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REVIEW

Role of phytoestrogens in prevention and management of type 2 diabetes

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Abstract

Type 2 diabetes (T2D) has become a major public health threat across the globe. It has been widely acknowledged that diet plays an important role in the development and management of T2D. Phytoestrogens are polyphenols that are structurally similar to endogenous estrogen and have weak estrogenic properties. Emerging evidence from pre-clinical models has suggested that phytoestrogens may have anti-diabetic function *via* both estrogen-dependent and estrogen-independent pathways. In the current review, we have summarized the evidence linking two major types of phytoestrogens, isoflavones and lignans, and T2D from epidemiological studies and clinical trials. The cross-sectional and prospective cohort studies have reported inconsistent results, which may due to the large variations in different populations and measurement errors in dietary intakes. Long-term intervention studies using isoflavone supplements have reported potential beneficial effects on glycemic parameters in postmenopausal women, while results from short-term small-size clinical trials are conflicting. Taken together, the current evidence from different study designs is complex and inconsistent. Although the widespread use of phytoestrogens could not be recommended yet, habitual consumption of phytoestrogens, particularly their intact food sources like soy and whole flaxseed, could be considered as a component of overall healthy dietary pattern for prevention and management of T2D.

Key words: Type 2 diabetes; Phytoestrogen; Isoflavone; Lignan; Epidemiological study; Clinical trial

Core tip: Phytoestrogens are a group of polyphenols that are structurally similar to endogenous estrogen. Animal experiments and pre-clinical models have provided strong evidence that phytoestrogens may have anti-diabetic function *via* both estrogen-dependent and estrogen-independent pathways. A number of epidemiological studies and clinical trials have thus been conducted in different populations linking two major types of phytoestrogens, isoflavones and lignans, to the prevention and management of diabetes. Although the current evidence is complex and inconsistent, habitual consumption of phytoestrogens, particularly their intact

food sources, could be considered as a component of overall healthy dietary pattern for prevention and management of diabetes.

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INTRODUCTION

Diabetes has become a global public health crisis, and the International Diabetes Federation estimated that 382 million adults were affected by diabetes in 2013, and 5.1 million deaths due to diabetes occurred annually. More than 90% of the diabetes cases are type 2 diabetes (T2D). The global prevalence of T2D has doubled in the last 30 years and is predicted to continue to rise at an alarming rate, and the number is projected to reach 592 million by 2035. The health and economic burden from diabetes is enormous[1]. T2D is a constellation of disorders precipitated by complex and poorly understood interactions between environmental and genetic factors, leading to diminished insulin sensitivity and pancreatic β cell failure. However, diabetes is largely preventable by the adoption of a healthier lifestyle, including normal body weight, not smoking, regular exercise, and a balanced and healthy diet.

It has been widely acknowledged that diet plays an essential role in the development of T2D. Historically, the prevalence of T2D was very low in the traditional Asian society. One hypothesis speculates that the traditional Asian diet, characterized with high intakes of whole grains, large amount of vegetables and fruits, but small portions of meat products, contains many protective components against the development of T2D. Among the many food groups, soybean and soy products as the unique element of traditional Asian diet have aroused much interest because of considerable difference in its intake levels comparing with Western diet[2]. Although there are several potential beneficial compounds (soy protein, dietary fiber, monounsaturated and polyunsaturated fat, vitamins and minerals) in soybean and soy products, one group of polyphenols concentrated in soy products, isoflavones, have been suggested to be beneficial for diabetes prevention and management[2,3].

Isoflavones belong to a group of phytochemicals called phytoestrogens[4,5]. Phytoestrogens are plant-derived compounds that are structurally similar to endogenous estrogen and also have weak estrogenic properties[4,5]. There are two major types of phytoestrogens: isoflavones and lignans[4,5]. The former is concentrated in beans and soy products, and the latter is concentrated in flaxseed, sesames, whole grain and other plant-based foods[4,5]. The other types of phytoestrogens, like prenylated flavonoids and coumestans, are not commonly consumed in daily diet and are not discussed in this article.

In this review, we aimed to examine the current evidence linking phytoestrogens and T2D from epidemiological studies and clinical trials, to explore the potential underlying mechanisms of phytoestrogens' effect on glucose metabolism from animal and experimental studies, and to propose research priorities for future investigations in this field.

PHYTOESTROGENS

Isoflavones are primarily found in members of leguminosae family and occur in varying amounts in legumes consumed by humans, but soy exceptionally contains the highest isoflavone content[6]. Isoflavone contents of soy food ranges from approximately 0.1 to 5 mg/g of soy protein[7,8]. Asians generally consume very high amount of soy products, and studies have reported that the daily mean intake level of soy protein ranged from 2.0 g in Thailand to 9.6 g in North Korea[9]. Other studies have reported similar results: 5-9 g in Japanese[10] and Chinese[11-13]. The mean isoflavone intake was reported to be from 6 to 75 mg/d in these countries[9], while it was approximately 0.4 mg/d in Spain[14] and Dutch[15] populations, and approximately 0.3 mg/d in the United States population[16].

There are three main soy isoflavones, genistin, daidzin, and glycitin, in which the first two are the major ones available as sugars conjugated form (glycosides) in soybeans and most soy foods in Asian cuisines[4,5]. These biologically inactive forms are hydrolyzed in intestinal wall by the bacterial β-glucosidases and converted into the corresponding bioactive aglycones, daidzein and genistein, which then could be absorbed by intestine[7]. After initial hydrolysis of the glucoside moiety in colon, daidzein can be further metabolized to equol by colonic bacteria. In addition to the conversion by intestinal microflora, genistin and daidzin can also be converted into bioactive forms by *in vitro* fermentation that is common in traditional Asian methods of preparing soy foods[8]. The blood isoflavone concentration would be in the nanomolar range (< 40 nmol/L) in people who do not eat soy food, and can be increased to micromolar range by acute ingestion of dietary soy. Isoflavones and their metabolites are rapidly excreted in urine with a half-life of about 9 h for daidzein and 7 h for genistein[7].

The other type of phytoestrogens, plant lignans, are more ubiquitous than isoflavones, and the common food sources include oilseeds (flaxseed, sesame, soy, rapeseed), whole-grain cereals (wheat, oats, rye), and various vegetables[17,18]. Cereal fiber and wholegrain foods are among few food groups with established preventive effect for T2D[19], and lignans may be partially responsible for protective effects of dietary fiber complex[20]. Studies have suggested the use of urinary lignan excretion as a marker for fiber and whole

grain intake[21,22]. Plant lignans (secoisolariciresinol and matairesinol) are converted to mammalian lignans, enterolactone and enterodiol, by mammalian gut microflora, and enterodiol can also be further oxidized to enterolactone[4,5]. Like isoflavones, the main factors influencing circulating concentration of enterolactone are the food contents of lignans and microflora function[20].

Because of the lack of complete databases of dietary phytoestrogens, large variations of phytoestrogen contents of foods, and comprehensive metabolism pathways influencing circulating concentrations of phytoestrogens, studies have started to use objectively measured blood or urinary phytoestrogen concentrations as a good indicator of dietary intake[22-24]. In Asians with high variations of soy intakes, studies have reported a reasonably well correlation between urinary concentrations of isoflavone metabolites and dietary soy intakes (mostly assessed by food-frequency questionnaires), using morning spot urine[25], or overnight urine samples[26]. This was consistently observed in Japanese[27] and other populations as well[24]. Some studies in United States populations also confirmed that urinary concentrations of isoflavone metabolites are reasonable options for assessing isoflavone intake in epidemiologic studies[28-30]. Studies also suggested that urine samples performed better than serum samples for correlating with dietary intakes[31].

For lignans, studies in Western populations indicated that enterolactone concentrations in overnight urine samples moderately correlated with fruit and vegetables intake[32], concentrations of enterodiol and enterolactone in spot urines were significantly correlated with dietary intakes of fiber[32,33], vegetables and rye products[34]. Few studies have been performed to estimate the urinary lignan metabolites in Asian populations. A small study in 19 Japanese adults found that concentration of urinary lignan metabolites was about one third of isoflavone metabolites, and was correlated with intakes of green and yellow vegetables, pulses and beans[27]. A study in 75 Korean postmenopausal women found that the concentration of lignan metabolites in 24-h urine samples was about half of isoflavone metabolites[35], similar results were found in a study among 68 Chinese T2D patients using first morning urine samples[36]. In another large cross-sectional study of 2165 middle-aged and elderly Chinese women, despite that the concentrations of lignan metabolites were substantially lower compared to isoflavone metabolites in spot urines, the urinary enterodiol was higher than and enterolactone was similar to that among United States women of comparable age[12]. This was observed in another study that collected urine samples from several Asian countries (Japan, Vietnam, India, and Cambodia) and United States[37]: high concentrations of isoflavone metabolites were detected in urine samples from Japan and Vietnam, while the concentrations in urine samples from Cambodia and India were much lower and comparable to that found in United States samples; the differences between urinary lignan metabolites were relatively small among samples from the five countries.

RECENT HUMAN STUDIES LINKING PHYTOESTROGENS TO DIABETES AND GLUCOSE HOMEOSTASIS

The epidemiological studies on the relation between phytoestrogens and risk of T2D or diabetes biomarkers are shown in Table 1. We have described the findings by study designs as below.

Cross-sectional study evidence

Several cross-sectional studies have assessed the association between soy protein and isoflavone intakes and diabetes related markers. In the Shanghai Women's Health study of 39385 women aged 40-70 years, it was observed that soy protein intake was inversely associated with glycosuria, an important indicator of diabetes, but only in normal weight postmenopausal women[38]. However, in another study among 2811 Chinese adults, soy protein intake was significantly associated with increased odds of hyperglycemia in men, but null association in postmenopausal women[11]. The median soy protein intake was around 8 g/d in both studies[11,38]. The increased odds of hyperglycemia in men could be a chance finding, and residual confounding and reverse causation are possible in the cross-sectional studies. The sex-specific effects may also linked to the estrogen-like activity of isoflavones[4,5], but the underlying mechanisms are complex and unclear[11]. In a study of 208 American postmenopausal women who ate much lower levels of soy foods, genistein intake was significantly associated with 2-h post challenge insulin concentrations, but not fasting or 2-h glucose concentrations[39]. This suggested that isoflavones may have direct effect on β-cell function and insulin secretion, which is supported by experimental studies[40]. Among 299 pregnant women who participated in the United States NHANES 2001-2008 surveys, Shi *et al*[41] found that urinary concentrations of total isoflavone metabolites were inversely associated with fasting glucose, insulin and homeostatic model assessment of insulin resistance (HOMA-IR).

Consumption of soy products is generally low in Western diet leading to modest effect of isoflavones on metabolic markers, while lignans may be the major form of phytoestrogens and exert a stronger effect. Dietary lignan intake was inversely associated with fasting insulin and C-peptide in 468 United States men, but the association was not found for isoflavones[42]. In the Framingham Offspring Study with 939 postmenopausal women in United States, high intake of phytoestrogens was associated with a favorable metabolic cardiovascular risk profile (waist-to-hip ratio, triglyceride and overall metabolic score), with stronger association for lignans

Table 1 Epidemiological studies on the relation between phytoestrogens (lignans or isoflavones) and risk of diabetes or diabetes biomarkers

Ref.	Ethnicity	Population	Sample size, total (outcome)	Mean follow-up years	Main exposures	Outcome	Exposure level (mean or median)	Maximum effect (highest *vs* ref.)
Cross-sectional study								
Goodman-Gruen *et al*[39]	Mix[1]	Postmenopausal women, aged 45-74 yr	208	-	Dietary isoflavones	Diabetes biomarkers	4.4 mg/d genistein (mean)	Inverse with 2-h insulin (β = -0.2); not significant for FG and insulin
Yang *et al*[38]	Chinese	Women aged 40-70 yr	39385 (323)	-	Tofu and other soy products	Glycosuria	9 g/d soy protein	Inverse association in postmenopausal women
van der Schouw *et al*[42]	Caucasian	Men aged 47-83 yr	468	-	Dietary lignans and isoflavones	Diabetes biomarkers	Approximately 1 mg/d total phytoestrogens	Inverse association of lignans with fasting insulin and C-peptide; no significant association with isoflavones
Pan *et al*[11]	Chinese	Men and women aged 50-70 yr	2811	-	Dietary soy protein	Hyperglycemia (FG ⩾ 5.6 mmol/L)	7.8 g/d soy protein	Increased odds in men, but not in women
Shi *et al*[41]	Mix[1]	Pregnant women aged 28 yr	299	-	Urinary isoflavones	Diabetes biomarkers	502 mg/g creatinine	Inverse association with FG, insulin, and HOMA-IR
Longitudinal study								
Villegas *et al*[44]	Chinese	Women aged 40-70 yr	64191 (896)	4.6	Soy protein, soybeans, soy products	T2D	7.7 g/d soy protein	Inverse association with soybeans; inverse but not significant relation with soy protein or other products
Nanri *et al*[46]	Japanese	Men and women aged 45-75 yr	59791 (1114)	5	Soy products, daidzein, genistein	T2D	Approximately 73 g/d soy products, approximately 23 mg/d genistein, and 14.5 mg/d daidzein	No significant association
Morimoto *et al*[47]	Mix[2]	Men and women aged 45-75 yr	75344 (8564)	14	Soy products	T2D	Approximately 14.5 g/d in Japanese, approximately 8 g/d in Hawaiians, and 0 g/d in Caucasians	A modest increased risk in men and women
Mueller *et al*[45]	Chinese	Men and women aged 45-74 yr	43176 (2252)	5.7	Isoflavones, unsweetened and sweetened soy products	T2D	Approximately 5.2 g/d for soy protein, 15.8 mg/d for soy isoflavones	Inverse association for soy isoflavones and unsweetened soy products, while increased risk for sweetened soybean drinks
Zamora-Ros *et al*[48]	European whites	Men and women with mean age 52.4 yr	11559 cases and 15258 subcohort, case-cohort design	Approximately 12	Dietary isoflavones and lignans	T2D	0.9 mg/d isoflavones, 1.4 mg/d lignans	No significant association for isoflavones and lignans
Sun *et al*[49]	Caucasian	Women aged 65.6 yr from NHS and 45.4 from NHS Ⅱ	1107 cases and 1107 controls, nested case-control design	Approximately 6	Urinary lignin metabolites (enterodiol and enterolactone)	T2D	2.2 μmol/g creatinine for NHS women, and 1.9 μmol/g creatinine for NHS Ⅱ women	Inverse association and odds ratio 0.64 (95%CI: 0.45-0.91) comparing extreme quartiles

[1]Mostly non-Hispanic whites; [2]Caucasian, Japanese American, and Native Hawaiian. FG: Fasting glucose level; NHS: Nurses' Health Study; T2D: Type 2 diabetes; HOMA-IR: Homeostatic model assessment of insulin resistance.

compared to isoflavones[43]. No study has been conducted so far to investigate the cross-sectional relation between lignans and diabetes risk markers in Asian populations.

Prospective study evidence

A few larger prospective cohort studies have been conducted to investigate the relation between soy food consumption and risk of incident T2D in different populations. In a study with an average 4.6 years of follow-up among Chinese women from the Shanghai Women's Health Study, Villegas *et al*[44] reported that soybean and soymilk intakes were significantly associated with a lower risk of incident T2D, while soy protein and other soy products were related to a trend of reduced risk, although not statistically significant. In another large prospective study in Chinese population, the Singapore Chinese Health Study, Mueller *et al*[45] pointed out that consumption of unsweetened soy products was inversely associated with T2D risk in a graded fashion (*P* for trend = 0.02), while consuming sweetened soybean drink was positively associated with T2D risk. The findings underline the importance of food context and preparation method. Furthermore, after full adjustment including sweetened soy items, the authors observed a marginally significant inverse association between intake of isoflavones and T2D (relative risk comparing extreme quintile: 0.76; 95%CI: 0.58-1.00; *P* for trend = 0.08). In a large-scale study in middle-aged and elderly Japanese from the Japan Public Health Center-Based Prospective Study, Nanri *et al*[46] found no significant association between soy products and isoflavones with incident T2D in either men or women. The suggestive protective association in overweight women disappeared when energy-adjusted intake was considered[46]. In the Multiethnic Cohort study in Hawaii with three ethnicities (Caucasian, Japanese American, and Native Hawaiian), Morimoto *et al*[47] reported a moderately elevated risk of T2D with soy food consumption and risk of T2D during 14 years of follow-up in men and women, particularly in overweight adults. However, the consumption level of soy products was substantially lower compared to that in the Asian populations. In the European populations, the recent EPIC-InterAct case-cohort study in 12403 incident T2D cases and a subcohort of 16154 participants found no significant association between isoflavones and risk of T2D, while a suggestive trend with lignans (the hazard ratio comparing extreme quintiles 0.88; 95%CI: 0.72-1.07; *P* for trend = 0.12)[48].

Therefore, the current evidence from large longitudinal studies regarding the relation between phytoestrogen and related food sources and incident T2D is still inconsistent. One methodology challenge could be the measurement error of dietary assessment by questionnaire data. This may be due to the incomplete inclusion of phytoestrogen-enriched food items in the questionnaire and lack of comprehensive food composition databases of phytoestrogens. Furthermore, phytoestrogen metabolism and circulating concentrations in human body can be influenced by many other factors in addition to dietary intake. Thus, studies have started to measure blood or urinary phytoestrogens and evaluate the relation with disease outcomes. Recently, a nested cases-control was conducted among 1107 T2D cases and 1107 control subjects from the Nurses' Health Study (NHS) and NHS Ⅱ[49]. Urinary concentrations of the lignan metabolites were assayed by liquid chromatography-mass spectrometry. After multivariate adjustment for lifestyle and dietary risk factors of T2D, the odds ratio for T2D was 0.70 (95%CI: 0.53-0.92) for each SD increment of urinary concentrations of total lignan metabolites. The association was seen in both enterolactone [odds ratio comparing the extreme quartiles 0.62 (95%CI: 0.44-0.88), *P* for trend = 0.003] and enterodiol [odds ratio comparing the extreme quartiles 0.67 (95%CI: 0.48-0.96), *P* for trend = 0.08]. Thus far, this is the only prospective study using objectively measured phytoestrogen biomarkers to link with diabetes risk. More studies are needed to examine the relation of urinary phytoestrogen excretion and risk of developing T2D in different studies and populations with varying intake levels.

Clinical trial evidence in participants without T2D

A meta-analysis of 24 intervention studies (*n* = 1518 in total) on soy intake and glycemic control was done including trials published before March 2010[50]. While no significant effect on fasting glucose and insulin was generally observed for soy intake, the authors found 3.85 mg/dL (95%CI: 2.41-5.28) reduction in fasting glucose concentrations in a subgroup analysis of 9 studies that used whole soy foods or soy diets as the intervention regime. No statistically significant association was identified in 8 studies with isoflavone extract (ranged 40 to 132 mg/d isoflavones) or 6 trials with isolated soy protein containing isoflavones as the main intervention. This suggests that other components of soy like soy protein and fiber, polysaccharides, phytosterol, and unsaturated fatty acid or their interactions may play roles in glycemic control in addition to isoflavones. However, the majority of the studies in this meta-analysis had small sample size (ranged from 14 to 203) and short intervention period (ranged 4 to 52 wk). One of the largest studies so far was a 1-year double-blind, randomized, placebo-controlled trial in 203 Chinese postmenopausal women aged 48 to 62 years[51]. They were randomly assigned to receive daily doses of 0 mg (placebo, *n* = 67), 40 mg (*n* = 68), and 80 mg (*n* = 68) isoflavone supplements along with 500 mg calcium in all groups. The mean differences in the changes of fasting glucose between the intervention and placebo groups were -5.2 mg/dL (95%CI: -9.4 to -1.0) and -3.3 mg/dL (95%CI: -7.5 to 0.9), respectively, for the mid-dose and high-dose groups, and the effect was much more significant in women with higher baseline glucose levels[51].

Another meta-analysis of 12 clinical trials conducted before October 2010 focused on the effects of isoflavone supplementation on blood glucose and insulin in non-Asian postmenopausal women[52]. Zhang *et al*[52] found that isoflavone supplementation significantly reduced fasting glucose by 0.19 mmol/L (95%CI: 0.03-0.34), and this effect was limited to the studies with more than 6-mo period of intervention. The meta-analysis also reported a significant reduction in fasting insulin by 0.94 μU/mL (95%CI: 0.16-1.72). One of the largest and longest studies so far was done in Italian postmenopausal women with osteopenia[53]. Participants were randomly assigned to receive genistein (54 mg/d; *n* = 198) or placebo (*n* = 191) for 2 years. Both groups received 500 mg/d calcium carbonate and 400 IU/d vitamin D. Compared with placebo, genistein significantly reduced fasting glucose and insulin as well as HOMA-IR after both 12 and 24 mo of treatment[53].

Since 2010, a few more trials have been published on the effects of isoflavone supplementation on glucose homeostasis. Two long-term (24 mo) clinical trials by the same research group found that daily intake of 40 mg of soy isoflavones together with lifestyle modification (Mediterranean diet and exercise) reduced HOMA-IR compared to lifestyle modification alone among 116 Spanish postmenopausal women with insulin resistance[54], this was confirmed using same study design (except for 80 mg/d of soy isoflavones) among 80 Spanish postmenopausal women[55]. Improvement of fasting glucose and insulin was also reported[55]. Another 1-year clinical trial among 120 postmenopausal women with metabolic syndrome revealed that 54 mg/d genistein supplements (*n* = 60) significantly reduced HOMA-IR, fasting glucose and insulin compared to placebo (*n* = 60)[56]. However, the beneficial effects of isoflavones on glucose metabolism were not found in some short-term trials[57-60]. Since S-equol is considered the most biologically active metabolite of isoflavones, a study was specifically designed to evaluate the effects of S-equol on metabolic profiles among 54 Japanese overweight/obese men and women using a cross-over study design[61]. Significant improvement in HbA1c was observed using 10 mg/d *S*-equol for 12-wk compared to placebo[61].

As for flaxseed and lignans, a meta-analysis found that flaxseed and/or flaxseed lignan intervention significantly improved lipid profiles[62]. Two small cross-over clinical trials in overweight/obese glucose intolerant participants found that flaxseed reduced insulin resistance after 12-wk interventions[63,64]. A large intervention study in 293 Chinese adults with metabolic syndrome found that 30 g/d flaxseed significantly reduced HbA1c and glucose levels among those with central obesity at baseline[65]. A clinical trial in 55 hypercholesterolemic Chinese subjects found that 600 mg/d flaxseed lignan extract significantly lowered fasting glucose, particularly in those with a higher baseline glucose levels[66]. Another cross-over clinical trial in 22 healthy postmenopausal women reported that 500 mg/d flaxseed lignan extract significantly reduced C-reactive protein levels after 6 wk[67]. However, other studies have found null results[68-71].

Taken together, long-term intervention studies using isoflavone supplements have reported potential beneficial effects on glycemic parameters in postmenopausal women[51,53-56], while results from short-term small-size clinical trials are conflicting. Therefore, more high-quality long-term clinical trials are needed in men and premenopausal women, and to investigate the effect of lignans on glucose metabolism in humans.

Clinical trial evidence in patients with T2D

A number of clinical trials have been conducted in T2D patients to investigate the effects of phytoestrogens and related food sources on diabetes management. Jayagopal *et al*[72] found that 12-wk intervention of 30 g/d soy protein enriched with 132 mg isoflavones significantly reduced HbA1c (-0.6% *vs* 1.1% in placebo group), fasting insulin (-8.1% *vs* 9.9% in placebo group), and HOMA-IR (-6.5% *vs* 14.7% in placebo group) in postmenopausal women with T2D. Another long-term 4-year clinical trial among T2D patients with nephropathy reported a net change of -29 mg/dL in plasma glucose in the intervention group (*n* = 20; 0.8 g protein/kg body weight with 35% as soy protein, 35% as animal protein and 30% as vegetable protein) compared to the control group (*n* = 21; 70% as animal protein and 30% as vegetable protein)[73]. However, some small short-term trials among T2D patients failed to observe significant improvement for isoflavone-containing soy protein on glucose, insulin resistance or HbA1c[74-79]. On the other hand, clinical trials among T2D patients have reported improvement in lipid profiles[73,74,77,78,80], kidney function[73,78,81], endothelial function and blood pressures[76].

The effects of other isoflavone-enriched foods in T2D patients have also been tested: a 1-year intervention with 27 g/d flavonoid-enriched chocolate (containing 850 mg flavan-3-ols and 100 mg isoflavones) significantly reduced insulin resistance and improved insulin sensitivity and lipid profile compared to placebo in 93 postmenopausal women with T2D[82]. However, few studies have specifically investigated the effects of purified isoflavones supplements among T2D patients, and the available two interventions found no significant effects on glycemic control and lipid profiles[83,84], but the intervention periods were short (4 and 12 wk) and sample sizes were small (*n* = 16 and 32).

A few studies of flaxseed or lignans among diabetic patients also found promising results. Daily supplementation with 10 g flaxseed powder for 4 wk decreased fasting glucose by 19.7% and HbA1c by 15.6% in T2D patients[85], and also improved lipid profiles. Similarly, 5 g/d flaxseed gum for 12 wk significantly reduced serum glucose from 154 ± 8 mg/dL to 136 ± 7 mg/dL[86]. Moreover, 360 mg/d lignan for 12 wk slightly decreased HbA1c[36] and C-reactive

protein[87], although fasting glucose and insulin and lipid profiles remained unchanged[36]. Another study using 600 mg/d lignan for 3 mo found decreased HbA1c and glucose levels, but the results were not statistically significant after multivariate adjustment[88].

In summary, isoflavone-enriched soy products and lignin-enriched flaxseeds provide promising benefits in glycemic control, lipid profiles and other cardiovascular markers in T2D patients, but the long-term effect of purified isoflavone or lignan supplements remains unknown.

POTENTIAL MECHANISMS LINKING PHYTOESTROGENS AND PREVENTION OF T2D

The potential mechanisms linking phytoestrogens and glucose metabolism and prevention of diabetes have been extensively reviewed elsewhere[3,40,89,90], here we briefly discuss some animal studies and potential mechanisms on this topic.

A study in male C57BL/KsJ-*db/db* mice found that both genistein (0.02%, w/w) and daidzein (0.02%, w/w) supplements significantly decreased blood glucose and HbA1c levels, and this effect might be due to the suppression of hepatic glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK), fatty acid synthase, β-oxidation and carnitine palmitoyltransferase activities[91]. The same effects have been observed in the female non-obese diabetic mice as well, a T1D animal model[92]. Some other studies suggested that isoflavones may exert antidiabetic effect *via* peroxisome-proliferator activated receptors (PPAR) pathway. In the obese Zucker rats, a T2D model, high-isoflavone soy protein diet improved glucose tolerance relative to low-isoflavone soy protein and casein diets[93]. It was further found that genistein or daidzein significantly increased *PPARα*- and *PPARγ*-directed gene expression by 2-4 fold in RAW 264.7 cells[93]. The increased *PPARα* gene expression was also seen in another study[94]. In streptozotocin-induced diabetic rats, 3-wk genistein supplementation decreased HbA1c levels and G6Pase activity, while increased glucokinase level and antioxidant enzyme activities[95]. In an obese nongenetic T2D mouse model, dietary intake of genistein (250 mg/kg diet) improved hyperglycemia, glucose tolerance, and blood insulin level but did not affect insulin sensitivity, suggesting that genistein may increase the number of insulin-positive β-cells in islets, promote their survival, and preserve them by preventing apoptosis[96]. Numerous studies have suggested that genistein may have direct effects on β-cell proliferation, glucose-stimulated insulin secretion and protection against apoptosis[40]. Meanwhile, some other studies have shown insulin-sensitizing effect of genistein in male and female C57BL/6 mice[97], as well as ovariectomized rats[98].

Secoisolariciresinol diglucoside (SDG), the major dietary lignan in flaxseed, considerably reduced the incidence of diabetes in streptozotocin-induced diabetic rats[99], diabetes-prone BioBreeding rats, a T1D model[100], and ZDF rats, a T2D model[101]. In these experiments, SDG significantly decreased oxidative stress by reducing malondialdehyde and pancreatic-chemiluminescence level. Sesamin, the most abundant lignan in sesame seed, showed hypoglycemic effect in a dose-dependent manner in KK-Ay mice, a T2D model[102]. Sesamin was also found to attenuate vascular dysfunction and oxidative stress in streptozotocin-diabetic rats[103].

The effects of phytoestrogens on glucose metabolism are thought to be *via* estrogen-dependent pathway and non-estrogen dependent pathways. Estrogens have been shown to modulate lipid and glucose metabolism directly through lipogenesis, lipolysis, and adipogenesis, or indirectly through their effect on central nervous system influencing appetite and energy expenditure[104]. The relationship between endogenous sex hormones and development of T2D has been well established[105,106]. Because of structural similarity, phytoestrogens could act as estrogen agonists or antagonists, depending on the target tissues[107], doses[108-110], and endogenous circulating sex hormone profile[111]. Although the binding affinity to estrogen receptors (ERs) is much lower for phytoestrogens compared to 17β-estradiol[112], the concentration of phytoestrogens in blood is much higher than endogenous estrogens[113], making it still possible to compete with 17β-estradiol to bind the ERs. Therefore, it is hypothesized that phytoestrogens may influence glucose metabolism by directly modulating concentrations of circulating sex hormones, and this estrogenic effects of phytoestrogens have been supported by some human studies[114-119]. Oxidative stress is considered as one of the causes for T2D and phytoestrogens are known to have strong antioxidant activity[120]. For example, SDG, the major dietary lignan[121] and its mammalian metabolites enterodiol and enterolactone[122], were shown to have antioxidant activity even higher than that of vitamin E. Animal experiments found that lignans decreased lipid peroxidation in rats fed with docosahexaenoic acid[123], and flaxseed increased activities of catalase, superoxide dismutase, and peroxidase[124]. Similarly, isoflavones also showed antioxidant activity *in vitro*[125] and *in vivo*[95,126]. Several clinical trials in humans also found that high-isoflavone soy products increased antioxidant capacity[127-130].

Phytoestrogens may influence glucose metabolism and insulin resistance through other non-estrogen dependent mechanisms. For example, both lignans and isoflavones were found to suppress the *PEPCK* gene expression[92,131]. PEPCK enzyme catalyzes the first committed step in hepatic gluconeogenesis, and *PEPCK* gene transcription is induced by glucagon and glucocorticoids and inhibited by insulin. Thus, suppression of *PEPCK* gene will improve hyperglycemia through reduced gluconeogenesis[132]. Furthermore, phytoestrogens, mostly isoflavones, activate

PPAR and increase the *PPARα*- and *PPARγ*-directed gene expression[93,94,133,134], which is implicated in the glucose homeostasis and lipid metabolism. In the yeast model, genistein was shown to be a reversible, slow-binding, non-competitive inhibitor of alpha-glucosidase[135], which breaks down starch and disaccharides to glucose. Therefore, the alpha-glucosidase inhibitors may reduce the postprandial glucose levels by slowing down the carbohydrate digestion and absorption. In the rabbit model, isoflavones were found to inhibit glucose uptake into rabbit intestinal brush border membrane vesicles *in vitro*[136]. Genistein also directly acted on pancreatic β-cells, leading to activation of the cAMP/PKA signaling cascade to increases rapid glucose-stimulated insulin secretion[137]. The increased insulin secretion was also reported elsewhere[138-140]. Other studies have found that isoflavones may inhibit tyrosine-specific protein kinases[141], induce adiponectin, leptin and *GLUT4* gene expressions in 3T3-L1 adipocytes[142]; promote postprandial carbohydrate oxidation and energy expenditure[143], and protect against high glucose-induced pancreatic cell damage through ERβ and Bcl-2 dependent pathways[144].

IMPLICATIONS AND RECOMMENDATIONS FOR FUTURE STUDIES

As summarized in this review, there has been a long-lasting interest to examine the relation of phytoestrogens and related food sources with diabetes risk. Although the current evidence is promising, there are some knowledge gaps that should be addressed in future investigations.

The food composition databases of phytoestrogens have become the major concern in many epidemiological studies on the relation between phytoestrogens and diabetes risk. The phytoestrogen contents vary dramatically in different food items, and are also influenced by the geographic location, harvest time, and food preparation methods, *etc*. Therefore, it is urgent to establish accurate, up-to-date, and comprehensive databases in different countries. Particularly for lignans, there is a lack of databases available for research. To the best of our knowledge, there has been no prospective longitudinal study in Asian population investigating habitual intake of lignans and risk of developing T2D.

More prospective studies are needed to use objective biomarkers of phytoestrogens exposure, *e.g.*, urinary excretion concentrations. One methodology challenge of the dietary assessment by questionnaire data is the large measurement error from incomplete inclusion of phytoestrogen-enriched food items in the questionnaire and lack of comprehensive food composition databases. Furthermore, phytoestrogen metabolism and circulating concentrations in human body can be influenced by many other factors (*e.g.*, bioavailability and microflora function) in addition to dietary intake. In addition, phytoestrogen biomarker measurements can be easily done in epidemiological studies with archived biospecimen samples. Some large cohort studies have started to measure urinary concentrations of phytoestrogens and evaluate the relation with disease outcomes, but more investigations in different populations are still warranted. In these studies, repeated measures of phytoestrogen biomarkers are recommended to reduce measurement errors and address the issue of changes over time.

The results from clinical trials of the effects of phytoestrogens on glucose homeostasis are conflicting. Many trials have the limitations of small sample size and short intervention duration. Several recent trails in large sample size (n > 100) and longer duration ($\geqslant$ 1 year) have produced more consistent and promising evidence to support the use of phytoestrogens. However, those trials were all in postmenopausal women and used isoflavones as the intervention supplements; thus, more high-quality long-term clinical trials are needed in men and premenopausal women, and to investigate the effect of lignans on glucose metabolism. Furthermore, clinical trials in T2D patients have supported the use of isoflavone-enriched soy products and lignin-enriched flaxseed for glycemic and lipid control, but whether the beneficial effects are due to phytoestrogens or other active components in soy or flaxseed remains unclear. Therefore, long-term and high-quality trials using purified phytoestrogen supplements are necessary to explore the possibility of their routine use for diabetes management.

Some studies hypothesized that the observed variations in effect of isoflavones on osteoporosis, cardiovascular disease, or some cancers could be attributed to the equol production ability in human[145]. More investigations in epidemiological studies and clinical trials are needed to test whether this hypothesis is also true for T2D. Furthermore, some studies found that the effects of phytoestrogens on lipid profile[146], endometrial cancer[8], or breast cancer[147] could be modified by various polymorphisms in genes relevant to estrogen or sex hormone binding globulin, like *CYP1A1*, *CYP1B1*, and *COMT*. However, there are few studies that directly assess gene-phytoestrogen interaction for the T2D outcome or glucose metabolism. This line of investigation is important to help understand the potential mechanisms and design personalized interventions.

Although there are many *in vivo* and *in vitro* studies to explore the potential pathways for the effects of phytoestrogens, the exact anti-diabetic mechanisms are still unclear. Furthermore, the effective doses used in many experimental studies far exceed the physiological concentrations in human circulation. Thus, it is recommended to consider dosages applicable for human in future animal studies.

CONCLUSION

In conclusion, the current evidence of phytoestrogen and T2D from different study designs are complex and inconsistent. Findings from some high-quality prospective cohort studies and clinical trials are promising, but more

studies are needed to fill the aforementioned knowledge gaps. Although the widespread use of phytoestrogens could not be recommended due to the controversies, habitual consumption of phytoestrogens, particularly their intact food sources like soy and whole flaxseed, could be considered as a component of overall healthy dietary pattern for prevention and management of T2D.

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