Mini Review
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Kudzu (*pueraria lobata*) vine isoflavone, puerarin, improves weight gain, glucose metabolism and osteoporosis and their biokinetics in ovariectomized mouse

Abstract

Aging and unhealthy eating habits increase the risk of metabolic disorders such as obesity, diabetes and osteoporosis. One of the applicable ways to prevent these negative health outcomes is daily utilization of food materials and/or food factors which contains physiologically active and safe compounds. Kudzu (*Pueraria lobata*) is a creeping and tree-climbing plant with long vines belonging to Leguminosae family. It has been used as a food material over thousand years as well as a medicinal plant in oriental countries. This mini review introduces health-beneficial effects of kudzu vine isoflavones and their biokinetics in ovariectomized (OVX) mice. Dietary kudzu vine extracts and a diet consisting of puerarin, the major isoflavone, improved glucose metabolism, weight gain and osteoporosis independent of the estrogen receptor-mediated pathway in OVX mice. As population ages, health problems associated with age and menopause in women are becoming increasingly notable. The findings in this study suggest that dietary kudzu vine isoflavones and puerarin present a promising approach to prevent life style related diseases like obesity, diabetes and osteoporosis.

Keywords: kudzu, puerarin, isoflavone, obesity, diabetes, osteoporosis, postmenopause, ovariectomized mouse

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Abbreviations: OVX, ovariectomized; ER, estrogen receptor; SGLT, sodium dependent glucose transporter

Introduction

Aged people, especially postmenopausal women are at increased risk of metabolic disorders such as obesity, which in turn raises the risk of developing further serious conditions, including diabetes,[1,2] cancers, neurological disorders, hypertension, and other cardiovascular diseases.[3] Postmenopausal diabetes is induced by estrogen deficiency, which exacerbates insulin resistance.[4,5] The number of postmenopausal patients with diabetes has increased recently due to population aging; therefore, dietary strategies to reduce the risk of diabetes are expected to be necessary in order to improve postmenopausal health. OVX animals are used as a model of postmenopausal diabetes.[6–8] OVX mice show glucose intolerance, insulin resistance, and increased body weight.[7,8] This mini review aims to summarize recent findings in the area of weight and fat mass control by kudzu (*Pueraria lobata*) vine isoflavones and their biokinetics in OVX mice.

Kudzu vine as a food material applicable for metabolic disorders

Kudzu is a creeping and tree-climbing plant with long vines belonging to Leguminosae family. The plant has spread worldwide and is predominant in temperate climates. Puerariae radix is the dried root of kudzu, often called "kakkon." Prasain et al.,[9] demonstrated that kudzu root extract ameliorates impaired glucose and lipid metabolism in obese male mice. They also reported that diet containing kudzu root extract significantly lowers not only arterial pressure, but also blood cholesterol, glucose, and insulin levels in stroke-prone spontaneously hypertensive rats.[10] We evaluated the potential of kudzu root ethanol extracts in a diet to improve postmenopausal diabetes. The Pharmaceutical Affairs Law in Japan, however, classifies the kudzu root as a resource for medicine but not for food. Therefore, we investigated whether other parts of the plant have beneficial effects on postmenopausal diabetes.

We reported that kudzu vine ethanol extracts were rich in isoflavones, being composed of roughly 10% puerarin, 3.6% daidzin, 2.5% 6″-O-malonyldaidzin, and other minor isoflavones.[11] The relative composition of the isoflavones is generally similar between kudzu vine and kudzu root extracts,[12] although the minor components differ a little from each other. However, kudzu vine has the advantage over the root as a food resource. It is easier to harvest and more economical and effective to process into food material than the root does. Therefore, we focused on kudzu vine as an applicable food material.

Effect of kudzu vine isoflavones on weight gain, glucose metabolism and osteoporosis in ovx mice

We previously elucidated how kudzu vine isoflavones improved menopausal conditions of OVX mice.[11,13,14] Ten-week-old OVX or sham-operated mice were fed diets without kudzu isoflavones (control) and with 20mg/kg body weight/day kudzu isoflavones for 8weeks, 5mg/kg body weight/day kudzu isoflavones for 24weeks, 20mg/kg body weight/day puerarin (daidzein-8-C-glucoside), a major isoflavone present in kudzu vine extracts, for 10weeks, and 5mg/kg body weight/day puerarin for 8weeks. The effects of puerarin on glucose tolerance were also tested in OVX mice. The weight gain

and the serum glucose levels were increased and the bone mineral density was decreased in OVX mice. These negative phenomenon were significantly attenuated in OVX mice that consumed kudzu isoflavones (5 or 20mg/kg/day) or puerarin (5 or 20mg/kg/day).

The experimental diets were not associated with any abnormalities in all mice tested in our study, suggesting that kudzu isoflavones and a puerarin diet at this dose and up to 24weeks safely reduced hyperglycemia and fat accumulation and prevented bone loss. Puerarin-treated OVX mice also showed reduced serum glucose levels following the administration of 1000mg/kg glucose. The similar result is obtained in C57BL/6J-ob/ob mice.[15] These facts indicate that puerarin is attributable to kudzu isoflavone-mediated improvements in glucose metabolism in OVX mice.

Comparison between kudzu and soybean isoflavones

Soybean isoflavones including daidzein and genistein have been shown to improve lipid metabolism in ovariectomized (OVX) postmenopausal animal models.[16–19] These isoflavones have an affinity, although weak, for estrogen receptors (ERs), especifically for ERβ.[20,21] These compounds also cause the proliferation of ER-positive human breast cancer cells (MCF-7)[21–23] and promote hyperplasia of the uterus.[24,25] Hence, a diet with an excess of these isoflavones is probable to induce negative effects on breast cancer and uterine cancer via ERs. Therefore, it is extremely important to identify compounds that exhibit anti-osteoporotic activity independent of ER-mediated pathways.

Kudzu vine isoflavones might be considered to improve glucose metabolism in OVX mice via the ER pathway, but this was ruled out by the finding that kudzu vine extracts[11] and puerarin[14] have no or very low affinity for ER-α or ER-β. Moreover, there were no signs of uterine hypertrophy in the kudzu vine extract- or puerarin-fed mice.[11,13,14] These findings suggest that kudzu vine isoflavones and puerarin improve glucose metabolism without estrogen-like effects on the uterus in OVX mice.

Biokinetics of kudzu isoflavones

Understanding of the biokinetics of dietary kudzu isoflavones as distribution and transport rout in animal model is useful to clarify the potential mechanism by which kudzu isoflavones improve metabolic disorders like obesity, diabetes, and osteoporosis. O-glycoside isoflavones of kudzu such as daidzin, genistin, and glycitin are converted by bacterial β-glucosidase in the gut to their aglycons, daidzein, genistein, and glycitein, respectively.[26–28] On the other hand, puerarin was resistant to the enzyme due to its C-glycoside nature and not converted to the aglycon. In addition, it may differ in its biokinetics from other C-glycoside compounds, such as homoorientin and isovitexin, since they are hydrolyzed, resulting in the opening of its heterocyclic C ring.[29]

To human gut microflora, puerarin (daidzein-8-C-glucoside) has also been reported to be more resistant than didzin (daidzein-7-O-glycoside) *in vitro*.[30] A previous report indicated that nonmetabolized puerarin and a small amount of its glucuronide were detected in the serum of rats orally administered puerarin.[31] Moreover, Prasain et al.,[9] demonstrated that puerarin was widely distributed (kidney, liver, lung, pancreas, heart, eye, and brain) in rats orally administered puerarin.[31–33] Hence, almost all puerarin presumably is absorbed from the intestine, enters into the systemic circulation, and is distributed in the tissues without deglycosylation and conjugation.

Piskula et al.,[34] previously demonstrated that daidzein and genistein, but not their glucosides, were rapidly absorbed from the stomach in a rat model. In addition, the plasma concentration of isoflavone after a single ingestion of daidzein and genistein (T_{max}: approximately 2hours) was higher than that of the glucoside (Tmax: approximately 4hours) in humans.[35] The T_{max} of puerarin (approximately 0.5hours) was much shorter[36] than those of daidzein, genistein, and their glucosides. Prasain et al.,[9] also hypothesized that the sodium-dependent glucose transporter (SGLT) is involved in the transport system of puerarin in a rat model.[31–33] The rapid absorption of puerarin in our study might be attributable to the absorption from the small intestine via SGLT. The T1/2 and the elimination rate of puerarin in serum were shorter and higher, respectively,[36] than those of daidzin and genistein.[35] These reports support our understanding that almost all puerarin presumably enters into the systemic circulation quickly and is distributed in the tissues without deglycosylation and conjugation, suggesting the rapid clearance of puerarin. Keyler et al.,[37] showed the safety of the long-term oral administration of Chinese herbal medicine, which contains puerarin as a major component. The rapid clearance of puerarin in animal bodies may contribute to the lack of any side effects of orally administered puerarin.

Conclusion

The consumption of kudzu vine isoflavones and/or puerarin in the diet presents a safe and effective approach for preventing postmenopouse-related disorders such as obesity, diabetes, and osteoporosis. Further studies are still needed to clarify the molecular mechanism in detail by which dietary kudzu isoflavones improve these diseases.

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Conflict of interest

The author declares no conflict of interest.

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