The Pharmacokinetics of \textit{S}(-)-Equol Administered as SE5-OH Tablets to Healthy Postmenopausal Women$^{1,2}$

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Abstract

The soy isoflavone metabolite, \textit{S}(-)-equol, has selective affinity for estrogen receptor (ER)$\beta$ and also antagonizes in vivo the action of dihydrotestosterone. It is therefore of interest as a potential new therapeutic agent in hormone-dependent conditions and is under development as a nutraceutical. Our objective in this study was to define the pharmacokinetics of natural \textit{S}(-)-equol after administration of SE5-OH, a newly developed \textit{S}(-)-equol supplement made by incubation of the equol-producing bacterium Lactococcus garvieae with soy germ isoflavones. In a single-center, open-label, randomized, 2-period crossover design study, the pharmacokinetics of \textit{S}(-)-equol administrated as single-bolus oral doses of 10 and 30 mg in the form of SE5-OH tablets was determined in 12 healthy postmenopausal women. \textit{S}(-)-equol was measured in plasma and urine collected at timed intervals over a 48-h period postdosing using tandem MS. Equol-producer status was also determined after a soymilk challenge conducted after the pharmacokinetic sampling was complete. \textit{S}(-)-equol was rapidly absorbed after oral administration and attained high plasma concentrations, with a plasma elimination half-life of 8 h. The maximum plasma concentration/dose, area under the plasma concentration-time curve from time 0 to infinity/dose, and the fraction of dose excreted in urine ($\%f_{\text{e,u}}$) were similar for the 2 doses, indicating a dose-proportional response in total \textit{S}(-)-equol pharmacokinetics. The systemic bioavailability of \textit{S}(-)-equol was very high, as the $\%f_{\text{e,u}}$ was 82% for both doses, which is greater than published data for the soy isoflavones daidzein and genistein. Three participants were determined to be equol-producers, representing a 25% frequency, and equol-producer status had no effect on natural \textit{S}(-)-equol pharmacokinetics. J. Nutr. 139: 2037–2043, 2009.

Introduction

Equol [7-hydroxy-3-(4’-hydroxyphenyl)-chroman], a nonsteroidal estrogen, is a major intestinally derived bacterial metabolite of daidzin (1–3), one of the principal isoflavones found in soybeans and most soy foods (4,5). It has been proposed that the ability to make equol when soy is consumed may be an important factor in determining the clinical efficacy of a soy diet, the so-called “equol hypothesis” (6). Equol can occur in 2 enantiomeric forms, \textit{S}(-)-equol and \textit{R}(+)-equol, but our recent studies have shown that intestinal bacteria are enantioselective in their synthesis, producing exclusively \textit{S}(-)-equol when incubated in vitro with either soy isoflavones or with pure daidzein (7). Furthermore, when humans and most animal species consume soy isoflavones in the form of soy foods, or as the pure daidzein, it is the \textit{S}(-)-equol diastereoisomer that appears in plasma and is excreted in urine (7). The physiological relevance of this finding is that \textit{S}(-)-equol, unlike \textit{R}(+)-equol, has selective affinity for estrogen receptor (ER)$\alpha$ (7–9) and is thus by definition similar in characteristics to a selective ER modulator, whereas \textit{R}(+)-equol has negligible affinity for either ER$\alpha$ or ER$\beta$ (7). Both enantiomers, however, are able to antagonize the action of dihydrotestosterone (10). In this regard, equol possesses the unique ability to potentially act both as a selective ER modulator and as a selective androgen modulator and therefore may be of value in the prevention and/or treatment of a number of estrogen-dependent and androgen-mediated conditions.

1 Supported by an industry contract from the Otsuka Pharmaceutical Company, Tokyo, Japan.
2 Author disclosures: K. D. R. Setchell discloses a financial relationship as a consultant to the Otsuka Pharmaceutical Company Ltd, Tokyo, Japan. X. Zhao has no conflicts of interests to declare. S. E. Shoaf and K. Ragland are employed by OPDC, a subsidiary of the Otsuka Pharmaceutical Company, Japan. All bioanalytical analyses were performed without knowledge of the treatment groups by the investigators.
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Equol is not always formed in response to a soy food challenge (3). When we first reported the presence of equol in human urine (1), we observed that not all adults fed soy foods produced equol (3,11), an observation that has since been corroborated by others (12–14). Typically, only 20–30% of adults living in Western countries seem to produce equol when consuming soy diets containing isoflavones, whereas the frequency of equol-producers in Asian countries, where soy is more commonly consumed, is much greater at 50–60% (11). The reason for the difference among individuals in propensity to make equol in response to a soy challenge remains unclear (6,15), except that a crucial factor is the requirement of specific equol-producing bacteria in the intestine (7). This is evidenced by the fact that infants who are born with a sterile gut do not begin to produce equol before the age of 4–6 mo even when fed soy infant formula from birth (16–18) and germ-free animals fed commercial rodent diets that typically contain soy protein (19) also do not produce equol (20). Furthermore, treatment of monkeys with some antibiotics reduces plasma equol concentrations (21). A concerted search for the equol-producing bacteria has more recently led to the discovery of several strains of bacteria that are capable of producing equol in vitro when incubated with soy isoflavones (22–28). One of these bacterial strains, *Lactococcus garvieae* (29), has been shown to efficiently convert daidzin to *S*-(-)equol (22) and this bacterial culture has now been used to produce a natural *S*-(-)equol-containing supplement, referred to as SE5-OH, for development as a nutraceutical (30). The availability of an equol-rich supplement now offers the possibility of investigating more directly the potential benefits of *S*-(-)equol (6), particularly in those adults unable to synthesize *S*-(-)equol when consuming soy foods. As part of an ongoing development program, we report the results from a study aimed at determining the pharmacokinetics of natural *S*-(-)equol following its administration as the SE5-OH equol-containing supplement in healthy postmenopausal women. Knowledge of the pharmacokinetics of *S*-(-)equol is fundamental to optimizing the therapeutic dose of *S*-(-)equol in the design of future clinical studies aimed at evaluating its effectiveness in hormone-dependent conditions.

**Materials and Methods**

**Description of the SE5-OH supplement.** The SE5-OH supplement containing *S*-(-)equol, described previously (30), was manufactured by the fermentation of soy germ with *L. garvieae* using a patented and proprietary process by the Otsuka Pharmaceutical Company. Tablets were compressed from the fermented soy product and mixed with excipients for tablet stability and dissolution. The supplement formulated in 250-mg tablets contained 5 mg of *S*-(-)equol. Each tablet also contained 30–40% protein, 10–15% fat, 25–30% carbohydrate, and 5–15% fiber and a description of the product was recently published together with data on its subchronic toxicity and genotoxicity (30).

**Study design.** This dose-response pharmacokinetic study was an open-label, randomized, 2-period, crossover design conducted in healthy postmenopausal women aged 45–65 y. The clinical arm of the study was conducted at Community Research (Cincinnati, OH) on an in-patient basis and according to a protocol that was reviewed and approved by the internal Institutional Review Board. Study participants were recruited and screened from the local community through advertisements or from a database of participants that had previously volunteered for similar research studies. Screening was conducted within 2 wk of enrollment. Only women with a BMI <30 and with confirmed postmenopausal status, as evidenced from a serum follicle-stimulating hormone concentration of >50 μIU/L and serum estradiol of <100 pmol/L, were enrolled. Health was determined by a medical history, physical examination, and electrocardiogram. The following clinical chemistries were measured by routine laboratory methods: serum total protein and albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, creatinine, and total and direct bilirubin, thyroid stimulating hormone and thyroxine and triiodothyronine. Hematological tests included a complete blood count. Participants were not to have taken any prescription or over-the-counter estrogen, estrogenprogestin, or phytoestrogen products within 14 d prior to dosing. Prior use of antibiotics in the preceding 3 mo was an exclusion criterion. All participants were instructed to abstain from consuming soy-, flax- or lignan-containing foods and beverages for 7 d prior to dosing and to abstain from xanthine-containing foods and beverages, grapefruit and grapefruit juice, and alcohol for 3 d prior to and during the study.

Participants reported to the investigational site to begin the inpatient procedures on the night before administration of the SE5-OH supplement and then fasted overnight. On the following morning (d 1) a baseline (time 0 h) blood sample (10 mL) was collected. They were randomized into 1 of 2 treatment sequences to be given orally the SE5-OH *S*-(-)equol–containing supplement as either the 10-mg dose followed 48 h later by the 30-mg dose, or as the 30-mg dose followed by the 10-mg dose. A single dose of either 2 SE5-OH tablets or 6 SE5-OH tablets, taken with 240 mL of water, was separated by a 48-h period between administrations. No food or liquid was permitted for 4 h after administration. Sequential blood samples (10 mL) were then collected after 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 16, 24, 36, and 48 h postadministration. Blood was collected into potassium EDTA-containing tubes, gently mixed, and then centrifuged at −4°C for 10 min at 1200 x g to obtain plasma for measurement of the *S*-(-)equol concentration. The plasma samples were then stored at −20°C or below. Four 12-h pooled urine collections were obtained over the next 48 h for the measurement of total *S*-(-)equol excretion. During each collection interval, urine specimens were kept refrigerated at 4°C and at the end of each collection interval, the 12-h samples were pooled and the volume measured before small aliquots were taken and stored at −20°C until required for analysis.

On d 3, the participants fasted overnight and were then given the second assigned dose of SE5-OH supplement. Sequential blood samples and 12-h urine collections were obtained over the next 48 h. Throughout the study, safety was assessed by monitoring any reported adverse events, and from vital signs. Furthermore, physical examinations and safety laboratory tests were conducted at screening and upon completion of the study.

**Assessment of equol-producer status.** After completion of the pharmacokinetic study of the SE5-OH supplement, each participant was evaluated for her ability to produce *S*-(-)equol in response to a soy food challenge, the goal being to define her equol-producing status (11). This test was conducted on an outpatient basis starting on d 5 and exactly as defined previously by Setchell and Cole (11). After discharge from the clinic, participants were instructed to consume 2 × 240-mL glasses of soymilk, 1 in the morning and 1 in the evening, for 3 consecutive days. On the morning of d 6, the participants reported to the clinic and 2–4 h later a spot urine sample was collected and frozen at −20°C until it was analyzed. The participants were classified as equol-producers if the urine log10 ratio *S*-(-)equol/daidzein was <−1.75 after a 3-d challenge with soy foods (11).

**Plasma and urine *S*-(-)equol assay.** Plasma and urine samples were analyzed for total *S*-(-)equol concentrations using reverse-phase HPLC coupled to liquid chromatography-tandem MS with stable-isotope dilution analysis (31). After addition of (±)2,3,4,13C4*equol as the internal standard (50 ng/204 nmol) to plasma (0.25 mL) and dilution with 0.5 mL triethylamine sulfate, the sample was heated to 64°C and *S*-(-)equol and its conjugates were extracted by solid-phase extraction on a C18 Bond Elut cartridge as described elsewhere (11). Urine (0.1 mL), or urine diluted with water (1:3–1:30; vol:vol) based on the anticipated *S*-(-)equol concentration, was taken for analysis. The plasma extracts and urine samples were then hydrolyzed overnight using a mixed *β*-glucuronidase and sulfatase enzyme. *S*-(-)equol was then extracted and isolated by solid-phase extraction before conversion to the dansylated
derivative by reaction dansyl chloride (32). The derivatized samples were then quantified by liquid chromatography-tandem MS with multiple reaction ion monitoring of the positively charged molecular ion transition mass/charge ratio (m/z) 709 → 170 resulting from cleavage of the dansyl group. The (±)[2,3,4-13C]-equol internal standard was simultaneously monitored from the analogous transition m/z 712 → 170. S-(-)equol was quantified from the peak area ratio of m/z 709 → 170 transition to m/z 712 → 170 transition and interpolation against a calibration curve constructed from known concentrations of S-(-)equol to the same concentration of (±)[2,3,4-13C]equol. The assay was conducted under good laboratory practice and with inclusion of multiple quality control samples generated from a pool of plasma with known concentrations of S-(-)equol added. The plasma assay was linear in the range of 1–500 μg/L (4–2060 nmol/L) and the lower limit of quantification was set at 1.00 μg/L (4 nmol/L). The method had a lower limit of detection of 0.1 μg/L (0.4 nmol/L). The intersassay CV determined from replicate analysis of QC plasma samples was 5.2% at 50 μg/L (206 nmol/L) and 9.2% at 200 μg/L (824 nmol/L) based on the analysis of 3 samples of each in 10 separate analytical batches. The urine assay was linear in the range of 0–400 μg/L (0–1648 nmol/L). S-(-)equol and the interassay CV determined from replicate analysis of QC samples of urine was 2.7% at 100 μg/L (412 nmol/L) and 3.5% at 400 μg/L (1648 nmol/L) in 5 analytical batches.

Pharmacokinetic parameters. The actual plasma sample times were used for pharmacokinetic evaluations. S-(-)equol concentrations below the lower limit of quantification were assigned a value of zero. The plasma drug concentration time data were analyzed using noncompartmental methods (33). The following parameters were determined for plasma drug concentration time data were analyzed using noncompartmental methods (33). The following parameters were determined for plasma drug concentration time data: maximum plasma concentration (Cmax), time of the Cmax (tmax), area of the plasma concentration-time curve from time 0 to the time (t) of the last measurable plasma concentration (AUCt), terminal-phase elimination half-life (t1/2,z), Cmax/dose, AUCt/dose, and total S-(-)equol pharmacokinetics. Plasma S-(-)equol pharmacokinetics. The plasma S-(-)equol concentration time profiles showing the appearance and disappearance of S-(-)equol in the first 12 h following oral administration of the 10-mg (Fig. 1A) and 30-mg (Fig. 1B) SE5-OH doses were similar among the 12 women and showed a rapid appearance of S-(-)equol in plasma. There was a dose-dependent difference in the plasma S-(-)equol concentrations.

The log-linear plots of the plasma concentration time curves during the 48-h sampling period for the 2 doses of S-(-)equol revealed a linear slope for the terminal portion of the curve and established that elimination of S-(-)equol follows first-order kinetics (Fig. 2). A slight kink was present at 24 h in the elimination phase, typical of drugs that undergo enterohepatic recycling. A summary of the pharmacokinetic data is presented in Table 1. Values of t1/2,z, Cmax/dose, AUCt/dose, and %f,e,u which should be unaffected by dose administered, were similar for the 10- and 30-mg doses of the SE5-OH supplement. The geometric mean ratios (90% CI) for the natural logarithms of Cmax/dose and AUCt/dose were 0.92 (0.77–1.10) and 0.98 (0.91–1.04), respectively. Nine of the 12 participants had no detectable equol in urine and 3 women (25%) were equol-producers as defined previously (11). However, there were no observable differences between the equol-producers and non-producers in the plasma pharmacokinetics of S-(-)equol administered in the SE5-OH supplement.

Urinary excretion of S-(-)equol. The recovery of S-(-)equol for each 12-h collection interval and for the cumulative 48-h period for each dose administered showed that S-(-)equol rapidly appeared in urine with the greatest output during the first 12 h following administration of both doses (Fig. 3). The total

FIGURE 1 Individual time course plots of the plasma total S-(-)equol concentration following administration of single oral doses of 10 mg (A) and 30 mg (B) of S-(-)equol as SE5-OH tablets to 12 healthy postmenopausal women. For clarity, data are shown only for 0–12 h time points.
recovery of \(-\)(-)equol in 48 h following \(-\)(-)equol was 82% for both doses, representing for both a high fractional absorption
for the fraction of \(-\)(-)equol absorbed for both healthy postmenopausal women. Values are means ± SD, n = 12.

Discussion
Equol was first discovered in the urine of pregnant mares over 73 yrs ago (34,35) and attained notoriety because it proved to be the agent responsible for clover disease in sheep, an infertility syndrome that was prevalent in Australia in the 1940s (36). It was during the course of metabolic profiling of steroid hormones that equol was first discovered in human and rat urine (1,20). Thought initially to be a new hormone, it was later shown to be derived from the diet, being produced by the action of intestinal bacteria on the soy isoflavone daidzin (2,3). This discovery, and the finding that many, but not all, people who consumed soy foods excreted equol in urine at concentrations several orders of magnitude higher than endogenous estrogens led to the hypothesis that equol is naturally enriched in daidzin and daidzein, efficient conversion to \(-\)(-)equol was achieved and the resulting fermented soy germ product, which did not contain any live bacteria, was used to produce an equol-containing supplement (SE5-OH). This new supplement was recently subjected to acute and subchronic testing for toxicity and genotoxicity and found to be safe and not genotoxic (30). The availability of a naturally produced \(-\)(-)equol–containing supplement means that the clinical effects of soy foods can be studied in a physiological, rather than pharmacological, range.

The doses of \(-\)(-)equol used in this study were based upon a range anticipated to be sufficient for clinical effects and that would yield plasma \(-\)(-)equol concentrations within the range reported for adults who make \(-\)(-)equol when consuming soy foods (11). Furthermore, the intake of total soy isoflavones by Asians consuming soy foods is in the range of 25–50 mg (41–44), of which ~50% is usually daidzin or daidzein, the precursors to \(-\)(-)equol. Therefore, the doses tested in this pharmacokinetic study were in a physiological, rather than pharmacological, range.

\(-\)(-)equol was readily and rapidly absorbed from the SE5-OH supplement, with the time taken to attain Cmax being ~1 h (range 0.97–2.0 h) after oral intake, irrespective of the dose. This rapid absorption is consistent with the behavior of the isoflavone aglycons daidzein and genistein, which are also rapidly absorbed after ingestion (45,46). By contrast, isoflavone glycosides do not

TABLE 1 Plasma \(-\)(-)equol pharmacokinetics in healthy postmenopausal women administered 10- and 30-mg doses of \(-\)(-)equol in the form of SE5-OH tablets in a single bolus1

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>10-mg dose</th>
<th>30-mg dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax, nmol/L</td>
<td>1907 ± 693</td>
<td>4953 ± 747</td>
</tr>
<tr>
<td>tmax, h</td>
<td>1.00 (0.97–2.00)</td>
<td>1.01 (0.98–1.50)</td>
</tr>
<tr>
<td>AUCt, h ng/ml</td>
<td>8461 ± 1213</td>
<td>25,010 ± 3,079</td>
</tr>
<tr>
<td>t1/2,z, h</td>
<td>7.4 (2.8)1</td>
<td>8.2 (4.1)</td>
</tr>
<tr>
<td>AUCe, h ng/ml</td>
<td>8484 ± 11763</td>
<td>25,299 ± 3,021</td>
</tr>
<tr>
<td>Cmax/dose, nmol/L/mg</td>
<td>191 ± 69</td>
<td>166 ± 25</td>
</tr>
<tr>
<td>AUCe/dose, h nmol/L/mg</td>
<td>858 ± 119</td>
<td>842 ± 100</td>
</tr>
<tr>
<td>A0-4, mg</td>
<td>8.22 ± 2.86</td>
<td>24.6 ± 7.2</td>
</tr>
<tr>
<td>%A4, mg</td>
<td>82.2 ± 28.5</td>
<td>82.2 ± 23.9</td>
</tr>
</tbody>
</table>

1 Values are mean ± SD or median (minimum-maximum), n = 12 unless noted otherwise.
2 Total of free aglycone + conjugates.
3 n = 11.
4 Amount of total \(-\)(-)equol (free + conjugates) excreted in urine.

FIGURE 2 Log/linear plots of plasma total \(-\)(-)equol concentrations after single oral doses of 10 and 30 mg \(-\)(-)equol as SE5-OH tablets to healthy postmenopausal women. Values are means ± SD, n = 12.

FIGURE 3 Fraction of dose excreted following single oral administration of 10 and 30 mg of \(-\)(-)equol in SE5-OH tablets to healthy postmenopausal women. Values are means ± SD, n = 12.
cross the enterocyte (47) and hydrolysis by intestinal glucosidases (48) is a requirement for bioavailability and is a rate-limiting step that delays the time to attain peak plasma concentrations to 4–8 h in most adults consuming soy foods containing mainly isoflavone glycosides (49,50).

Following administration of SE5-OH tablets, plasma S-(−)equol concentrations showed a consistent and linear increase with dose, as the 30 mg:10 mg geometric mean ratios of log-transformed C_{max}/dose and AUC_{0-24h}/dose were very close to 1.00 at 0.92 and 0.98, respectively, and the 90% CI included 1.00. The variability among individuals of the computed C_{max}/dose and AUC_{0-24h}/dose was high given that the fraction of the administered dose absorbed and recovered in urine was >80%. This is slightly higher than, although consistent with, recent data from healthy adults given enantiomeric pure S-(−)[13C]equol where the reported fractional recovery in urine was 61.3 ± 19.5% (31). The fractional absorption of S-(−)equol in all studies, including this one, is substantially higher than either of the soy isoflavones daidzein and genistein, which have fractional absorptions of ~30–40% and 7–15%, respectively (50,51).

Compared with previously reported studies in which purified equol preparations were administered (6,7,31), plasma concentrations following administration of S-(−)equol in the form of SE5-OH tablets were 2- to 4-fold of previously reported C_{max}/dose values (Table 2). In part, this is accounted for by earlier t_{max} values for S-(−)equol given in the form of the SE5-OH supplement compared with purified equol formulations. Similarly, the dose-adjusted systemic bioavailability of S-(−)equol determined from the plasma AUC_{0-24h} was ~50% higher for the SE5-OH supplement than for published data on purified compounds (6,7,31). It is possible that differences between the formulations account for these different characteristics and unlikely that they could be due to degradation of S-(−)equol, because this is a relatively stable molecule and in vitro is stable in the presence of gastric and intestinal fluids (52). Although not previously reported, the purified equol preparations were administered as a powder in gelatin capsules (6,7,31) and followed by a meal, whereas the SE5-OH supplement used in this study was in tablet form and no food was consumed for the first 4 h after dosing. Differences in dissolution and solubility of S-(−)equol from these different formulations, or the meal effect, probably account for the differences in t_{max} values and therefore the C_{max} values, because for a given dose, slower absorption would lead to lower peak plasma concentrations.

The reported elimination rates of S-(−)equol in various studies are similar at ~8 h (Table 2). This value represents the aggregate elimination rate of unconjugated and conjugated S-(−)equol. In this study, as with most previously reported studies, plasma total S-(−)equol concentrations were measured after complete hydrolysis of all the conjugates, because it has been previously shown that all isoflavones, including S-(−)equol, undergo efficient Phase II metabolism by conjugation with glucuronic and sulfuric acids during and after absorption (1,53). These conjugates are the major circulating forms of the isoflavones and are also the major metabolites excreted in urine (1,2,20,54,55).

Within the cohort, 3/12 (25%) women were equol-producers when tested for their ability to make S-(−)equol after a soy-food challenge test (11,12). This is consistent with the known frequency of equol-producers in the Western population (11). There was no difference in the calculated pharmacokinetics between the equol-producers and nonproducers (Fig. 4). This new SE5-OH S-(−)equol–containing supplement, therefore, offers a means of providing S-(−)equol to those adults who do not make S-(−)equol. In this regard, acute and subacute toxicity studies have shown the supplement to be safe (30) and in this study, acute administration, albeit a single-dose, did not result in any serious adverse effects.

In conclusion, we report on the pharmacokinetics and disposition of S-(−)equol delivered in the form of a new supplement that was manufactured by the incubation of soy germ with the specific S-(−)equol–producing bacterium, L. garvieae. After oral administration, S-(−)equol was rapidly absorbed from the supplement, attained high plasma concentrations, and showed a linear dose response in its pharmacoki-

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**TABLE 2** Comparison of S-(−)equol plasma pharmacokinetic parameters among different studies

<table>
<thead>
<tr>
<th>Formulation administered</th>
<th>Dose</th>
<th>C_{max}/dose</th>
<th>t_{max}</th>
<th>t_{1/2}</th>
<th>%f_{u}</th>
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<tbody>
<tr>
<td>This study</td>
<td>SE5-OH tablets</td>
<td>30</td>
<td>166 ± 25</td>
<td>1.00²</td>
<td>7.4 ± 2.8</td>
</tr>
<tr>
<td>This study</td>
<td>SE5-OH tablets</td>
<td>10</td>
<td>191 ± 69</td>
<td>1.01²</td>
<td>8.2 ± 4.1</td>
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<tr>
<td>(6)</td>
<td>Pure S-(−)equol</td>
<td>25</td>
<td>54</td>
<td>6</td>
<td>8.8</td>
</tr>
<tr>
<td>(7)</td>
<td>Pure S-[3]C-(−)equol</td>
<td>20</td>
<td>61 ± 19</td>
<td>2.3 ± 0.3</td>
<td>10 ± 15</td>
</tr>
<tr>
<td>(31)</td>
<td>Pure S-[4]C-(−)equol</td>
<td>20</td>
<td>81 ± 7</td>
<td>3.17 ± 0.7</td>
<td>78.9 ± 0.78</td>
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</tbody>
</table>

¹ Values are mean ± SD or single measures unless otherwise indicated.
² Median.
³ nd, Not determined.
netics. Natural S-(±)-equol is highly bioavailable and has a terminal elimination half-life of 8 h.

Acknowledgments
K.D.R.S. was the principal investigator and was responsible for the conception and design of the study protocol, data interpretation, and preparation of the manuscript. X.Z. performed the mass spectrometric analysis of S-(±)-equol in plasma and urine samples. S.E.S. performed the pharmacokinetic and statistical analysis of plasma and urinary data and K.R. monitored the clinical study. All authors read and approved the final manuscript.

Literature Cited


