amelioration of type 2 diabetes (Bhathena and Velasquez 2002). However, other studies have not found enough evidence of this association (Glisic et al. 2018; Talaei et al. 2016). Genistein has been suggested to improve the glucose metabolism, by means of inhibiting tyrosine kinases, with positive results on post-menopausal women (Fang et al. 2016; Liu et al. 2017). Enterolignans have been also associated with lowering the risk of type 2 diabetes (Sun et al. 2014), although a meta-analysis has found this association only for flax seed intake and not for enterolignans (Mohammadi-Sartang et al. 2018).

Factors affecting the determination of the association of PE and health

The potential beneficial effects of PE on human health have been reported by many works and positive data are piling up every year. Nevertheless, the current available studies do not give enough evidence for a definitive conclusion on this issue (Rietjens, Louisse, and Beekmann 2017).

In vitro research has revealed multiple evidences of the estrogenic/antiestrogenic, antioxidant, anti-inflammatory, antineoplastic and apoptotic activity of PE (Cassidy 2005; Kasimsetty et al. 2010; Kitts et al. 1999; Larrosa et al. 2006; Muthyala et al. 2004; Prasad 2000; Zhu, Kawaguchi, and Kiyama 2017). However, while those studies are appropriate to elucidate the mechanisms of action of PE, with fewer variables and amplified reactions, the extrapolation of their results to humans is difficult. This kind of experiments do not take into account several factors affecting the bioavailability and bioactivity of PE during their pass through the gastrointestinal tract, and thus *in vivo* studies are necessary to corroborate the effects of PE.

On their part, studies assessing the *in vivo* impact of PE on health have shown discrepancies that can be due to several factors. To start off, many epidemiological studies measure the PE exposure by means of food frequency questionnaires that, while can give a general idea of the long-term PE exposure, are also prone to error. These dietary assessments are subject to self-reporting bias (Zamora-Ros et al. 2014), do not consider all possible food sources of PE and rely on food composition tables that may be incomplete and that do not cover the effect of food processing and cooking (Rienks, Barbaresko, and Nothlings 2017). Moreover, it has been described that a correlation between PE intake and circulating PE compounds in the organisms cannot be stablished due to the high inter-individual variability (Peterson et al. 2010; van der Velpen et al. 2014), which is probably associated with the variability of the intestinal microbiota. Measuring PE exposure by means of dietary assessments, or PE intake in clinical studies, do not reflect the actual presence of PE in the organism, since it does not comprise the biotransformation of PE by the intestinal microbiota and their absorption. In those studies, it is not possible to unveil the effects of compounds produced by the microbiota, such as equol, *O*-DMA and enterolignans. Within this scenario, the measurement of bioactive PE as biomarkers in blood or urine samples seems a better approach in order to have an objective and more accurate estimation of PE exposure.

Several studies have been carried out measuring PE biomarkers and, although many of them show beneficial effect of specific PE compounds, there have been also studies with null results (Table 1). In this aspect, it is important to consider that the presence of PE in the organism is not constant and depends on the time since the last intake, with varying pharmacokinetics for each metabolite (Frankenfeld 2017; Zamora-Ros et al. 2014). Punctual samples can be missing acute PE intake and fail in representing the long-term PE exposure. Therefore, it is of paramount importance the implement of an adequately designed and multiple-point sampling planning. In this regard, the analysis of 24 h urine samples has been proposed as the better approach for a more representative measurement of the PE exposure (Rienks, Barbaresko, and Nothlings 2017). Although studies using PE biomarkers have shown certain limitations, they are a more accurate tool than those using PE intake. These kind of measurements are able to encompass the inter-individual variability due to the intestinal microbiota and differences in the intestinal absorption of PE.

Other important factor interfering with the assessment of PE efficacy seems to be the low levels of PE achieved with a normal diet. In this way, beneficial effect of isoflavones have been proved easier in Asian populations, where the soy intake is higher, than in other populations (Xie et al. 2013b). Likewise, the uncertainties on the effectiveness of lignans by epidemiological studies may be caused by a low intake in the usual diet (Saarinen et al. 2010), also reflected in how the beneficial effects tend to be more evident in the highest quartiles of intake (Peterson et al. 2010). The epidemiological studies may be missing the importance of PE on health due to an insufficient intake of PE with the diet, which would cause circulating concentrations of PE to be below their active level.

Besides the proper measurement of the circulating PE and the achievement of sufficient levels in the organisms, it must be taken into account that the polymorphisms in ER may be associated with different effects of PE. Thus, varying

Table 1. Works studying the relationship between the presence of PE in plasma, serum or urine and health benefits in humans.

Study	Health aspect	PE analized	Population	Scientific evidence
	Cancer			
Verheus et al. (2007)	Breast	DAI, GEN, GLY, *O*-DMA, EQ, END, ENL	Nested case-control study, Netherlands, 383 cases, 383 controls	High GEN circulation levels are associated with reduced breast cancer risk.
Ward et al. (2008a)	Breast	DAI, GEN, GLY, *O*-DMA, EQ, END, ENL	Nested case-control study, UK, 237 cases, 937 controls	Urinary or serum phytoestrogens were not associated with protection from breast cancer.
Iwasaki et al. (2008)	Breast	DAI, GEN	Case-control study, Japan, 144 cases, 288 controls	Inverse association between plasma GEN and the risk of breast cancer.
Goodman et al. (2009)	Breast	DAI, GEN, EQ	Nested case-control study, USA, 151 cases, 462 controls	High urinary DAI associated with low risk of breast cancer in Japanese-American women. High urinary EQ associated with low risk in white women.
Piller, Chang-Claude, and Linseisen (2006)	Breast	GEN, ENL	Nested case-control study, Germany, 237 cases, 237 controls	Inverse association between plasma ENL and premenopausal breast cancer risk.
den Tonkelaar et al. (2001)	Breast	GEN, ENL	Nested case-control study, the Netherlands, 88 cases, 268 controls	Non-significant association of urinary GEN or ENL with a reduced breast cancer risk.
Olsen et al. (2004)	Breast	ENL	Nested case-control study, Denmark, 381 cases, 381 controls	Lower risk for ERα-negative breast cancer with higher concentrations of ENL in plasma.
Sonestedt et al. (2008)	Breast	ENL	Nested case-control study, Sweden, 366 cases, 733 controls	Protective association of ENL more evident in tumors that express ERα but not ERβ.
Xie et al. (2013a)	Breast	ENL	Nested case-control study, USA, 802 cases, 802 controls	Significant inverse association between plasma ENL and breast cancer risk only in premenopausal women with low follicular estradiol levels.
Pietinen et al. (2001)	Breast	ENL	Nested case-control study, Finland, 194 cases, 204 controls	Serum ENL level was significantly inversely associated with risk of breast cancer.
Zaineddin et al. (2012)	Breast	ENL	Nested case-control, Germany, 1250 cases, 2164 controls, and meta-analysis of 7 other studies	Inverse association between higher serum ENL levels and postmenopausal breast cancer risk.
Kilkkinen et al. (2004)	Breast	ENL	Nested case-control, Finland, 215 controls, 215 controls	No association of serum ENL with breast cancer risk.
Ward et al. (2008b)	Colorectal	DAI, GEN, GLY, *O*-DMA, EQ, END, ENL	Nested case-control study, UK, 221 cases, 889 controls	No association between serum or urinary isoflavones or enterolignans with colorectal cancer risk.
Ko et al. (2018)	Colorectal	GEN, DAI, ENL	Two nested case-control studies; Korea and Vietnam; 101 + 222 cases, 391 + 206 controls	High plasma levels of GEN and DAI had relationship with a decreased risk of colorectal cancer.
Kuijsten et al. (2008)	Colorectal	ENL, END	Nested case-control study, Netherlands, 160 cases, 387 controls	No association of plasma END or ENL concentrations with reduced risk of colorectal cancer.
Johnsen et al. (2010)	Colorectal	ENL	Case-cohort study, Denmark, 381 cases, 370 controls	Higher ENL levels in plasma associated with lower risk of colon cancer in women but higher risk of rectal cancer in men.
Kuijsten et al. (2006)	Colorectal adenomas	ENL, END	Nested case-control study, Netherlands, 532 cases, 503 controls	Plasma END and ENL associated with a lower risk of first colorectal adenomas.
Atteritano et al. (2008)	Cytogenetic biomarkers	GEN	Randomized, placebo-controlled study, Italy, 57 postmenopausal women	Plasma GEN related with a reduction of cytogenetic biomarkers in peripheral lymphocytes.
Aarestrup et al. (2013)	Endometrial	ENL	Case-cohort study, Denmark, 173 cases, 149 controls	Some support to an inverse association of plasma ENL concentration and

(*continued*)

Table 1. Continued.

Study	Health aspect	PE analized	Population	Scientific evidence
				endometrial cancer incidence.
Ko et al. (2010)	Gastric	DAI, GEN, EQ, ENL	Nested case-control study, Korea, 131 cases, 393 controls.	High serum concentrations of GEN, DAI and EQ associated with decreased risk of gastric cancer.
Hara et al. (2013)	Gastric	DAI, GEN	Nested case-control study, Japan, 483 cases, 483 controls	Overall distribution of plasma isoflavone concentrations not associated with the development of gastric cancer.
Ward et al. (2008b)	Prostate	DAI, GEN, GLY, *O*-DMA, EQ, END, ENL	Nested case-control study, UK, 193 cases, 828 controls	No association between serum or urinary isoflavones or enterolignans with prostate cancer risk.
Travis et al. (2009)	Prostate	DAI, GEN, EQ, ENL, END	Nested case-control study, Europe, 950 cases, 1042 controls	High concentrations of circulating GEN associated with lower risk of prostate cancer.
Jackson et al. (2010)	Prostate	DAI, GEN, EQ, ENL	Case-control study, Jamaica, 175 cases, 194 controls	EQ-producers at decreased risk of prostate cancer. ENL may increase risk of prostate cancer.
Heald et al. (2007)	Prostate	DAI, GEN, ENL	Nested case-control study, Scotland, 433 cases, 483 controls	Lower prostate cancer risk inversely associated with increased serum concentrations of ENL.
Kurahashi et al. (2008)	Prostate	DAI, GEN, EQ	Nested case-control study, Japan, 201 cases, 402 controls	GEN and EQ plasma levels inversely associated with the risk of prostate cancer.
Ozasa et al. (2004)	Prostate	DAI, GEN, EQ	Nested case-control study, Japan, 52 cases, 151 controls	Serum GEN, DAI and EQ seem to reduce prostate cancer risk in a dose-dependent manner.
Park et al. (2009)	Prostate	DAI, GEN	Nested case-control study, USA, 249 cases, 404 controls	Urinary excretion of DAI and GEN inversely associated with prostate cancer.
Hedelin et al. (2006)	Prostate	ENL	Case-control study, Sweden, 209 cases, 214 controls	Inverse but non-linear association between serum ENL and prostate cancer.
Kilkkinen et al. (2003)	Prostate	ENL	Nested Case-control study, Finland, 214 cases, 214 controls	No association of serum ENL with prostate cancer risk.
Stattin et al. (2002)	Prostate	ENL	Nested case-control study, Finland, Norway and Sweden 794 cases, 2550 controls	Serum ENL not associated with prostate cancer risk.
deVere White et al. (2010)	Prostate specific antigen (PSA)	DAI, GEN, EQ	Double-blind, placebo controlled, randomized trial, USA, 53 men	Increase in serum DAI and GEN did not lower PSA levels in men with low-volume prostate cancer.
	Cardiovascular disease			
Bredsdorff et al. (2013)	Acute coronary syndrome	DAI, GEN	Nested case-control study, Denmark, 393 cases, 393 controls	Significant association between DAI urinary excretion and risk of acute coronary syndrome.
Vanharanta et al. (2003)	Acute coronary events	ENL	Nested case-control study, Finland, 167 cases, 167 controls	Healthy men with high ENL serum concentrations had a lower risk of acute coronary events.
Morelli et al. (2007)	Cardiometabolic risk factors	Total isoflavones, EQ	Single-crossover parallel-group, randomized controlled, blinded trial, Italy, 62 hypercholesterolemia patients	Improvement in cardiovascular risk markers greatest in EQ producers.
Liu et al. (2014)	Cardiometabolic risk factors	*O*-DMA, EQ	Cross-sectional study, China, 595 postmenopausal women	Equol and *O*-DMA associated with more favorable cardiovascular risk profiles.
Frankenfeld (2014)	Cardiometabolic risk factors	ENL, END	Observational study, USA, 2260 participants	High urinary ENL improved cardiovascular risk factors.
Zhang et al. (2012)	Coronary heart disease	DAI, GEN, GLY, *O*-DMA, EQ, DHD, DHG	Nested case-control study, Shanghai, 377 cases, 753 controls	Urinary EQ inversely associated with risk of coronary heart disease in women.

(*continued*)

Table 1. Continued.

Study	Health aspect	PE analized	Population	Scientific evidence
Ahuja et al. (2017)	Coronary artery calcification	DAI, GEN, EQ	Observational study, Japan, 272 men	EQ-producers (serum) had significantly lower CAC than EQ non-producers.
Cai et al. (2012)	Lipid profiles and intima–media thickness	DAID, EQ	Observational study, China, 527 subjects	EQ producers (urine) with higher dietary isoflavone consumption associated with lower serum triacylglycerol and common carotid intimal medial thickness.
Hall et al. (2006)	Blood lipids	EQ	Randomized, double-blind, placebo-controlled, crossover trial, Europe, 117 postmenopausal women	No influence of EQ producing status in plasma lipids.
Struja et al. (2014)	Metabolic syndrome	DAI, GEN, *O*-DMA, EQ, ENL, END	Observational study, USA, 1748 participants	Increasing excretion of ENL associated with a decreased presence of the metabolic syndrome.
	Menopause			
Pawlowski et al. (2015)	Bone loss	DAI, GEN, EQ, GLY, DHD, *O*-DMA, BIA, FOR, END, ENL	Blinded, randomized, crossover intervention trial, USA, 24 postmenopausal women	Isoflavone supplementation increased serum GEN with a bone-preserving effect, regardless of EQ-producing status.
Brink et al. (2008)	Bone loss	DAI, GEN, EQ, *O*-DMA	Randomized, double-blind, placebo-controlled, parallel, multicentre trial, Europe, 237 postmenopausal women	Bone density and bone turnover not affected by isoflavones levels in plasma/urine.
Kenny et al. (2009)	Bone loss	DAI, GEN, EQ	Randomized, double-blind, placebo-controlled trial, USA, 131 postmenopausal women	No significant influence of serum isoflavones on bone mineral density.
Tai et al. (2012)	Bone loss	DAI, GEN	Blinded, randomized, two arm study, Taiwan, 431 postmenopausal women	No effect of isoflavone treatment on bone mineral density despite the high DAI and GEN concentrations in serum.
Frankenfeld et al. (2006)	Bone loss	EQ, *O*-DMA	Interventional study, USA, 92 postmenopausal women	*O*-DMA producers had greater bone mineral density.
Tousen et al. (2011)	Bone loss	EQ	Double-blind, randomized, placebo-controlled trial, Japan, 93 subjects	EQ supplementation increase serum EQ and inhibit bone resorption in non-producing postmenopausal women.
Wu et al. (2007)	Bone loss	EQ	Blind placebo-controlled trial, Japan, 54 postmenopausal women	Significant lower bone loss in EQ producers.
Uchiyama et al. (2007)	Menopausal symptoms	DAI, GEN, EQ	Observational study, 108 postmenopausal women	Higher levels of urinary levels of equol in patients with lower simplified menopausal index.
Jou et al. (2008)	Menopausal symptoms	DAI, GEN, EQ	Randomized, double-blind, placebo-controlled trial, Taiwan, 96 postmenopausal women	Menopausal symptoms ameliorated after isoflavone supplementation only in EQ-producing group.
Ishiwata et al. (2009)	Menopausal symptoms	EQ	Randomized, double-blind placebo-controlled trial, Japan, 134 subjects	Urine EQ concentrations showed good correlation with the EQ supplement intake and improved mood-related symptoms in EQ non producers.
Aso et al. (2012)	Menopausal symptoms	EQ	Double-blind placebo-controlled trial, Japan, 160 subjects	EQ supplementation increased urine EQ and showed beneficial effects on hot flashes and neck or shoulder muscle stiffness, in EQ non-producers.
Kreydin et al. (2015)	Urinary incontinence	DAI, GEN, EQ, *O*-DMA, ENL, END	Cross-sectional, population based cohort survey, USA, 1789 participants	Increasing urine concentrations of END and ENL associated with a protective effect against incontinence in postmenopausal women.
Crawford et al. (2013)	Vasomotor symptoms	DAI, EQ	Randomized, placebo-controlled trial, USA, 130 subjects	Beneficial effect of high doses/ frequency of isoflavone

(*continued*)

Table 1. Continued.

Study	Health aspect	PE analized	Population	Scientific evidence
				consumption in EQ producers.
Newton et al. (2015)	Vasomotor symptoms	EQ	Observational study, USA, 375 soy food consumer participants	Among EQ producers, higher EQ in urine, attributable to higher DAI consumption, is associated with decreased vasomotor symptoms.
	Diabetes			
Nikander et al. (2004)	Insulin resistance	EQ	Double-blind, randomized, placebo-controlled trial, Finland, 56 postmenopausal women	Being EQ producer had no effect on insulin resistance.
Hall et al. (2006)	Plasma glucose and insulin, insulin resistance	EQ	Randomized, double-blind, placebo-controlled, crossover trial, Europe, 117 postmenopausal women	No influence of EQ producing status in diabetes biomarkers.
Talaei et al. (2016)	Type 2 diabetes risk	DAI, GEN, GLY, EQ, ENL, END	Nested case-control study, China, 564 cases, 564 controls	No significant association between urine phytoestrogens and risk of type 2 diabetes.
Ko et al. (2015)	Type 2 diabetes risk	DAI, GEN, GLY, EQ	Observational study, Korea, 693 subjects	High plasma concentrations of GEN were associated with a decreased risk of type 2 diabetes in women but not in men.
Ding et al. (2015)	Type 2 diabetes risk	DAI, GEN, *O*-DMA, DHG, DHD	Nested case-control study, USA, 1111 cases, 1111 controls, women	Urinary excretion of DAI and GEN associated with a lower type 2 diabetes in women.
Sun et al. (2014)	Type 2 diabetes risk	END, ENL	Nested case-control study, USA, 1107 cases, 1107 controls, women	ENL (urine) associated with a lower risk of type 2 diabetes in women.

Abbreviations: BIA, biochanin A; DAI, daidzein; DHD, dihydrodaidzein; DHG, dihydrogenistein; END, enterodiol; ENL, enterolactone; EQ, equol; FOR, formononetin; GEN, genistein; GLY, glycitein; *O*-DMA, *O*-desmethylangolensin; PE, phytoestrogens.

effects of isoflavones on cardiovascular disease risk factors have been described depending on differences in ERβ genotypes (Hall et al. 2005; Hall et al. 2006; Qin et al. 2014; Vafeiadou, Hall, and Williams 2006).

The heterogeneity of the published studies, with different compounds and doses tested, exposition times, populations and end points, together with the variability of the individual intestinal microbiota and ER polymorphism, may be hindering the establishment of the effective dose of the different PE. Hence, there is a need for more randomized controlled trials, which should include adequate PE biomarkers determination, different doses of PE tested and even genotyping in their design, in order to stablish the effective dose of the different PE.

PE metabolism by bacteria

The benefits provided by PE to human health are influenced to a great extent by the intestinal microbiota (Frankenfeld 2017; Hullar et al. 2015; Rietjens, Louisse, and Beekmann 2017). The presence of specific bacteria or bacteria communities is key to the formation of PE metabolites, such as equol, *O*-DMA and enterolignans, which will have different impact than their precursors on human health. The knowledge about the bacteria involved in PE metabolism is increasing. Nowadays, several strains have been identified as able to perform the complete metabolism of PE from the dietary precursor to more bioavailable and bioactive compounds (Table 2).

Bacterial metabolism of isoflavones

Isoflavones are usually found in nature in their glycosylated forms (daidzin, genistin, glycitin, puerarin) and to a less extend in their methylated forms (formononetin, biochanin A). The isoflavone glycosides are not absorbed and their bioavailability relies on their transformation into aglycones (daidzein, genistein and glycitein) and other metabolites. The deglycosilation starts in the small intestine due to luminal enzymes (Larkin, Price, and Astheimer 2008) and continues in the large intestine due to microbial metabolism. Subsequently, the aglycones can be absorbed or can undergo a series of transformations carried out by intestinal bacteria, which lead to several isoflavone metabolites (Figure 1). As a result of these transformations, the most frequent isoflavones in blood and urine, and more studied, are daidzein, genistein, *O*-DMA and equol (Atkinson, Frankenfeld, and Lampe 2005; Frankenfeld 2011; Poluzzi et al. 2014). The degree of transformation of the different isoflavones varies among individuals and could be linked to a different composition of the gut microbiota. As an example, while the production of *O*-DMA is quite extended, the more active equol is only produced by around a 30% of the western population (Rafii 2015).

Hence, there has been put an effort to investigate which bacterial species are involved in the transformation of isoflavones. The first step in the transformation of isoflavones seems to be quite widespread (Sánchez-Calvo et al. 2013) and the production of aglycones has been depicted in

Table 2. Bacterial strains capable to performing the complete biotransformation phytoestrogens.

Strain	Phytoestrogen precursor	Product of metabolism	Reference
	Isoflavones		
Clostridium sp. HGH136	Daidzein	*O*-DMA	Hur et al. (2002)
Clostridium sp. SY8519	Daidzein	*O*-DMA	Yokoyama et al. (2010)
Clostridium sp. Aeroto-AUH-JLC108	Daidzein	*O*-DMA	Li et al. (2015)
Eubacterium ramulus	Daidzein	*O*-DMA	Schoefer et al. (2002)
Enterococcus faecium INIA P553	Daidzein; genistein	*O*-DMA; 6-hydroxy-*O*-DMA	Gaya et al. (2018a)
Adlercreutzia equolifaciens FJC-B9T	Daidzein	Equol	Maruo et al. (2008)
Bifidobacterium breve ATCC 15700	Daidzein	Equol	Elghali et al. (2012)
Bifidobacterium longum BB536	Daidzein	Equol	Elghali et al. (2012)
Eggerthella sp. YY7918	Daidzein	Equol	Yokoyama and Suzuki (2008)
Lactococcus garviae 20–92	Daidzein	Equol	Uchiyama, Ueno, and Suzuki (2007)
Slackia equolifaciens DZE^T	Daidzein	Equol	Jin et al. (2010)
Slackia isoflavoniconvertens HE8	Daidzein; genistein	Equol; 5 hydroxy-equol	Matthies, Blaut, and Braune (2009)
Pediococcus pentosaceus CS1	*Pueraria* extract	Equol	Kwon et al. (2018)
Lactobacillus sp. CS2	*Pueraria* extract	Equol	Kwon et al. (2018)
Lactobacillus sp. CS3	*Pueraria* extract	Equol	Kwon et al. (2018)
	Lignans		
Bifidobacterium adolescentis INIA P784	Flax seed extracts	Enterodiol	Gaya et al. (2017)
Lactobacillus salivarius INIA P448	SECO and flax seed extracts	Enterolactone and enterodiol	Bravo et al. (2017); Peirotén et al. (2019)
Lb. salivarius INIA P183	SECO and flax seed extracts	Enterolactone and enterodiol	Bravo et al. (2017); Peirotén et al. (2019)
Lactobacillus gasseri INIA P508	SECO and flax seed extracts	Enterolactone and enterodiol	Bravo et al. (2017); Peirotén et al. (2019)
Bifidobacterium pseudolongum INIA P2	SECO	Enterolactone and enterodiol	Peirotén et al. (2019)
Bifidobacterium bifidum INIA P466	SECO	Enterolactone and enterodiol	Peirotén et al. (2019)
Bifidobacterium catenulatum INIA P732	SECO	Enterolactone and enterodiol	Peirotén et al. (2019)
	Ellagitannins		
Eggerthellaceae family CEBAS 4A4	Ellagic acid	Isourolithin A	Selma et al. (2017)
Bifidobacterium pseudocatenulatum INIA P815	Ellagic acid	Urolithins A and B	Gaya et al. (2018b)

Abbreviations: *O*-DMA, *O*-desmethylangolensin; SECO, secoisolariciresinol.

different bacterial species (Braune and Blaut 2016). Moreover, the metabolization of biochanin A and genistin into the intermediate dihydrogenistein, and of formononetin, daidzin and puerarin into dihydrodaidzein, has been observed by our group in different *Lactococcus*, *Lactobacillus*, *Enterococcus* and *Bifidobacterium* strains (Gaya, Peirotén, and Landete 2017). On the contrary, the complete metabolism carried out by single strains with the result of *O*-DMA or equol is less common. Thus, the production of *O*-DMA has been described in an *Enterococcus faecium* strain and in other strains placed in the Clostridiales order (Table 2). So far, equol production from daidzein by single bacteria has been depicted in strains belonging to the family Coriobacteriaceae, more specifically of the genus *Slackia* spp., *Eggerthella* spp. and *Adlercreutzia* spp., and in several lactic acid bacteria and bifidobacteria strains (Table 2).

Bacterial metabolism of lignans

Plant lignans are not easily absorbed at the intestine and must be metabolized into enterolignans by the intestinal microbiota before entering the organism and exert their effects (Clavel, Dore, and Blaut 2006). Deglycosylation of secoisolariciresinol-diglucoside (SDG) and other lignan glucosides present in plants is the first step towards the formation of enterolignans (Figure 1). Microbiota hydrolyze the sugar moiety to release secoisolariciresinol (SECO) and other lignans, which undergo successive demethylation and dihydroxylation microbial reactions to produce enterodiol or enterolactone. Enterodiol can be additionally transformed into enterolactone by means of a dehydrogenation reaction (Landete 2012). Enterolignan production presents a wide variation among individuals, which seems to be related to microbiota composition (Hullar et al. 2015).

Until recently, the production of enterolignans had been described as the result of the activity of a consortium of different bacterial species. Thus, strains belonging to the species *Clostridium saccharogumia*, *Eggerthella lenta*, *Blautia producta*, *Lactonifactor longoviformis* and *Ruminococcus* sp. have been described as capable of performing specific reactions of the metabolic route leading to enterodiol and enterolactone (Clavel et al. 2007; Jin, Kakiuchi, and Hattori 2007; Woting et al. 2010). Lately, there have been described *Lactobacillus* and *Bifidobacterium* strains that can perform the complete transformation of lignan extracts into enterodiol and/or enterolactone (Table 2).

Bacterial metabolism of ellagitannins and ellagic acid

Ellagitannins and their hydrolysis product, ellagic acid, are present in a variety of plant foods. After ingestion, ellagic acid is poorly absorbed into the blood stream, instead, intestinal bacteria gradually metabolize it by means of lactone-ring cleavage, decarboxylation and dehydroxylation reactions, which lead to the formation of a series of compounds named urolithins (González-Barrio et al. 2011) (Figure 1). Urolithins are not produced equally in all individuals, with important differences in the concentrations and kind of urolithins produced (Tomás-Barberán et al. 2017). Hence, isourolithin A and urolithins A and B, which have been described to have higher bioactivity, do not appear in the same level in all individuals.

Microbial metabolism of urolithins has been less explored than that of other PE. The production of intermediate urolithins has been described in strains of the species *Gordonibacter pamelaeae* and *Gordonibacter urolithinfaciens*

(Selma et al. 2014). More recently, there has been depicted the production of isourolithin A by a strain of the family Eggerthellaceae and of urolithins A and B by a *Bifidobacterium pseudocatenulatum* strain (Table 2).

How to enhance the beneficial effect of PE on human health?

As we have seen, there are several factors that could influence the effects of PE on health. The bioavailability and effect of PE may be determined by the microbiome and genetics of each individual, thus a personalized approach in the use of PE supplements could be recommended. Moreover, the role of bacterial metabolism in the bioactivation of PE could be applied to overcome those inter-individual differences on PE metabolism.

The bacterial strains able to metabolize PE could be used as probiotics together with the intake of food products rich in PE. These kind of probiotics could ensure the protective effect of PE by means of facilitating sufficient levels of bioactive PE through different mechanisms. On one hand, a strain able to complete the PE metabolism, such those listed in Table 2, could produce those metabolites in the gut. On the other hand, strains able to produce precursors of equol, urolithins and enterolignans would facilitate the metabolism of other strains present in the intestinal microbiota. In this regard, Tamura, Hori, and Nakagawa (2011) described how *Lactobacillus rhamnosus* JCM 2771, a strain able to deglycosidate daidzin to daidzein, caused an increment in the equol concentrations produced by fecal microbiota from an equol-producer individual.

Another approach to enhance the benefits of PE could consist in the utilization of bacterial strains able to metabolize PE (Table 2) to obtain enriched foods with higher levels of bioactive PE. These strategies entailing bacteria able to metabolize PE represent an opportunity to ensure the input of bioactive PE. Nevertheless, it must be taken into account that both applications require the selection of bacteria with suitable technological properties, such as their ability to grow at industrial scale and to survive the food processes. Moreover, it is important to test the safety of the bacterial strains. In this regard, several species of *Lactobacillus* and *Bifidobacterium* species are included in the Qualified Presumption of Safety (QPS) list of EFSA (Ricci et al. 2018), which makes them interesting targets for the development of new products. The development of functional products enriched in PE also requires the evaluation of their sensory attributes. So, the added bacterial strains should not have detrimental effects in the final product.

Conclusions

The beneficial effects of PE on health depend greatly on their metabolization by the intestinal microbiota. The result of this bacterial metabolism are compounds such as genistein, equol, enterolignans and certain urolithins, which possess increased biological activities. These activities have been corroborated *in vitro* and also by several human studies, in which PE have shown beneficial effects on ameliorating the menopausal symptoms or on reducing the risk of certain cancers, cardiovascular disease or diabetes. Nevertheless, not all studies have reached the same conclusions and many of them have found null results on the influence of PE on health. Several factors may be interfering with the proper measurement of the actual effects of PE, such as the heterogeneity of the published studies and the genomic polymorphism of ER. Of great importance is also to ensure a representative measurement of the actual PE levels in the organism, which should encompass the role of the intestinal microbiota in their bioactivation and the variation in circulating PE due to different pharmacokinetics. Thus, there is a need for more interventional studies that take those aspects into account in order to establish the effective doses of PE. Given the increasing knowledge about the bacterial strains involved in PE bioactivation, it would be also of interest the use of these bacteria as probiotics or to produce functional foods in order to ensure sufficient levels of bioactive PE in the organism.

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References

Aarestrup, J., C. Kyrø, K. E. B. Knudsen, E. Weiderpass, J. Christensen, M. Kristensen, A. M. L. Würtz, N. F. Johnsen, K. Overvad, A. Tjønneland, and A. Olsen. 2013. Plasma enterolactone and incidence of endometrial cancer in a case–cohort study of Danish women. *British Journal of Nutrition* 109 (12):2269–75. doi: 10.1017/S0007114512004424.

Abdi, F., Z. Alimoradi, P. Haqi, and F. Mahdizad. 2016. Effects of phytoestrogens on bone mineral density during the menopause transition: A systematic review of randomized, controlled trials. *Climacteric* 19 (6):535–45. doi: 10.1080/13697137.2016.1238451.

Adlercreutz, H., E. Hämäläinen, S. Gorbach, and B. Goldin. 1992. Dietary phyto-oestrogens and the menopause in Japan. *Lancet (London, England)* 339 (8803):1233.

Ahuja, V., K. Miura, A. Vishnu, A. Fujiyoshi, R. Evans, M. Zaid, N. Miyagawa, T. Hisamatsu, A. Kadota, T. Okamura, et al. 2017. Significant inverse association of equol-producer status with coronary artery calcification but not dietary isoflavones in healthy Japanese men. *British Journal of Nutrition* 117 (2):260–6. doi: 10.1017/S000711451600458X.

Aso, T., S. Uchiyama, Y. Matsumura, M. Taguchi, M. Nozaki, K. Takamatsu, B. Ishizuka, T. Kubota, H. Mizunuma, and H. Ohta. 2012. A natural S-equol supplement alleviates hot flushes and other menopausal symptoms in equol nonproducing postmenopausal Japanese women. *Journal of Women's Health (Larchmt)* 21 (1):92–100. doi: 10.1089/jwh.2011.2753.

Atkinson, C., C. L. Frankenfeld, and J. W. Lampe. 2005. Gut bacterial metabolism of the soy isoflavone daidzein: Exploring the relevance to human health. *Experimental Biology and Medicine* 230 (3):155–70. doi: 10.1177/153537020523000302.

Atteritano, M., F. Pernice, S. Mazzaferro, S. Mantuano, A. Frisina, R. D'Anna, M. L. Cannata, A. Bitto, F. Squadrito, N. Frisina, and M. Buemi. 2008. Effects of phytoestrogen genistein on cytogenetic biomarkers in postmenopausal women: 1 year randomized, placebo-

controlled study. *European Journal of Pharmacology* 589 (1–3):22–6. doi: 10.1016/j.ejphar.2008.04.049.

Bhathena, S. J., and M. T. Velasquez. 2002. Beneficial role of dietary phytoestrogens in obesity and diabetes. The American Journal of Clinical Nutrition 76 (6):1191–201. doi: 10.1093/ajcn/76.6.1191.

Bolaños, R., A. Del Castillo, and J. Francia. 2010. Soy isoflavones versus placebo in the treatment of climacteric vasomotor symptoms: Systematic review and meta-analysis. *Menopause* 17 (1):660–666. doi: 10.1097/gme.0b013e3181cb4fb5.

Braune, A., and M. Blaut. 2016. Bacterial species involved in the conversion of dietary flavonoids in the human gut. *Gut Microbes* 7 (3): 216–34. doi: 10.1080/19490976.2016.1158395.

Bravo, D., Á. Peirotén, I. Alvarez, and J. M. Landete. 2017. Phytoestrogen metabolism by lactic acid bacteria: Enterolignan production by *Lactobacillus salivarius* and *Lactobacillus gasseri* strains. *Journal of Functional Foods* 37:373–8. doi: 10.1016/j.jff.2017.08.015.

Bredsdorff, L., T. Obel, C. Dethlefsen, A. Tjonneland, E. B. Schmidt, S. E. Rasmussen, and K. Overvad. 2013. Urinary flavonoid excretion and risk of acute coronary syndrome in a nested case-control study. The American Journal of Clinical Nutrition 98 (1):209–16. doi: 10.3945/ajcn.112.046169.

Brink, E., V. Coxam, S. Robins, K. Wahala, A. Cassidy, and F. Branca. 2008. Long-term consumption of isoflavone-enriched foods does not affect bone mineral density, bone metabolism, or hormonal status in early postmenopausal women: A randomized, double-blind, placebo controlled study. *The American Journal of Clinical Nutrition* 87 (3): 761–70. doi: 10.1093/ajcn/87.3.761.

Buck, K., A. K. Zaineddin, A. Vrieling, J. Linseisen, and J. Chang-Claude. 2010. Meta-analyses of lignans and enterolignans in relation to breast cancer risk. The American Journal of Clinical Nutrition 92 (1):141–53. doi: 10.3945/ajcn.2009.28573.

Cai, Y., K. Guo, C. Chen, P. Wang, B. Zhang, Q. Zhou, F. Mei, and Y. Su. 2012. Soya isoflavone consumption in relation to carotid intima-media thickness in Chinese equol excretors aged 40–65 years. *British Journal of Nutrition* 108 (9):1698–704. doi: 10.1017/S0007114511007331.

Cano, A., M. A. García-Pérez, and J. J. Tarín. 2010. Isoflavones and cardiovascular disease. *Maturitas* 67 (3):219–26. doi: 10.1016/j.maturitas.2010.07.015.

Carreau, C., G. Flouriot, C. Bennetau-Pelissero, and M. Potier. 2008. Enterodiol and enterolactone, two major diet-derived polyphenol metabolites have different impact on ERalpha transcriptional activation in human breast cancer cells. *Journal of Steroid Biochemistry and Molecular Biology* 110 (1–2):176–85. doi: 10.1016/j.jsbmb.2008.03.032.

Cassidy, A. 2005. Dietary phyto-oestrogens: Molecular mechanisms, bioavailability and importance to menopausal health. *Nutrition Research Reviews* 18 (2):183–201. doi: 10.1079/NRR2005102.

Clavel, T., J. Dore, and M. Blaut. 2006. Bioavailability of lignans in human subjects. *Nutrition Research Reviews* 19 (2):187–96. doi: 10.1017/S0954422407249704.

Clavel, T., R. Lippman, F. Gavini, J. Doré, and M. Blaut. 2007. *Clostridium saccharogumia* sp. nov. and *Lactonifactor longoviformis* gen. nov., sp. nov., two novel human faecal bacteria involved in the conversion of the dietary phytoestrogen secoisolariciresinol diglucoside. *Systematic and Applied Microbiology* 30 (1):16–26. doi: 10.1016/j.syapm.2006.02.003.

Crawford, S. L., E. A. Jackson, L. Churchill, J. W. Lampe, K. Leung, and J. K. Ockene. 2013. Impact of dose, frequency of administration, and equol production on efficacy of isoflavones for menopausal hot flashes: A pilot randomized trial. *Menopause* 20:936–45.

Chen, M. N., C. C. Lin, and C. F. Liu. 2015. Efficacy of phytoestrogens for menopausal symptoms: A meta-analysis and systematic review. *Climacteric*: The Journal of the International Menopause *Society* 18 (2):260–9. doi: 10.3109/13697137.2014.966241.

de Cremoux, P., P. This, G. Leclercq, and Y. Jacquot. 2010. Controversies concerning the use of phytoestrogens in menopause management: Bioavailability and metabolism. *Maturitas* 65 (4): 334–9. doi: 10.1016/j.maturitas.2009.12.019.

de Kleijn, M. J., Y. T. van der Schouw, P. W. Wilson, D. E. Grobbee, and P. F. Jacques. 2002. Dietary intake of phytoestrogens is associated with a favorable metabolic cardiovascular risk profile in postmenopausal U.S. women: The Framingham study. *The Journal of Nutrition* 132 (2):276–82. doi: 10.1093/jn/132.2.276.

DeLuca, J. A. A., E. L. García-Villatoro, and C. D. Allred. 2018. Flaxseed bioactive compounds and colorectal cancer prevention. *Current Oncology Reports* 20 (8):59.

den Tonkelaar, I., L. Keinan-Boker, P. V. Veer, C. J. Arts, H. Adlercreutz, J. H. Thijssen, and P. H. Peeters. 2001. Urinary phytoestrogens and postmenopausal breast cancer risk. *Cancer Epidemiology, Biomarkers and Prevention* 10:223–8.

deVere White, R. W., A. Tsodikov, E. C. Stapp, S. E. Soares, H. Fujii, and R. M. Hackman. 2010. Effects of a high dose, aglycone-rich soy extract on prostate-specific antigen and serum isoflavone concentrations in men with localized prostate cancer. *Nutrition and Cancer* 62 (8):1036–43. doi: 10.1080/01635581.2010.492085.

Ding, M., A. A. Franke, B. A. Rosner, E. Giovannucci, R. M. van Dam, S. S. Tworoger, F. B. Hu, and Q. Sun. 2015. Urinary isoflavonoids and risk of type 2 diabetes: A prospective investigation in US women. *British Journal of Nutrition* 114 (10):1694–701. doi: 10.1017/S0007114515003359.

Dixon, R. A. 2004. Phytoestrogens. *Annual Review of Plant Biology* 55: 225–61. doi: 10.1146/annurev.arplant.55.031903.141729.

Elghali, S., S. Mustafa, M. Amid, M. Y. A. B. D. Manap, A. Ismail, and F. Abas. 2012. Bioconversion of daidzein to equol by *Bifidobacterium breve* 15700 and *Bifidobacterium longum* BB536. *Journal of Functional Foods* 4 (4):736–45. doi: 10.1016/j.jff.2012.04.013.

Espín, J. C., M. Larrosa, M. T. García-Conesa, and F. A. Tomás-Barberán. 2013. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: The evidence so far. *Evidence-Based Complementary and Alternative Medicine* 10:270418. doi: 10.1155/2013/270418.

Fang, K., H. Dong, D. Wang, J. Gong, W. Huang, and F. Lu. 2016. Soy isoflavones and glucose metabolism in menopausal women: A systematic review and meta-analysis of randomized controlled trials. *Molecular Nutrition & Food Research* 60:1602–14. doi: 10.1002/mnfr.201501024.

Farooq, A. 2015. Structural and functional diversity of estrogen receptor ligands. *Current Topics in Medicinal Chemistry* 15 (14):1372–84.

Frankenfeld, C. L. 2011. O-Desmethylangolensin: The importance of equol's lesser known cousin to human health. *Advances in Nutrition* (Bethesda, Md.) 2 (4):317–24. doi: 10.3945/an.111.000539.

Frankenfeld, C. L. 2014. Cardiometabolic risk factors are associated with high urinary enterolactone concentration, independent of urinary enterodiol concentration and dietary fiber intake in adults. *The Journal of Nutrition* 144 (9):1445–53. doi: 10.3945/jn.114.190512.

Frankenfeld, C. L. 2017. Cardiometabolic risk and gut microbial phytoestrogen metabolite phenotypes. *Molecular Nutrition & Food Research* 61 (1). doi: 10.1002/mnfr.201500900.

Frankenfeld, C. L., A. McTiernan, W. K. Thomas, K. LaCroix, L. McVarish, V. L. Holt, S. M. Schwartz, and J. W. Lampe. 2006. Postmenopausal bone mineral density in relation to soy isoflavone-metabolizing phenotypes. *Maturitas* 53 (3):315–24. doi: 10.1016/j.maturitas.2005.05.016.

García-Muñoz, C., and F. Vaillant. 2014. Metabolic fate of ellagitannins: Implications for health, and research perspectives for innovative functional foods. *Critical Reviews in Food Science and Nutrition* 54:1584–98. doi: 10.1080/10408398.2011.644643.

Gaya, P., Á. Peirotén, I. Álvarez, M. Medina, and J. M. Landete. 2018a. Production of the bioactive isoflavone O-desmethylangolensin by *Enterococcus faecium* INIA P553 with high efficiency. *Journal of Functional Foods* 40:180–6. doi: 10.1016/j.jff.2017.11.008.

Gaya, P., Á. Peirotén, and J. M. Landete. 2017. Transformation of plant isoflavones into bioactive isoflavones by lactic acid bacteria and bifidobacteria. *Journal of Functional Foods* 39:198–205. doi: 10.1016/j.jff.2017.10.029.

Gaya, P., Á. Peirotén, M. Medina, I. Álvarez, and J. M. Landete. 2018b. *Bifidobacterium pseudocatenulatum* INIA P815: The first bacterium

able to produce urolithins A and B from ellagic acid. *Journal of Functional Foods* 45:95–9. doi: 10.1016/j.jff.2018.03.040.

Gaya, P., Á. Peirotén, M. Medina, and J. M. Landete. 2017. *Bifidobacterium adolescentis* INIA P784: The first probiotic bacterium capable of producing enterodiol from lignan extracts. *Journal of Functional Foods* 29:269–74. doi: 10.1016/j.jff.2016.12.044.

Glisic, M., N. Kastrati, V. González-Jaramillo, W. M. Bramer, F. Ahmadizar, R. Chowdhury, A. H. J. Danser, A. J. M. Roks, T. Voortman, O. H. Franco, and T. Muka. 2018. Associations between phytoestrogens, glucose homeostasis, and risk of diabetes in women: A systematic review and meta-analysis. *Advances in Nutrition* 9 (6): 726–40. doi: 10.1093/advances/nmy048.

González-Barrio, R., P. Truchado, H. Ito, J. C. Espín, and F. A. Tomás-Barberán, 2011. UV and MS identification of urolithins and nasutins, the bioavailable metabolites of ellagitannins and ellagic acid in different mammals. *Journal of Agricultural and Food Chemistry* 59 (4):1152–62. doi: 10.1021/jf103894m.

González-Sarrías, A., M. Angeles Núñez-Sánchez, R. García-Villalba, F. A. Tomás-Barberán, and J. C. Espín. 2017. Antiproliferative activity of the ellagic acid-derived gut microbiota isourolithin a and comparison with its urolithin a isomer: The role of cell metabolism. *European Journal of Nutrition* 56 (2):831–41. doi: 10.1007/s00394-015-1131-7.

González Cañete, N., and S. Durán Agüero. 2014. [Soya isoflavones and evidences on cardiovascular protection]. *Nutricion Hospitalaria* 29:1271–82.

Goodman, M. T., Y. B. Shvetsov, L. R. Wilkens, A. A. Franke, L. Le Marchand, K. K. Kakazu, A. M. Nomura, B. E. Henderson, and L. N. Kolonel. 2009. Urinary phytoestrogen excretion and postmenopausal breast cancer risk: The multiethnic cohort study. *Cancer Prevention Research (Philadelphia, Pa.)* 2 (10):887–94. doi: 10.1158/1940-6207.CAPR-09-0039.

Greendale, G. A., C. H. Tseng, W. Han, M. H. Huang, K. Leung, S. Crawford, E. B. Gold, L. E. Waetjen, and A. S. Karlamangla. 2015. Dietary isoflavones and bone mineral density during midlife and the menopausal transition: Cross-sectional and longitudinal results from the Study of Women's Health across the Nation Phytoestrogen Study. *Menopause* 22 (3):279–88. doi: 10.1097/GME.0000000000000305.

Grosso, G., J. Godos, R. Lamuela-Raventos, S. Ray, A. Micek, A. Pajak, S. Sciacca, N. D'Orazio, D. Del Rio, and F. Galvano. 2017. A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: Level of evidence and limitations. *Molecular Nutrition & Food Research* 61 (4). doi: 10.1002/mnfr.201600930.

Ha, B. G., M. Nagaoka, T. Yonezawa, R. Tanabe, J. T. Woo, H. Kato, U. I. Chung, and K. Yagasaki. 2012. Regulatory mechanism for the stimulatory action of genistein on glucose uptake in vitro and in vivo. *The Journal of Nutritional Biochemistry* 23 (5):501–9. doi: 10.1016/j.jnutbio.2011.02.007.

Hall, W. L., K. Vafeiadou, J. Hallund, S. Bugel, C. Koebnick, M. Reimann, M. Ferrari, F. Branca, D. Talbot, T. Dadd, et al. 2005. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: Interactions with genotype and equol production. The American Journal of Clinical Nutrition 82 (6):1260–8; quiz 1365–66. doi: 10.1093/ajcn/82.6.1260.

Hall, W. L., K. Vafeiadou, J. Hallund, S. Bugel, M. Reimann, C. Koebnick, H. J. Zunft, M. Ferrari, F. Branca, T. Dadd, et al. 2006. Soy-isoflavone-enriched foods and markers of lipid and glucose metabolism in postmenopausal women: Interactions with genotype and equol production. The American Journal of Clinical Nutrition 83 (3):592–600. doi: 10.1093/ajcn.83.3.592.

Hara, A., S. Sasazuki, M. Inoue, T. Miura, M. Iwasaki, N. Sawada, T. Shimazu, T. Yamaji, and S. Tsugane. 2013. Plasma isoflavone concentrations are not associated with gastric cancer risk among Japanese men and women. The Journal of Nutrition 143:1293–8. doi: 10.3945/jn.113.175505.

He, J., S. Wang, M. Zhou, W. Yu, Y. Zhang, and X. He. 2015. Phytoestrogens and risk of prostate cancer: A meta-analysis of observational studies. *World Journal of Surgical Oncology* 13:231.

Heald, C. L., M. R. Ritchie, C. Bolton-Smith, M. S. Morton, and F. E. Alexander. 2007. Phyto-oestrogens and risk of prostate cancer in Scottish men. *British Journal of Nutrition* 98 (2):388–96. doi: 10.1017/S0007114507700703.

Hedelin, M., A. Klint, E. T. Chang, R. Bellocco, J. E. Johansson, S. O. Andersson, S. M. Heinonen, H. Adlercreutz, H. O. Adami, H. Gronberg, and K. A. Balter. 2006. Dietary phytoestrogen, serum enterolactone and risk of prostate cancer: The cancer prostate Sweden study (Sweden). Cancer Causes & Control 17:169–80. doi: 10.1007/s10552-005-0342-2.

Hullar, M. A. J., S. M. Lancaster, F. Li, E. Tseng, K. Beer, C. Atkinson, K. Wähälä, W. K. Copeland, T. W. Randolph, K. M. Newton, and J. W. Lampe. 2015. Enterolignan producing phenotypes are associated with increased gut microbial diversity and altered composition in premenopausal women in the United States. *Cancer Epidemiology, Biomarkers & Prevention: a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 24:546–54. doi: 10.1158/1055-9965.EPI-14-0262.

Hur, H. G., R. D. Beger, T. M. Heinze, J. O. Lay, Jr., J. P. Freeman, J. Dore, and F. Rafii. 2002. Isolation of an anaerobic intestinal bacterium capable of cleaving the C-ring of the isoflavonoid daidzein. *Archives in Microbiology* 178 (1):8–12. doi: 10.1007/s00203-002-0414-6.

Ishiwata, N., M. K. Melby, S. Mizuno, and S. Watanabe. 2009. New equol supplement for relieving menopausal symptoms: Randomized, placebo-controlled trial of Japanese women. *Menopause* 16 (1): 141–8. doi: 10.1097/gme.0b013e31818379fa.

Iwasaki, M., M. Inoue, T. Otani, S. Sasazuki, N. Kurahashi, T. Miura, S. Yamamoto, and S. Tsugane. 2008. Plasma isoflavone level and subsequent risk of breast cancer among Japanese women: A nested case-control study from the Japan Public Health Center-based prospective study group. *Journal of Clinical Oncology* 26 (10):1677–83. doi: 10.1200/JCO.2007.13.9964.

Jackson, M. D., N. D. McFarlane-Anderson, G. A. Simon, F. I. Bennett, and S. P. Walker. 2010. Urinary phytoestrogens and risk of prostate cancer in Jamaican men. *Cancer Causes & Control* 21 (12):2249–57. doi: 10.1007/s10552-010-9648-9.

Jin, J.-S., N. Kakiuchi, and M. Hattori. 2007. Enantioselective oxidation of enterodiol to enterolactone by human intestinal bacteria. *Biological & Pharmaceutical Bulletin* 30 (11):2204–6. doi: 10.1248/bpb.30.2204.

Jin, J.-S., M. Kitahara, M. Sakamoto, M. Hattori, and Y. Benno. 2010. *Slackia equolifaciens* sp. nov., a human intestinal bacterium capable of producing equol. *International Journal of Systematic and Evolutionary Microbiology* 60 (8):1721–4. doi: 10.1099/ijs.0.016774-0.

Johnsen, N. F., A. Olsen, B. L. Thomsen, J. Christensen, R. Egeberg, K. E. Bach Knudsen, S. Loft, K. Overvad, and A. Tjonneland. 2010. Plasma enterolactone and risk of Colon and rectal cancer in a case-cohort study of Danish men and women. *Cancer Causes & Control* 21 (1):153–62. doi: 10.1007/s10552-009-9445-5.

Jou, H.-J., S.-C. Wu, F.-W. Chang, P.-Y. Ling, K. S. Chu, and W.-H. Wu. 2008. Effect of intestinal production of equol on menopausal symptoms in women treated with soy isoflavones. *International Journal of Gynecology & Obstetrics* 102:44–9. doi: 10.1016/j.ijgo.2008.01.028.

Kasimsetty, S. G., D. Bialonska, M. K. Reddy, G. Ma, S. I. Khan, and D. Ferreira. 2010. Colon cancer chemopreventive activities of pomegranate ellagitannins and urolithins. *Journal of Agricultural and Food Chemistry* 58 (4):2180–7. doi: 10.1021/jf903762h.

Kenny, A. M., K. M. Mangano, R. H. Abourizk, R. S. Bruno, D. E. Anamani, A. Kleppinger, S. J. Walsh, K. M. Prestwood, and J. E. Kerstetter. 2009. Soy proteins and isoflavones affect bone mineral density in older women: A randomized controlled trial. *The American Journal of Clinical Nutrition* 90 (1):234–42. doi: 10.3945/ajcn.2009.27600.

Kilkkinen, A., J. Virtamo, E. Vartiainen, R. Sankila, M. J. Virtanen, H. Adlercreutz, and P. Pietinen. 2004. Serum enterolactone concentration is not associated with breast cancer risk in a nested case-control

study. *International Journal of Cancer* 108 (2):277–80. doi: 10.1002/ijc.11519.

Kilkkinen, A., J. Virtamo, M. J. Virtanen, H. Adlercreutz, D. Albanes, and P. Pietinen. 2003. Serum enterolactone concentration is not associated with prostate cancer risk in a nested case-control study. *Cancer Epidemiology, Biomarkers and Prevention* 12:1209–12.

Kitts, D. D., Y. V. Yuan, A. N. Wijewickreme, and L. U. Thompson. 1999. Antioxidant activity of the flaxseed lignan secoisolariciresinol diglycoside and its mammalian lignan metabolites enterodiol and enterolactone. *Molecular and Cellular Biochemistry* 202 (1/2):91–100.

Kiyama, R. 2016. Biological effects induced by estrogenic activity of lignans. *Trends in Food Science & Technology* 54:186–96. doi: 10.1016/j.tifs.2016.06.007.

Kladna, A., P. Berczynski, I. Kruk, T. Piechowska, and H. Y. Aboul-Enein. 2016. Studies on the antioxidant properties of some phytoestrogens. *Luminescence* 31:1201–6. doi: 10.1002/bio.3091.

Ko, K. P. 2014. Isoflavones: Chemistry, analysis, functions and effects on health and cancer. *Asian Pacific Journal of Cancer Prevention* 15 (17):7001–10. doi: 10.7314/APJCP.2014.15.17.7001.

Ko, K. P., C. S. Kim, Y. Ahn, S. J. Park, Y. J. Kim, J. K. Park, Y. K. Lim, K. Y. Yoo, and S. S. Kim. 2015. Plasma isoflavone concentration is associated with decreased risk of type 2 diabetes in Korean women but not men: Results from the Korean Genome and Epidemiology Study. *Diabetologia* 58 (4):726–35. doi: 10.1007/s00125-014-3463-x.

Ko, K. P., S. K. Park, B. Park, J. J. Yang, L. Y. Cho, C. Kang, C. S. Kim, J. Gwack, A. Shin, Y. Kim, et al. 2010. Isoflavones from phytoestrogens and gastric cancer risk: A nested case-control study within the Korean Multicenter Cancer Cohort. Cancer *Epidemiology, Biomarkers and Prevention* 19 (5):1292–300. doi: 10.1158/1055-9965.EPI-09-1004.

Ko, K. P., Y. Yeo, J. H. Yoon, C. S. Kim, S. Tokudome, L. T. Ngoan, C. Koriyama, Y. K. Lim, S. H. Chang, H. R. Shin, et al. 2018. Plasma phytoestrogens concentration and risk of colorectal cancer in two different Asian populations. *Clinical Nutrition* 37 (5):1675–82. doi: 10.1016/j.clnu.2017.07.014.

Kreydin, E. I., M. M. Kim, G. W. Barrisford, D. Rodríguez, A. Sánchez, Y. Santiago-Lastra, and D. S. C. Ko. 2015. Urinary lignans are associated with decreased incontinence in postmenopausal women. *Urology* 86 (4):716–20. doi: 10.1016/j.urology.2015.07.024.

Kuijsten, A., I. C. Arts, P. C. Hollman, P. van't Veer, and E. Kampman. 2006. Plasma enterolignans are associated with lower colorectal adenoma risk. *Cancer Epidemiology, Biomarkers and Prevention* 15 (6):1132–6. doi: 10.1158/1055-9965.EPI-05-0991.

Kuijsten, A., P. C. Hollman, H. C. Boshuizen, M. N. Buijsman, P. van 't Veer, F. J. Kok, I. C. Arts, and H. B. Bueno-de-Mesquita. 2008. Plasma enterolignan concentrations and colorectal cancer risk in a nested case-control study. *American Journal of Epidemiology* 167 (6):734–42. doi: 10.1093/aje/kwm349.

Kurahashi, N., M. Iwasaki, M. Inoue, S. Sasazuki, and S. Tsugane. 2008. Plasma isoflavones and subsequent risk of prostate cancer in a nested case-control study: The Japan Public Health Center. *Journal of Clinical Oncology* 26 (36):5923–9. doi: 10.1200/JCO.2008.16.8807.

Kwon, J. E., J. Lim, I. Kim, D. Kim, and S. C. Kang. 2018. Isolation and identification of new bacterial stains producing equol from *Pueraria lobata* extract fermentation. *PLoS One* 13 (2):e0192490. doi: 10.1371/journal.pone.0192490.

Landete, J. M. 2011. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Research International* 44 (5):1150–60. doi: 10.1016/j.foodres.2011.04.027.

Landete, J. M. 2012. Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health. *Food Research International* 46 (1):410–24. doi: 10.1016/j.foodres.2011.12.023.

Landete, J. M., J. Arqués, M. Medina, P. Gaya, B. de Las Rivas, and R. Muñoz. 2016. Bioactivation of phytoestrogens: Intestinal bacteria and health. *Critical Reviews in Food Science and Nutrition* 56 (11):1826–43. doi: 10.1080/10408398.2013.789823.

Larkin, T., W. E. Price, and L. Astheimer. 2008. The key importance of soy isoflavone bioavailability to understanding health benefits. *Critical Reviews in Food Science and Nutrition* 48 (6):538–52. doi: 10.1080/10408390701542716.

Larrosa, M., A. González-Sarrías, M. T. García-Conesa, F. A. Tomás-Barberán, and J. C. Espín. 2006. Urolithins, ellagic acid-derived metabolites produced by human colonic microflora, exhibit estrogenic and antiestrogenic activities. *Journal of Agricultural and Food Chemistry* 54 (5):1611–20. doi: 10.1021/jf0527403.

Lecomte, S., F. Demay, F. Ferrière, and F. Pakdel. 2017. Phytochemicals targeting estrogen receptors: Beneficial rather than adverse effects? *International Journal of Molecular Sciences* 18:1381.

Lethaby, A., J. Marjoribanks, F. Kronenberg, H. Roberts, J. Eden, and J. Brown. 2013. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database of Systematic Reviews* (12):CD001395.

Li, M., H. Li, C. Zhang, X. L. Wang, B. H. Chen, Q. H. Hao, and S. Y. Wang. 2015. Enhanced biosynthesis of O-desmethylangolensin from daidzein by a novel oxygen-tolerant cock intestinal bacterium in the presence of atmospheric oxygen. *Journal of Applied Microbiology* 118 (3):619–28. doi: 10.1111/jam.12732.

Liu, Y., J. Li, T. Wang, Y. Wang, L. Zhao, and Y. Fang. 2017. The effect of genistein on glucose control and insulin sensitivity in postmenopausal women: A meta-analysis. *Maturitas* 97:44–52. doi: 10.1016/j.maturitas.2016.12.004.

Liu, Z-m, S. C. Ho, Y-m Chen, J. Liu, and J. Woo. 2014. Cardiovascular risks in relation to daidzein metabolizing phenotypes among Chinese postmenopausal women. *PLoS One* 9 (2):e87861. doi: 10.1371/journal.pone.0087861.

Maruo, T., M. Sakamoto, C. Ito, T. Toda, and Y. Benno. 2008. *Adlercreutzia equolifaciens* gen. nov., sp. nov., an equol-producing bacterium isolated from human faeces, and emended description of the genus *Eggerthella*. *International Journal of Systematic and Evolutionary Microbiology* 58 (5):1221–7. doi: 10.1099/ijs.0.65404-0.

Matthies, A., M. Blaut, and A. Braune. 2009. Isolation of a human intestinal bacterium capable of daidzein and genistein conversion. *Applied and Environmental Microbiology* 75 (6):1740–4. doi: 10.1128/AEM.01795-08.

Mohammadi-Sartang, M., Z. Sohrabi, R. Barati-Boldaji, H. Raeisi-Dehkordi, and Z. Mazloom. 2018. Flaxseed supplementation on glucose control and insulin sensitivity: A systematic review and meta-analysis of 25 randomized, placebo-controlled trials. *Nutrition Reviews* 76 (2):125–39. doi: 10.1093/nutrit/nux052.

Morelli, A., C. Clerici, D. Castellani, E. Nardi, G. Sabatino, M. Baldoni, O. Morelli, S. Asciutti, S. Orlandi, V. Giuliano, et al. 2007. Pasta naturally enriched with isoflavone aglycons from soy germ reduces serum lipids and improves markers of cardiovascular risk. *The Journal of Nutrition* 137:2270–8. doi: 10.1093/jn/137.10.2270.

Muthyala, R. S., Y. H. Ju, S. Sheng, L. D. Williams, D. R. Doerge, B. S. Katzenellenbogen, W. G. Helferich, and J. A. Katzenellenbogen. 2004. Equol, a natural estrogenic metabolite from soy isoflavones: Convenient preparation and resolution of R- and S-equols and their differing binding and biological activity through estrogen receptors alpha and beta. *Bioorganic and Medicinal Chemistry* 12 (6):1559–67. doi: 10.1016/j.bmc.2003.11.035.

Newton, K. M., S. D. Reed, S. Uchiyama, C. Qu, T. Ueno, S. Iwashita, G. Gunderson, S. Fuller, and J. W. Lampe. 2015. A cross-sectional study of equol producer status and self-reported vasomotor symptoms. *Menopause* 22 (5):489–95. doi: 10.1097/GME.0000000000000363.

Nie, Q., M. Xing, J. Hu, X. Hu, S. Nie, and M. Xie. 2017. Metabolism and health effects of phyto-estrogens AU – Nie, Qixing. *Critical Reviews in Food Science and Nutrition* 57 (11):2432–54.

Nikander, E., A. Tiitinen, K. Laitinen, M. Tikkanen, and O. Ylikorkala. 2004. Effects of isolated isoflavonoids on lipids, lipoproteins, insulin sensitivity, and ghrelin in postmenopausal women. *Journal of Clinical Endocrinology and Metabolism* 89 (7):3567–72. doi: 10.1210/jc.2003-032229.

Nooyens, A. C., I. E. Milder, B. M. van Gelder, H. B. Bueno-de-Mesquita, M. P. van Boxtel, and W. M. Verschuren. 2015. Diet and cognitive decline at middle age: The role of antioxidants. *British Journal of Nutrition* 113 (9):1410–7. doi: 10.1017/S0007114515000720.

Olsen, A., K. E. Knudsen, B. L. Thomsen, S. Loft, C. Stripp, K. Overvad, S. Moller, and A. Tjonneland. 2004. Plasma enterolactone and breast cancer incidence by estrogen receptor status. *Cancer Epidemiology, Biomarkers and Prevention* 13:2084–9.

Ozasa, K., M. Nakao, Y. Watanabe, K. Hayashi, T. Miki, K. Mikami, M. Mori, F. Sakauchi, M. Washio, Y. Ito, et al. 2004. Serum phytoestrogens and prostate cancer risk in a nested case-control study among japanese men. *Cancer Science* 95 (1):65–71. doi: 10.1111/j.1349-7006.2004.tb03172.x.

Park, S. Y., L. R. Wilkens, A. A. Franke, L. Le Marchand, K. K. Kakazu, M. T. Goodman, S. P. Murphy, B. E. Henderson, and L. N. Kolonel. 2009. Urinary phytoestrogen excretion and prostate cancer risk: A nested case–control study in the multiethnic cohort. *British Journal of Cancer* 101 (1):185–91. doi: 10.1038/sj.bjc.6605137.

Pawlowski, J. W., B. R. Martin, G. P. McCabe, L. McCabe, G. S. Jackson, M. Peacock, S. Barnes, and C. M. Weaver. 2015. Impact of equol-producing capacity and soy-isoflavone profiles of supplements on bone calcium retention in postmenopausal women: A randomized crossover trial. The American Journal of Clinical Nutrition 102 (3):695–703. doi: 10.3945/ajcn.114.093906.

Peirotén, Á., P. Gaya, I. Álvarez, D. Bravo, and J. M. Landete. 2019. Influence of different lignan compounds on enterolignan production by *Bifidobacterium* and *Lactobacillus* strains. *International Journal of Food Microbiology* 289:17–23. doi: 10.1016/j.ijfoodmicro.2018.08.028.

Pérez-Cornago, A., P. N. Appleby, H. Boeing, L. Gil, C. Kyro, F. Ricceri, N. Murphy, A. Trichopoulou, K. K. Tsilidis, K.-T. Khaw, et al. 2018. Circulating isoflavone and lignan concentrations and prostate cancer risk: A meta-analysis of individual participant data from seven prospective studies including 2828 cases and 5593 controls. *International Journal of Cancer* 143 (11):2677–86.

Peterson, J., J. Dwyer, H. Adlercreutz, A. Scalbert, P. Jacques, and M. L. McCullough. 2010. Dietary lignans: Physiology and potential for cardiovascular disease risk reduction. *Nutrition Reviews* 68 (10): 571–603. doi: 10.1111/j.1753-4887.2010.00319.x.

Pietinen, P., K. Stumpf, S. Mannisto, V. Kataja, M. Uusitupa, and H. Adlercreutz. 2001. Serum enterolactone and risk of breast cancer: A case-control study in Eastern Finland. *Cancer Epidemiology, Biomarkers and Prevention* 10:339–44.

Piller, R., J. Chang-Claude, and J. Linseisen. 2006. Plasma enterolactone and genistein and the risk of premenopausal breast cancer. *European Journal of Cancer Prevention* 15 (3):225–32. doi: 10.1097/01.cej.0000197449.56862.75.

Poluzzi, E., C. Piccinni, E. Raschi, A. Rampa, M. Recanatini, and F. Ponti. 2014. Phytoestrogens in postmenopause: The state of the art from a chemical, pharmacological and regulatory perspective. *Current Medicinal Chemistry* 21 (4):417–36. doi: 10.2174/09298673113206660297.

Prasad, K. 2000. Antioxidant activity of secoisolariciresinol diglucoside-derived metabolites, secoisolariciresinol, enterodiol, and enterolactone. *International Journal of Angiology* 9 (4):220–5. doi: 10.1007/BF01623898.

Qin, L.-Q., J.-Y. Xu, P.-Y. Wang, and K. Hoshi. 2006. Soyfood intake in the prevention of breast cancer risk in women: A meta-analysis of observational epidemiological studies. *Journal of Nutritional Science and Vitaminology* 52 (6):428–36. doi: 10.3177/jnsv.52.428.

Qin, Y., F. Shu, Y. Zeng, X. Meng, B. Wang, L. Diao, L. Wang, J. Wan, J. Zhu, J. Wang, and M. Mi. 2014. Daidzein supplementation decreases serum triglyceride and uric acid concentrations in hypercholesterolemic adults with the effect on triglycerides being greater in those with the GA compared with the GG genotype of ESR-beta RsaI. *The Journal of Nutrition* 144 (1):49–54. doi: 10.3945/jn.113.182725.

Rafii, F. 2015. The role of colonic bacteria in the metabolism of the natural isoflavone daidzin to equol. *Metabolites* 5 (1):56–73. doi: 10.3390/metabo5010056.

Reger, M. K., T. W. Zollinger, Z. Liu, J. Jones, and J. Zhang. 2017. Association between urinary phytoestrogens and C-reactive protein in the continuous National Health and Nutrition Examination Survey. *Journal of the American College of Nutrition* 36 (6):434–41. doi: 10.1080/07315724.2017.1318722.

Ricci, A., A. Allende, D. Bolton, M. Chemaly, R. Davies, P. S. Fernández Escámez, R. Girones, K. Koutsoumanis, R. Lindqvist, B. Nørrung, et al. 2018. Update of the list of QPS-recommended biological agents intentionally added to food or feed as notified to EFSA 8: Suitability of taxonomic units notified to EFSA until March 2018. *EFSA Journal* 16:e05315.

Rienks, J., J. Barbaresko, and U. Nothlings. 2017. Association of isoflavone biomarkers with risk of chronic disease and mortality: A systematic review and meta-analysis of observational studies. *Nutrition Reviews* 75 (8):616–41. doi: 10.1093/nutrit/nux021.

Rietjens, I. M. C. M., J. Louisse, and K. Beekmann. 2017. The potential health effects of dietary phytoestrogens. *British Journal of Pharmacology* 174 (11):1263–80. doi: 10.1111/bph.13622.

Saarinen, N. M., J. Tuominen, L. Pylkkanen, and R. Santti. 2010. Assessment of information to substantiate a health claim on the prevention of prostate cancer by lignans. *Nutrients* 2 (2):99–115. doi: 10.3390/nu2020099.

Salari Sharif, P., S. Nikfar, and M. Abdollahi. 2011. Prevention of bone resorption by intake of phytoestrogens in postmenopausal women: A meta-analysis. *Age* (Dordrecht, Netherlands) 33 (3):421–31. doi: 10.1007/s11357-010-9180-6.

Sánchez-Calvo, J. M., M. A. Rodríguez-Iglesias, J. M. G. Molinillo, and F. A. Macías. 2013. Soy isoflavones and their relationship with microflora: Beneficial effects on human health in equol producers. *Phytochemistry Reviews* 12 (4):979–1000. doi: 10.1007/s11101-013-9329-x.

Schoefer, L., R. Mohan, A. Braune, M. Birringer, and M. Blaut. 2002. Anaerobic C-ring cleavage of genistein and daidzein by *Eubacterium ramulus*. *FEMS Microbiology Letters* 208 (2):197–202. doi: 10.1111/j.1574-6968.2002.tb11081.x.

Selma, M. V., D. Beltrán, R. García-Villalba, J. C. Espín, and F. A. Tomás-Barberán. 2014. Description of urolithin production capacity from ellagic acid of two human intestinal *Gordonibacter* species. *Food & Function* 5:1779–84. doi: 10.1039/C4FO00092G.

Selma, M. V., D. Beltrán, M. C. Luna, M. Romo-Vaquero, R. García-Villalba, A. Mira, J. C. Espín, and F. A. Tomás-Barberán. 2017. Isolation of human intestinal bacteria capable of producing the bioactive metabolite isourolithin a from ellagic acid. *Frontiers in Microbiology* 8:1521.

Sonestedt, E., S. Borgquist, U. Ericson, B. Gullberg, H. Olsson, H. Adlercreutz, G. Landberg, and E. Wirfalt. 2008. Enterolactone is differently associated with estrogen receptor beta-negative and -positive breast cancer in a Swedish nested case-control study. *Cancer Epidemiology, Biomarkers and Prevention* 17 (11):3241–51. doi: 10.1158/1055-9965.EPI-08-0393.

Soni, M., L. R. White, A. Kridawati, S. Bandelow, and E. Hogervorst. 2016. Phytoestrogen consumption and risk for cognitive decline and dementia: With consideration of thyroid status and other possible mediators. *Journal of Steroid Biochemistry and Molecular Biology* 160:67–77. doi: 10.1016/j.jsbmb.2015.10.024.

Sotoca, A. M., D. Ratman, P. van der Saag, A. Ström, J. A. Gustafsson, J. Vervoort, I. M. Rietjens, and A. J. Murk. 2008. Phytoestrogen-mediated inhibition of proliferation of the human T47D breast cancer cells depends on the ERalpha/ERbeta ratio. *The Journal of Steroid Biochemistry and Molecular Biology* 112 (4–5):171–8. doi: 10.1016/j.jsbmb.2008.10.002.

Stattin, P., H. Adlercreutz, L. Tenkanen, E. Jellum, S. Lumme, G. Hallmans, S. Harvei, L. Teppo, K. Stumpf, T. Luostarinen, et al. 2002. Circulating enterolactone and prostate cancer risk: A Nordic nested case-control study. *International Journal of Cancer* 99 (1): 124–9. doi: 10.1002/ijc.10313.

Struja, T., A. Richard, J. Linseisen, M. Eichholzer, and S. Rohrmann. 2014. The association between urinary phytoestrogen excretion and components of the metabolic syndrome in NHANES. *European Journal of Nutrition* 53 (6):1371–81. doi: 10.1007/s00394-013-0639-y.

Sun, Q., N. M. Wedick, A. Pan, M. K. Townsend, A. Cassidy, A. A. Franke, E. B. Rimm, F. B. Hu, and R. M. van Dam. 2014. Gut microbiota metabolites of dietary lignans and risk of type 2 diabetes: A prospective investigation in two cohorts of U.S. women. *Diabetes Care* 37 (5):1287–95. doi: 10.2337/dc13-2513.

Tai, T. Y., K. S. Tsai, S. T. Tu, J. S. Wu, C. I. Chang, C. L. Chen, N. S. Shaw, H. Y. Peng, S. Y. Wang, and C. H. Wu. 2012. The effect of soy isoflavone on bone mineral density in postmenopausal taiwanese women with bone loss: A 2-year randomized double-blind placebo-controlled study. *Osteoporosis International* 23 (5):1571–80. doi: 10.1007/s00198-011-1750-7.

Taku, K., M. K. Melby, F. Kronenberg, M. S. Kurzer, and M. Messina. 2012. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: Systematic review and meta-analysis of randomized controlled trials. *Menopause* (New York, N.Y.) 19 (7):776–90. doi: 10.1097/gme.0b013e3182410159.

Talaei, M., B. L. Lee, C. N. Ong, R. M. van Dam, J. M. Yuan, W. P. Koh, and A. Pan. 2016. Urine phyto-oestrogen metabolites are not significantly associated with risk of type 2 diabetes: The Singapore Chinese health study. *British Journal of Nutrition* 115 (9):1607–15. doi: 10.1017/S0007114516000581.

Tamura, M., S. Hori, and H. Nakagawa. 2011. *Lactobacillus rhamnosus* JCM 2771: Impact on metabolism of isoflavonoids in the fecal flora from a male equol producer. *Current Microbiology* 62 (5):1632–7. doi: 10.1007/s00284-011-9904-6.

Thaung-Zaw, J. J., P. R. C. Howe, and R. H. X. Wong. 2017. Does phytoestrogen supplementation improve cognition in humans? A systematic review. *Annals of the New York Academy of Sciences* 1403:150–63. doi: 10.1111/nyas.13459.

Tikkanen, M. J., K. Wähälä, S. Ojala, V. Vihma, and H. Adlercreutz. 1998. Effect of soybean phytoestrogen intake on low density lipoprotein oxidation resistance. *Proceedings of the National Academy of Sciences of the United States of America* 95 (6):3106–10. doi: 10.1073/pnas.95.6.3106.

Tomás-Barberán, F. A., A. González-Sarrías, R. García-Villalba, M. A. Núñez-Sánchez, M. V. Selma, M. T. García-Conesa, and J. C. Espín. 2017. Urolithins, the rescue of "old" metabolites to understand a "new" concept: Metabotypes as a nexus among phenolic metabolism, microbiota dysbiosis, and host health status. *Molecular Nutrition & Food Research* 61 (1). doi: 10.1002/mnfr.201500901.

Tousen, Y., J. Ezaki, Y. Fujii, T. Ueno, M. Nishimuta, and Y. Ishimi. 2011. Natural S-equol decreases bone resorption in postmenopausal, non-equol-producing Japanese women: A pilot randomized, placebo-controlled trial. *Menopause* 18 (5):563–74. doi: 10.1097/gme.0b013e3181f85aa7.

Travis, R. C., E. A. Spencer, N. E. Allen, P. N. Appleby, A. W. Roddam, K. Overvad, N. F. Johnsen, A. Olsen, R. Kaaks, J. Linseisen, et al. 2009. Plasma phyto-oestrogens and prostate cancer in the European Prospective Investigation into Cancer and Nutrition. *British Journal of Cancer* 100 (11):1817–23. doi: 10.1038/sj.bjc.6605073.

Uchiyama, S., T. Ueno, K. Masaki, S. Shimizu, T. Aso, and T. Shirota. 2007. Thee cross-sectional study of the relationship between soy isoflavones, equol and the menopausal symptoms in Japanese women. *The Journal of the Japan Society for Menopause and Women's Health* 15:28–37.

Uchiyama, S., T. Ueno, and T. Suzuki. 2007. Identification of a newly isolated equol-producing lactic acid bacterium from the human feces. *Journal of Intestinal Microbiology* 21:217–20.

Vafeiadou, K., W. L. Hall, and C. M. Williams. 2006. Does genotype and equol-production status affect response to isoflavones? Data from a pan-European study on the effects of isoflavones on cardiovascular risk markers in post-menopausal women. *Proceedings of the Nutrition Society* 65 (1):106–15. doi: 10.1079/PNS2005483.

van der Schouw, Y. T., S. Kreijkamp-Kaspers, P. H. Peeters, L. Keinan-Boker, E. B. Rimm, and D. E. Grobbee. 2005. Prospective study on usual dietary phytoestrogen intake and cardiovascular disease risk in Western women. *Circulation* 111 (4):465–71. doi: 10.1161/01.CIR.0000153814.87631.B0.

van der Velpen, V., P. C. Hollman, M. van Nielen, E. G. Schouten, M. Mensink, P. Van't Veer, and A. Geelen. 2014. Large inter-individual variation in isoflavone plasma concentration limits use of isoflavone intake data for risk assessment. *European Journal of Clinical Nutrition* 68 (10):1141–7. doi: 10.1038/ejcn.2014.108.

Vanharanta, M., S. Voutilainen, T. H. Rissanen, H. Adlercreutz, and J. T. Salonen. 2003. Risk of cardiovascular disease–related and all-cause death according to serum concentrations of enterolactone: Kuopio ischaemic heart disease risk factor study. *Archives of Internal Medicine* 163 (9):1099–104. doi: 10.1001/archinte.163.9.1099.

Velentzis, L. S., M. M. Cantwell, C. Cardwell, M. R. Keshtgar, A. J. Leathem, and J. V. Woodside. 2009. Lignans and breast cancer risk in pre- and post-menopausal women: Meta-analyses of observational studies. *British Journal of Cancer* 100 (9):1492. doi: 10.1038/sj.bjc.6605003.

Verheus, M., C. H. van Gils, L. Keinan-Boker, P. B. Grace, S. A. Bingham, and P. H. Peeters. 2007. Plasma phytoestrogens and subsequent breast cancer risk. *Journal of Clinical Oncology* 25 (6):648–55. doi: 10.1200/JCO.2006.06.0244.

Virk-Baker, M. K., T. R. Nagy, and S. Barnes. 2010. Role of phytoestrogens in cancer therapy. *Planta Medica* 76 (11):1132–42. doi: 10.1055/s-0030-1250074.

Vitale, D. C., C. Piazza, B. Melilli, F. Drago, and S. Salomone. 2013. Isoflavones: Estrogenic activity, biological effect and bioavailability. *European Journal of Drug Metabolism and Pharmacokinetics* 38 (1):15–25. doi: 10.1007/s13318-012-0112-y.

Ward, H., G. Chapelais, G. G. Kuhnle, R. Luben, K. T. Khaw, and S. Bingham. 2008a. Breast cancer risk in relation to urinary and serum biomarkers of phytoestrogen exposure in the European Prospective into Cancer-Norfolk cohort study. *Breast Cancer Research* 10:R32.

Ward, H., G. Chapelais, G. G. Kuhnle, R. Luben, K. T. Khaw, and S. Bingham. 2008b. Lack of prospective associations between plasma and urinary phytoestrogens and risk of prostate or colorectal cancer in the European Prospective into Cancer-Norfolk study. *Cancer Epidemiology, Biomarkers & Prevention: a Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology* 17 (10):2891–4. doi: 10.1158/1055-9965.EPI-08-0335.

Watanabe, S., S. Uesugi, and Y. Kikuchi. 2002. Isoflavones for prevention of cancer, cardiovascular diseases, gynecological problems and possible immune potentiation. *Biomedicine and Pharmacotherapy* 56 (6):302–12. doi: 10.1016/S0753-3322(02)00182-8.

Woting, A., T. Clavel, G. Loh, and M. Blaut. 2010. Bacterial transformation of dietary lignans in gnotobiotic rats. *FEMS Microbiology Ecology* 72 (3):507–14. doi: 10.1111/j.1574-6941.2010.00863.x.

Wu, J., J. Oka, J. Ezaki, T. Ohtomo, T. Ueno, S. Uchiyama, T. Toda, M. Uehara, and Y. Ishimi. 2007. Possible role of equol status in the effects of isoflavone on bone and fat mass in postmenopausal Japanese women: A double-blind, randomized, controlled trial. *Menopause* 14 (5):866–74. doi: 10.1097/gme.0b013e3180305299.

Wuttke, W., H. Jarry, S. Westphalen, V. Christoffel, and D. Seidlova-Wuttke. 2002. Phytoestrogens for hormone replacement therapy? *Journal of Steroid Biochemistry and Molecular Biology* 83 (1–5):133–47. doi: 10.1016/S0960-0760(02)00259-5.

Xie, J., S. S. Tworoger, A. A. Franke, K. L. Terry, M. S. Rice, B. A. Rosner, W. C. Willett, S. E. Hankinson, and A. H. Eliassen. 2013a. Plasma enterolactone and breast cancer risk in the Nurses' Health Study II. *Breast Cancer Research and Treatment* 139 (3):801–9. doi: 10.1007/s10549-013-2586-y.

Xie, Q., M. L. Chen, Y. Qin, Q. Y. Zhang, H. X. Xu, Y. Zhou, M. T. Mi, and J. D. Zhu. 2013b. Isoflavone consumption and risk of breast cancer: A dose-response meta-analysis of observational studies. *Asia Pacific Journal of Clinical Nutrition* 22:118–27.

Yang, Z., Y. Zhao, Y. Yao, J. Li, W. Wang, and X. Wu. 2016. Equol induces mitochondria-dependent apoptosis in human gastric cancer cells via the sustained activation of ERK1/2 pathway. *Molecules and Cells* 39 (10):742–9. doi: 10.14348/molcells.2016.0162.

Yeung, J., and T.-F. Yu. 2003. Effects of isoflavones (soy phyto-estrogens) on serum lipids: A meta-analysis of randomized controlled trials. *Nutrition Journal* 2:15.

Yokoyama, S., T. Niwa, T. Osawa, and T. Suzuki. 2010. Characterization of an O-desmethylangolensin-producing bacterium isolated from human feces. *Archives of Microbiology* 192 (1):15–22. doi: 10.1007/s00203-009-0524-5.

Yokoyama, S., and T. Suzuki. 2008. Isolation and characterization of a novel equol-producing bacterium from human feces. *Bioscience, Biotechnology, and Biochemistry* 72 (10):2660–2666. doi: 10.1271/bbb.80329.

Zaineddin, A. K., A. Vrieling, K. Buck, S. Becker, J. Linseisen, D. Flesch-Janys, R. Kaaks, and J. Chang-Claude. 2012. Serum enterolactone and postmenopausal breast cancer risk by estrogen, progesterone and herceptin 2 receptor status. *International Journal of Cancer* 130 (6):1401–1410. doi: 10.1002/ijc.26157.

Zamora-Ros, R., M. Touillaud, J. A. Rothwell, I. Romieu, and A. Scalbert. 2014. Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: Current tools and applications and their limits. The American Journal of Clinical Nutrition 100 (1):11–26. doi: 10.3945/ajcn.113.077743.

Zhang, X., Y. T. Gao, G. Yang, H. Li, Q. Cai, Y. B. Xiang, B. T. Ji, A. A. Franke, W. Zheng, and X. O. Shu. 2012. Urinary isoflavonoids and risk of coronary heart disease. *International Journal of Epidemiology* 41 (5):1367–1375. doi: 10.1093/ije/dys130.

Zhu, Y., K. Kawaguchi, and R. Kiyama. 2017. Differential and directional estrogenic signaling pathways induced by enterolignans and their precursors. *PLoS One* 12 (2):e0171390. doi: 10.1371/journal.pone.0171390.