ABSTRACT: Isoflavones comprise a group of phytoestrogenic polyphenols with antioxidant properties occurring especially in plants of the Leguminosae family, and are consumed by humans mostly in form of soy (Glycine max (L.) Merr.) and products. Soy rich isoflavone products have been promoted recently as foods or supplements with functional or nutraceutical characteristics, especially for the prevention of osteoporosis, for improved cardio-vascular function, and against prostate and breast cancer. However, there is controversial discussion on the bioavailability of isoflavones, a prerequisite for their action in the human body, depending potentially on the type of isoflavonoid, its chemical binding state (aglycon vs. glucosides), and the food matrix, such as the presence of dietary fibre. In addition, dosing and factors altering gut microflora, such as prebiotics, have been suggested to affect utilization of isoflavones.

KEYWORDS: isoflavonoids, health, supplements, food matrix, bioavailability.

INTRODUCTION

Isoflavonoids or isoflavones are plant polyphenols chemically similar to the parent compound isoflavone, occurring predominantly in several Fabaceae varieties, including psoralea, kudzu, fava- and soy bean, and in a variety of nuts, such as peanuts (Table 1). In terms of human food sources, soybeans constitute the major dietary source, with concentrations of isoflavones typically ranging between 1-30 mg/100g (1), however, higher concentrations up to 155mg/100g can be found (Table 1). In Western countries, the intake of isoflavones from dietary sources is estimated at <1 mg/d, while in Asian countries, much higher amounts are consumed within the diet, approx. 20-100mg/d (2).

The most abundant isoflavones are the aglycons genistein, daidzein, glycitein, the genistein precursor biochanin, the daidzein precursor formononetin, and their respective conjugates, the b-glucosides, the 6''-o-acetyl-b-glucosides, and the 6''-o-malonyl-b-glucosides (Figure 1). While in the native soybean, isoflavones are present mainly in form of the malonylgucosides followed by b-glucosides (1), heating or fermentation can lead to higher amounts of the free, more hydrophobic aglycons. Different isoflavone composition patterns may be important, as these can impact the amount of isoflavones absorbed, kinetics of absorption and excretion, and also metabolisation, such as the formation of microbial metabolites, e.g. equol, which have been suggested, based on high antioxidant properties and estrogenic activities, to possess health benefits, possibly even superior compared to the native isoflavones (3).

However, especially soy and soy products rich in isoflavones have been advertised as health promoting agents, for delaying or preventing of a number of chronic diseases, including cardiovascular complications, hormone related cancers, especially breast and prostate, and osteoporosis (3, 4). A health claim, but only with respect to soy protein (i.e. for products containing at least 6.25 g per serving), was approved by the US Food and Drug Administration for its cholesterol lowering effect. Indeed, it has been suggested that the combination of both soy protein and isoflavones results in higher health beneficial effects (2). While information on the content of soy isoflavonoids is available, the data situation on isoflavone bioavailability is scant. However, as will be shown in this review, it has been suggested that factors including composition of soy isoflavones and food matrix could impact uptake and use of isoflavones by the human body, and should therefore be of interest for several stakeholders, including consumers and the food industry.

ISOFLAVONE RICH FOODS AND SUPPLEMENTS

Among the most sold isoflavone containing products range probably soy protein isolate, soy flour, soy milk, tofu, tempeh...
A number of dietary factors have been suggested to impact isoflavonoid bioavailability, however, more studies in this area are needed.

Dietary factors potentially impacting isoflavone bioavailability include dietary fiber, dosing, and type of isoflavone ingested.

ISOFLAVONE DOSING AND BIOAVAILABILITY

For low to medium concentrations, until ca. 35 mg intake, it has earlier been proposed that isoflavone absorption is linearly related to the given dose (17), i.e. following a non-saturable absorption process such as passive diffusion, suggesting also no significant competition between isoflavones for absorption. Medium to higher concentrations however, above ca. 30-40 mg, have meanwhile shown in several studies (e.g. 18, 19) to go along with decreased fractional absorption compared to lower doses. It has been hypothesized that the rate limiting step of absorption is the transfer of the isoflavone from the intestinal bulk to the cell wall (2). Thus, it appears that at low concentrations this is indeed the rate-limiting step of absorption, but that at higher concentrations, other mechanisms also become limiting factors, such as the cleavage rate of the glucosides into the aglycon.

TYPE OF ISOFLAVONES IMPACTING BIOAVAILABILITY

An impact exists of the type of the isoflavone and its binding state, i.e. free aglycon vs. glucoside on the bioavailability. As aglycons do not require further cleavage, these are the most readily available forms for absorption, with uptake starting in the proximal small intestine. Consequently, this form is also less likely to undergo significant bacterial metabolism prior to absorption. This is in contrast to the glucosides, which may be, at least partly, cleaved at the more distal parts of the small or even large intestine.
allowing for additional bacterial metabolism. Even though it is estimated that only about 30-40 percent of the population is able to produce equol, (20), it can be assumed that other bacterial products are formed, such as oDMA, and that these are then available for absorption in the large intestine. Thus, isoflavones present in the more native, glucoside forms, are a) absorbed slightly less rapidly compared to their aglycons (21); b) metabolized into more metabolites (22), and therefore c) appear later in the plasma with a longer half-life, however, the overall bioavailability (especially when taking metabolite forms into account) does not seem to differ between both forms in the majority of carefully conducted studies (19, 21, 22), see also Table 2. It can be speculated that the disadvantage of requiring cleavage prior to absorption is somewhat counterbalanced by a more rapid diffusion of the glucosides to the epithelial cells, due to their higher water solubility. In addition, reduced matrix binding and protective effects of the glucoside forms have also been discussed (24). In contrast to the somewhat controversial aglycon/glycoside discussion, genistein has been consistently reported of having the highest bioavailability based on dose-corrected appearance of plasma values, followed by daidzein, with a lack of data for glycitein (25). The reasons are not fully understood, but it is possible that the more polar daidzein is absorbed and excreted more rapidly, as suggested by its higher urinary recovery rates. It is also possible that daizein is more prone to bacterial metabolism than genistein and therefore less available for direct absorption or absorption following enteric or enterohepatic recirculation, or that genistein glucosides are faster hydrolyzed by LPH (12). Some dietary components have been suggested to potentially alter isoflavone bioavailability. It has been discussed whether prebiotics could alter isoflavone bioavailability, as these nonfermentable carbohydrates may stimulate fermentability and metabolism of isoflavones. This has been suggested for fructooligosaccharides in rats (31), and for inulin in humans (32), and a trend for higher isoflavone and metabolite bioavailability was observed following ingestion of resistant starch and probiotics (33).

FOOD FACTORS IMPACTING ISOFLAVONE BIOAVAILABILITY

As the food matrix can be related to gastrointestinal passage time, and prolonged passage time and/or delayed release of isoflavones has been suggested to increase bacterial metabolites, matrix is expected to impact bioavailability of isoflavones. For example, in a recent study, isoflavone absorption from a liquid juice was faster compared to cookies and chocolate bars (26), similar as for a beverage compared to capsules (27) which was explained by faster stomach emptying and gut transit time. These results are in agreement with the majority of studies investigating soy drinks (Table 2). Whether this rapid absorption goes along with higher bioavailability is questionable, especially when comparing matrices with similar levels of aglycons to glucosides over sufficiently long plasma appearance. A complex matrix that slows down gastrointestinal (GI) passage time has even been suggested to improve isoflavone bioavailability (21), but this remains to be elucidated in further studies.

Table 2. Dietary factors impacting isoflavone bioavailability.

<table>
<thead>
<tr>
<th>Dietary factor</th>
<th>Major findings regarding bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dietary fiber</td>
<td>Negative impact in few studies</td>
</tr>
<tr>
<td>High dosage</td>
<td>Negative effects in most of a dozen studies, especially above 30-40 mg.</td>
</tr>
<tr>
<td>Liquid matrix</td>
<td>Reduced bioavailability or no effect in several studies.</td>
</tr>
<tr>
<td>Supplements vs. complex food matrix</td>
<td>Lineral, some of the few studies suggesting higher, some lower absorption. Results confusing due to confounding factors, e.g. different matrix, varying amounts of isoflavones.</td>
</tr>
<tr>
<td>Higher bioavailability of glucosides vs. aglycons</td>
<td>Many of the over a dozen studies showing no effect, some suggesting higher, some lower absorption. Results confusing due to confounding factors, e.g. different matrix, varying amounts of isoflavones.</td>
</tr>
<tr>
<td>Higher bioavailability of genistein vs. daidzein</td>
<td>Higher bioavailability of genistein in several studies, due to faster clearance and excretion of daidzein.</td>
</tr>
</tbody>
</table>

There is currently limited information that apart from liquid vs. solid foods and the form of isoflavones, i.e. aglycons vs. glucosides, matrix does have a large impact on bioavailability. For example, bioavailability of the daidzein and genistein precursors foromononoin and biochanin A from red clover vs. soy were comparable (28), as was isoflavone bioavailability from biscuits vs. cereal bars (29) and from soymilk powder vs. soy germ (30). However, studies in this area are lacking.

Whether supplements possess better isoflavone bioavailability compared to food items is controversial. While higher bioavailability was found from supplements as opposed to soy cheese (5), higher bioavailability was suggested from various soyfoods vs. tablets (34). In the first study, the amount glycosides vs. aglycons remains uncertain, in the second this was similar between the soyfood and the tablets. It is not always possible to compare studies, as some trials base bioavailability on a single bolus dose, while others investigate bioavailability following a longer dietary intervention. It deems possible that prolonged ingestion increases absorption of isoflavones originating from glycosides such as through increased activity of beta-glucosidase in the intestine. However, as soy products do not necessarily rank high in the consumers’ perception in the Western Culture, isoflavone supplements are regularly used, and likewise ways seeking to improve the absorption of isoflavones.
Microencapsulation with modified cellulose for improved solubility and delayed release of isoflavones and altered metabolism was tried, resulting in higher daidzein compared to genistein absorption, with reasons being unclear [10]. Another way to increase bioavailability seems by complexation with beta-cyclodextrins [35] or by incorporation into pluronic micelles [36]. Another possibility rests in the chemical modification of the isoflavones, e.g. in form of daidzein 7-O triglucosides [37].

CONCLUSIONS

A number of dietary factors have been shown to alter isoflavone bioavailability, including the type of isoflavone and the presence of dietary and fermentable fibre, while others such as aglycon vs. glucoside form, and liquid vs. solid foods are still under discussion. Future studies in this area are warranted with respect to the several potential health beneficial effects of isoflavones, and to improve the quality and characterization of isoflavones in foods and supplements.

REFERENCES AND NOTES