REVIEW

Review of the Factors Affecting Bioavailability of Soy Isoflavones in Humans

Inge Lise Finné Nielsen and Gary Williamson

Abstract: Soy isoflavones have anticarcinogenic, antioxidant, and antiatherosclerotic activities. They also interact with the estrogen receptor, which makes them weak or moderate phytoestrogens. Because of their bioactivity, isoflavone bioavailability has been extensively studied in humans. This review summarizes data from intervention studies in humans, focusing on the factors that affect bioavailability. Summarizing data from 16 studies shows that the maximum concentration in plasma normalized to a constant dose of genistin is \( \sim 1.6 \) times that of genistein, and daidzin is \( \sim 1.8 \)-fold higher than daidzein, whereas the half-life is not significantly different for aglycone and glucoside. There is a wide variation in the reported percentage urinary excretion that is not dependent on dose. Bioavailability is increased by a rapid gut transit time and by low fecal digestion rates and is decreased by a fiber-rich diet. There is no difference in bioavailability between pre- and postmenopausal women. The daily ingestion of soymilk for 1 wk does not affect bioavailability, but daily ingestion for a month increases excretion of equol in women. The factors or habitual diet characteristics that influence equol production are not clear, but equol production is limited with an immature flora. There is no consensus on which source of isoflavones results in the highest isoflavone bioavailability, and published studies present different results, although bioavailability is affected by whether the dose is given as food or drink. In conclusion, it is important to consider the factors affecting bioavailability of isoflavones when designing intervention studies.

Introduction

The interest in soy isoflavones, especially genistein and daidzein, has increased owing to scientific data showing a wide range of biological activities by these phytoestrogens. Much of the interest in soy is related to women’s health due to promising data from clinical studies showing beneficial effects of phytoestrogen-rich soy protein on a range of hormone-dependent conditions such as breast cancer, osteoporosis, postmenopausal symptoms, and hypercholesterolemia (1–5).

To optimize the beneficial effects in target tissues and reduce the risk of adverse effects due to their estrogenic properties, it is important to know which factors might influence isoflavone absorption and excretion. Several human studies have been performed investigating isoflavone bioavailability as measured in plasma, urine, and feces after ingestion of soy products or pure compounds. Different factors have been suggested to influence the bioavailability of isoflavones, but the results are not always in agreement, probably due to the use of different study designs, isoflavone sources, or food matrices between and within studies. The focus of this review is on the compounds genistein and daidzin and their glucosides genistin and daidzein (Fig. 1) because these are the only isoflavones for which enough information is available to obtain a general consensus on factors affecting their bioavailability. The bioavailability of isoflavones compared with other flavonoids has been reviewed (6). Most of the data used for this review are compiled in Table 1.

Route and Mechanism of Absorption

Genistein and daidzein are present as glucosides in soy and many unfermented foods. As a prerequisite for absorption, the sugar must be removed from the isoflavone molecule at some point during digestion. It was originally thought that deglycosylation was only catalyzed by colon microflora, but it is now known that most deglycosylation is carried out by the enterocyte brush border enzyme lactase phlorizin hydrolase (LPH) (7). There is some absorption in the small intestine, as shown by the appearance of a small plasma peak after approximately 1 h (8). The main peak always appears after
5–8 h, which is due to enterohepatic recycling of conjugates, first-time absorption in the colon, or a combination of both. Most of the absorbed genistein and daidzein is conjugated in plasma, although a proportion is present in plasma as the aglycone (never the glucoside); the proportion of aglycone decreases with time owing to further conjugation (Fig. 2) (9). In approximately 40% of the population, specific colon microflora (10) are present and can convert daidzein into equol (11). The ability to produce equol in these subjects may improve the outcome in studies involving measuring health benefits from isoflavones (10).

Factors Influencing Bioavailability

Aglycone versus Glycoside

The comparison between absorption of aglycones and glucosides is more complex than it first appears because the conversion of glucoside into aglycone implies a different food matrix, and apparently conflicting results are reported in the literature. However, compilation of the data from several different studies as shown in Figs. 3 and 4 allows some conclusions to be drawn. For equivalent doses, the $C_{\text{max}}$ of genistin is $\sim 1.6$ times that of genistein, and the $C_{\text{max}}$ of daidzin is $\sim 1.8$-fold more than daidzein, whereas the half-life is not significantly different for aglycone and glucoside. This increase in absorption of the glucosides may be accounted for by the lower solubility of the aglycones during digestion compared with the glucosides. Furthermore, the glucosides are more stable and water soluble than the aglycones, and so the sugar moiety may provide convenient delivery to the brush border $\beta$-glucosidase LPH. A higher bioavailability, assessed as the percent of dose excreted through urine, was observed after ingestion of isoflavones from the fermented soy product tempeh (containing mainly aglycones) than after ingestion of nonfermented soybean pieces (containing the naturally

![Figure 1. Chemical structures of isoflavones.](image)

![Figure 2. Hypothesis for the mechanism of absorption of isoflavones in the small intestine. LPH, lactase phlorizin hydrolase; glc, glucose; UGT, UDP-glucuronosyltransferase; glcA, glucuronic acid. Absorbed isoflavone glucuronides are transported into the blood, from where they can be excreted by the kidney or undergo enterohepatic recycling after transport by the liver into the bile. In addition, isoflavones that are not absorbed, either in the glucoside or the (putative) effluxed glucuronide form, are deglycosylated by the gut microflora. Genistein can then be absorbed in the colon. Daidzein can either be absorbed in the colon or can be converted into equol by the gut microflora of some individuals. MRP2, multidrug resistant protein-2 (ABCC2). UDP, uridine diphosphate.](image)
### Table 1. Summary of Human Studies Measuring Isoflavone Bioavailability via Plasma, Urine, or Feces

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Isoflavone Dose and Design</th>
<th>Sampling and Units</th>
<th>Cmax (µM)</th>
<th>tmax (h)</th>
<th>t1/2 (h)</th>
<th>AUC (µM h)</th>
<th>Urinary Excretion (± SD)</th>
<th>Fecal Excretion (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose; two studies to study absorption and excretion separately; 6-day washout</td>
<td>Debitetted-soy flour; D:G ratio: 1:1.3 (mol)</td>
<td>Absorption study Plasma: 0-8 h</td>
<td>D: 3.14 ± 0.36</td>
<td>G: 4.09 ± 0.94</td>
<td>D: 7.42 ± 0.74</td>
<td>G: 8.00 ± 0.68</td>
<td>D: 47.1 ± 0.06</td>
<td>G: 57.4 ± 1.27</td>
</tr>
<tr>
<td>Single dose; two studies to study absorption and excretion separately; 6-day washout</td>
<td>Isoflavone extract or treated with β-glucosidase</td>
<td>D: 3.3 ± 0.2</td>
<td>G: 0.8 ± 0.1</td>
<td>D: 6.7 ± 0.4</td>
<td>G: 7.4 ± 0.6</td>
<td>D: 50 ± 0.3</td>
<td>G: 44 ± 0.1</td>
<td></td>
</tr>
<tr>
<td>Single dose; two studies to study absorption and excretion separately; 6-day washout</td>
<td>Purified isoflavone aglycones and aglycone-glucosides</td>
<td>D: 0.0624</td>
<td>G: 0.0256</td>
<td>D: 0.53 ± 0.21</td>
<td>G: 0.53 ± 0.33</td>
<td>D: 8.3 ± 0.2</td>
<td>G: 8.3 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>Single dose, crossover; 3 study days; minimum 2-wk washout</td>
<td>Soybean milk powder; D:G ratio: 1.3 (mol)</td>
<td>Plasma: 0-24 h</td>
<td>D: 1.43 ± 0.77</td>
<td>G: 3.74 ± 3.5</td>
<td>D: 4.98 ± 0.12</td>
<td>G: 10.6 ± 2.2</td>
<td>D: 8.3 ± 2.6</td>
<td>G: 8.3 ± 0.2</td>
</tr>
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<td>Single dose, crossover; 3 study days; minimum 2-wk washout</td>
<td>Soy germ, each giving 4.5 µg/kg BW</td>
<td>Urine: 0-72 h</td>
<td>0.08 ± 1.0</td>
<td>0.031 ± 0.07</td>
<td>0.071 ± 0.13</td>
<td>0.048 ± 0.08</td>
<td>5.35 ± 0.85</td>
<td>6.3 ± 0.85</td>
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<td>Soybean milk powder; D:G ratio: 1.3 (mol)</td>
<td>Plasma: 0-72 h</td>
<td>1.38 ± 0.10</td>
<td>0.31 ± 0.07</td>
<td>0.71 ± 0.13</td>
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</tbody>
</table>

(Continued on next page)
## Table 1. Summary of Human Studies Measuring Isoflavone Bioavailability via Plasma, Urine, or Feces (Continued)

<table>
<thead>
<tr>
<th>Number and Characteristics of Subjects</th>
<th>Study Design</th>
<th>Source</th>
<th>Isoflavone Dose and Design</th>
<th>Sampling and Units</th>
<th>$C_{\text{max}}$ (µM)</th>
<th>$t_{\text{max}}$ (h)</th>
<th>$t_{1/2}$ (h)</th>
<th>AUC (µM × h)</th>
<th>Urinary Excretion (% ± SD)</th>
<th>Fecal Excretion (% ± SD)</th>
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</thead>
<tbody>
<tr>
<td>35 Asian + 33 Caucasian (18–43 yr) (18)</td>
<td>Single-dose trial</td>
<td>Soybean milk powder</td>
<td>1.2 mg = 4.57 µmol/kg BW</td>
<td>Plasma: no collection, Urine: 0–24 h, Feces: 0 h</td>
<td>GTT† Results: mean ± SE</td>
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<tr>
<td>10† comprising 5 premenopausal (39 ± 3.6 yr; 74.0 ± 5.6 kg), 5 postmenopausal (54 ± 4.2 kg) (27)</td>
<td>Single dose, RT, on 3 study days; minimum 1-wk washout</td>
<td>Toasted soy nuts</td>
<td>1) D: 66; 2) D: 13.2; 3) D: 26.4; G: 39.2 mg measured as aglycones</td>
<td>Plasma: 0–48 h, Urine: 0–24 h, Feces: 0 h</td>
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<tr>
<td>12–13 (premenopausal) (43)</td>
<td>Not indicated</td>
<td>Soymilk</td>
<td>0.45 (n = 27)</td>
<td>Plasma: 0–72 h, Urine: 0–72 h</td>
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<tr>
<td>20 (premenopausal)</td>
<td>Single dose, RT, crossover, on 3 study days; minimum 2-wk washout</td>
<td>Soymilk, TVP, tempeh</td>
<td></td>
<td>Plasma: 0–96 h, Results: mean ± SD</td>
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</tbody>
</table>

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† = Not indicated. The number of subjects is given in parentheses. The study designs are specified in the table. The isoflavone dose and design, sampling and units, $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, AUC, and urinary and fecal excretion percentages are provided. The results are mean ± SE.
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Subjects</th>
<th>Description</th>
<th>Treatment Details</th>
<th>Results</th>
</tr>
</thead>
</table>
| **Kinako** | 70 kg (23-54 yr; median weight 70 kg) | Soybean milk powder; D:G ratio: 1:1.3 (mol) | Plasma: 0–24 h, Urine: 0–24 h, Feces: 0 h | Low excretion (n = 5), Low excretion (n = 2),  
1) D: 0.76 ± 0.12  
2) 1.26 ± 0.27  
3) 1.55 ± 0.24  
4) 1.22 ± 0.47  
5) 1.0762 ± 0.12  
6) 2.93 ± 0.27  
7) 3.01 ± 0.32  
8) 4.5 ± 0.47  
9) 7.02 ± 0.76  
10) 4.95 ± 0.13  
11) 6.62 ± 1.36  
12) 3.32 ± 1.13  
13) 9.02 ± 1.0  
14) 4.59 ± 0.5  
15) 7.02 ± 0.76  
16) 4.95 ± 0.13  |
| **Soy protein beverage** | 60.2 ± 6.4 kg (35-47 yr; median weight 70 kg) | Soy protein beverage | Plasma: 0–24 h, Urine: 0–24 h, Feces: 0 h | Low excretion (n = 5), Low excretion (n = 2),  
1) D: 0.76 ± 0.12  
2) 1.26 ± 0.27  
3) 1.55 ± 0.24  
4) 1.22 ± 0.47  
5) 1.0762 ± 0.12  
6) 2.93 ± 0.27  
7) 3.01 ± 0.32  
8) 4.5 ± 0.47  
9) 7.02 ± 0.76  
10) 4.95 ± 0.13  
11) 6.62 ± 1.36  
12) 3.32 ± 1.13  
13) 9.02 ± 1.0  
14) 4.59 ± 0.5  
15) 7.02 ± 0.76  
16) 4.95 ± 0.13  |

**Notes:**  
- Dose ingested after 2 and 7 days of soymilk consumption.  
- GTT determined as time for 1 g carmine red ingested with dose to be completely excreted through feces.  
- GTT determined as time for 12 of 16 glass beads ingested with dose to appear in the stools.  
- Grouped according to fecal genistein disappearance phenotype (23).
Figure 3. Relationship between $C_{\text{max}}$ and dose for 16 studies shown in Table 1. Correlation coefficients are genistein, $r^2 = 0.50$; daidzein, $r^2 = 0.87$; genistein, $r^2 = 0.73$; and daidzein, $r^2 = 0.72$.

Figure 4. Summary of factors affecting isoflavone bioavailability. ∗: No uniform consensus among available literature. ↑: Increased level. ↓: Decreased level. Solid arrows show the general direction of the factors in the box on the pharmacokinetic curve and are intended as a guide to the observations in the literature.
occurring isoflavone glucosides) (12). This result is probably at least partially due to a food matrix effect rather than attachment of a sugar per se. The observation was partly supported by Izumi et al. (13). Richelle et al. (14) found similar AUCs for isoflavone glucosides and aglycones provided from the same source with or without previous hydrolysis, and this finding was supported (15) using purified compounds. This probably indicates that LPH (or subsequent colon microflora) deglycosylation, although an essential step for absorption, is not a rate-limiting step.

The time of the maximal plasma concentration after administration (t\text{max}) also depends on the presence of the glucose moiety. In the studies by Izumi et al. (13) and Setchell et al. (16), faster t\text{max} values were measured for the aglycones alone, whereas Richelle et al. (14) found similar t\text{max} for the aglycones and their respective glucosides. In the studies by Richelle et al. and Izumi et al., all subjects ingested all treatments, eliminating the large variance that has been detected in t\text{max} between subjects (17), whereas, in the study by Setchell et al. (16), the subjects ingested one treatment each.

When women were fed pure genistin, daidzein, or their respective aglycones, more equol was excreted after ingestion of the glucoside daidzin than the aglycone daidzein (15,16). This is in line with Zheng et al. (18), where a higher fecal disappearance rate constant was measured for genistin than daidzein in both Asian and Caucasian subjects (18). The relative urinary recovery of isoflavones was glycine = daidzein > genistin in one study (19) and daidzein > glycine = genistin in another (14).

Dose

A compilation among several studies shows that equivalent doses of genistin and daidzein lead to similar C\text{max} values and that the correlation between dose and C\text{max} is reasonably good considering the diversity of the study conditions (Fig. 3). For the area under curve (AUC), there is no apparent correlation with dose when all studies are analyzed together. For doses less than 3.5 \text{ µmol/kg body weight}, the correlation coefficients for AUC against dose are genistin, r\text{2} = 0.27; daidzein, r\text{2} = 0.19; genistin, r\text{2} = 0.34; and daidzein, r\text{2} = 0.12. Urinary excretion depends on the compounds administered: genistin was 20% of dose (range = 5–39%), independent of dose, r\text{2} = 0.01; n = 18), daidzein was 36% (range = 15–62%), independent of dose, r\text{2} = 0.27; n = 18), genistin was 11% (range = 8–18%), independent of dose, r\text{2} = 0.67; n only = 3), and daidzein was 34% (range = 26–50%, independent of dose, r\text{2} = 0.39; n only = 4). There is a larger distribution volume (V\text{d}) for daidzein than for genistin with V\text{d} of 236 l and 161 l, respectively (16).

From the studies summarized in Table 1, the average C\text{max}, t\text{max}, t\text{1}/2, AUC, and urinary and fecal excretions normalized to ingestion of 1 \text{ µmol/kg body weight} are shown in Table 2.

<table>
<thead>
<tr>
<th>Isoflavone</th>
<th>C\text{max}</th>
<th>t\text{max}</th>
<th>t\text{1}/2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genistin</td>
<td>0.64 ± 0.11</td>
<td>5.7 ± 1.8</td>
<td>9.5 ± 3.2</td>
</tr>
<tr>
<td>Daidzein</td>
<td>0.50 ± 0.16</td>
<td>6.2 ± 1.5</td>
<td>7.7 ± 3.3</td>
</tr>
<tr>
<td>Genistin</td>
<td>1.02 ± 0.27</td>
<td>6.8 ± 1.4</td>
<td>9.5 ± 1.7</td>
</tr>
<tr>
<td>Daidzein</td>
<td>0.88 ± 0.19</td>
<td>7.5 ± 1.6</td>
<td>7.0 ± 1.6</td>
</tr>
</tbody>
</table>

\text{*}: Calculated as after ingestion of 1 \text{ µmol/kg body weight.}
\text{b}: P = 0.14 between C\text{max} for genistin and daidzein.
\text{c}: P = 0.24 between t\text{1}/2 for genistin and daidzein.
\text{d}: P = 0.35 between C\text{max} for genistin and daidzein.
\text{e}: P = 0.44 between t\text{1}/2 for genistin and daidzein.

Different Isoflavone Sources

No difference was detected between the bioavailability of isoflavones from soymilk powder or soy germ (19) (Table 1). However, when comparing soymilk, texturized vegetable protein (TVP), and tempeh in men and pre- and postmenopausal women, there was a significantly higher percentage of the genistin dose excreted through urine after ingestion of soymilk than after TVP, an effect that only was detected in women (20) (Table 1). Furthermore, in premenopausal women, an even higher urinary recovery of genistin was detected after tempeh consumption than after soymilk. In men, no differences were detected in the bioavailability of genistin or daidzein among the three food sources (20). These findings were not in agreement with studies by Xu et al. (21) and Tew et al. (22) on premenopausal women. Xu et al. (21) found no difference in the bioavailability of daidzein or genistin from cooked soybeans, TVP, tofu, or tempeh, and Tew et al. (22) found similar urinary excretion of genistin after ingestion of tofu or TVP. In a study by Hutchins et al. (12), a higher bioavailability, assessed as the percent of dose excreted in the urine, was observed after ingestion of isoflavones from the fermented soy product tempeh (containing mainly aglycones) than after ingestion of non-fermented soybean pieces (containing the naturally occurring isoflavone glucosides). However, this difference could very well be due to a more difficult release of the compounds from the soybean pieces than from the processed product as observed for most other plant compounds.

Among equol producers, Faughnan et al. (20) observed a much higher urinary excretion of equol after ingestion of tempeh than soymilk or TVP. The solid food matrix of tempeh might protect daidzein from degradation until it reaches the large intestine, where it may be metabolized to equol by the microflora. The observation that a food source consisting of a mixture of isoflavone glucosides and aglycones results in the highest equol production is surprising because it was found in the studies by Setchell et al. (16) and Zubik and Meydani (15) that ingestion of daidzin resulted in a higher equol production than ingestion of the aglycone daidzein alone.
Frequency of Ingestion

After 2-wk washout or after 7 days of soy consumption (50 mg isoflavones per day, 0.4 mg aglycone per kilogram body weight, Table 1), no significant differences were detected in the pharmacokinetics of $[^{13}\text{C}]$daidzein or $[^{13}\text{C}]$genistein (23). Furthermore, the frequency of soy milk powder feeding had no significant effect on the proportion of genistein and daidzein metabolites detected in plasma or urine when given as a single dose on two separate days 1 wk apart or after 6 days of consecutive feeding (18,24). However, Lu and Anderson (26) showed that, after 1 mo of daily soy milk feeding, the urinary excretion of genistein and daidzein was decreased, whereas that of equol was increased.

Gender

Several studies have been performed comparing the bioavailability of isoflavones between genders, demonstrating no difference in the percentage of dose excreted through urine or the plasma pharmacokinetics of genistein or daidzein or their phase II enzyme metabolites (19,20,25). However, in a long-term feeding study by Lu and Anderson (26), differences were detected between genders, with an initially higher urinary excretion of isoflavone conjugates in women than in men. Over time the urinary excretion of genistein and daidzein decreased and that of equol increased in women, whereas it remained constant in men; furthermore, the elimination rate became progressively shorter in women and longer in men. In the study by Faughnan et al. (20), a tendency was detected for more equol producers among postmenopausal women than among premenopausal women and men, which suggests that gender and age might be determinants for the intestinal metabolism of isoflavones. This tendency was not supported in a study by Lampe et al. (11), where no differences were detected in the prevalence of equol excreters between genders.

Age

No differences were observed in the single-dose pharmacokinetics of either genistein or daidzein between pre- and postmenopausal women (Table 1) (20,27). One significant age-related difference is lower plasma and urine levels of equol during the first months of life compared with during adulthood, which probably is due to an immature gut flora (28).

Microfloral Subgrouping and Gut Transit Time

The fecal excretion of genistin was $\sim$3% (range = 0.3–9%) but with no correlation to dose $r^2 = 0.01$ and was similar for daidzin, 3% (range = 0.6–6%, with no correlation with dose $r^2 = 0.03$). Some studies reported large interindividual differences; for example, Xu et al. (29) found that 2 of 7 subjects exhibited a 10 to 20 times higher fecal excretion of isoflavones than the remaining 5. The two subjects showed likewise a slightly but not equally higher urinary excretion and plasma level of the compounds reflecting a higher systemic bioavailability. This subgrouping was not confirmed in a study by Watanabe et al. (30), but it could have been missed because again only seven subjects were examined.

A correlation was seen among a rapid gut transit time, fecal excretion, and urinary excretion, reflecting a higher bioavailability (18,29). The increased bioavailability was determined in subjects who had gut flora that degraded genistein more slowly in vitro than the gut flora of the remaining subjects (18). One logical explanation could be that the isoflavones are available for absorption for a longer period of time within these subjects due to the slow degradation rate, which leads to a higher bioavailability even though their gut transit time was increased. However, this hypothesis needs to be confirmed. The subgrouping of subjects found by Zheng et al. (18) was evident within the group of Asian women ($n = 35$) and between Asian and Caucasian women ($n = 32$). The group of Caucasian women showed homogenous and low urinary and fecal levels and a high gut transmission time independently of the rate by which their gut flora degraded genistein.

It was hypothesized by Setchell et al. (31) that equol production was influenced by several factors such as the intestinal microflora composition, gut transit time, and the redox potential of the colon. During the first months of life, plasma and urine levels of equol have been found to be significantly lower than in adults, as stated above (28).

Food Matrix and Diet

The isolated effect of a fiber-rich food matrix on isoflavone bioavailability was investigated; the recovery of urinary genistein from tofu or TVP was lower when ingested with 40 g wheat fiber than with 15 g dietary fiber. However, the total urinary excretion of daidzein was not affected by the ingestion of a high-fiber diet (22), indicating that equol production in these subjects would not be reduced due to the limited bioavailability of daidzein. Epidemiological studies have been performed investigating the effect of habitual diet on equol production. Adlercreutz et al. (32) found that the intake of total fat and meat and the dietary ratio of fat to fiber correlated with the urinary excretion of equol, and consequently it was hypothesized that subjects consuming large quantities of meat and fat and low quantities of fiber might harbor the gut flora required for equol production. However, other studies have shown that equol production is more prevalent in subjects with a high consumption of carbohydrates and dietary fiber and a low dietary fat-to-fiber ratio (11,33). A recent study (34) showed that neither plasma levels of daidzein nor urinary excretion (33–34% of dose) were altered by different food matrices (cookies, chocolate bars, and juice). Peak genistein concentrations in blood appeared
earlier when consumed from a liquid matrix (compared with a solid matrix) but with lower urinary recovery.

**Effect of Processing and Storage**

Several factors have been reported to influence the amount of isoflavones actually consumed, therefore, indirectly influencing bioavailability. There is a seasonal variation in isoflavone levels (35). Surprisingly, storage of soybeans increases the levels of isoflavones; in soybeans stored at room temperature for up to 3 yr, all glucosides (daidzein, glycycin, and genistin) increased, all aglycones increased but to a lesser extent, and malonylglucosides decreased (36). However, in soymilk stored at room temperature, genistin is rapidly lost (37). The thermal stability of daidzein is higher than that of glycitein or genistein. For the glycosides, daidzein is more stable than genistin, which is in turn more stable than glycitin (38).

Processing can have a direct effect on bioaccessibility. For example, the amount of (80% aqueous methanol) extractable isoflavones decreased after extrusion of a corn–soy mixture (39). Micellarization is required for optimal bioaccessibility (38). The thermal stability of daidzein is higher than that of glycine or genistein. For the glycosides, daidzein is more stable than genistin, which is in turn more stable than glycitin (38).

**Isoflavone Conjugates in Blood**

Genistein-glucuronide exhibited a later $t_{\text{max}}$ than genistein-sulfate, daidzein-sulfate, and daidzein-glucuronide. Both genistein conjugates showed longer $t_{1/2}$ than the corresponding daidzein conjugates (25) (Table 1).

**Conclusions**

We have made some generalizations based on published data to construct a theoretical pharmacokinetic curve and the influence of exogenous factors on the shape and magnitude of this curve (Fig. 4). It is designed to aid in understanding rather than provide a strict quantitative prediction of pharmacokinetic changes. Clearly, there are many factors that can influence bioavailability, and these factors should be considered if bioavailability is to be optimized in future intervention studies.

**Acknowledgments and Notes**

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