Equol: History, Chemistry, and Formation¹,²

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Abstract

Equol, first isolated from equine urine in 1932 and identified 50 years later in human urine as a metabolite of the soy isoflavones, daidzin and daidzein, is produced by intestinal bacteria in some, but not all, adults. This observation led to the term equol-producers to define those adults that could make equol in response to consuming soy isoflavones and the hypothesis that the health benefits of soy-based diets may be greater in equol-producers than in equol nonproducers. By virtue of a chiral center, equol occurs as a diastereoisomer and intestinal bacteria are enantiospecific in synthesizing exclusively the (S)-equol enantiomer, an enantiomer that has selective affinity for the estrogen receptor-β. Both enantiomers are of interest from a clinical and pharmacological perspective and are currently being developed as nutraceutical and pharmacological agents. The wide range of biological activities these enantiomers possess warrants their investigation for the treatment of a number of hormone-related conditions involving estrogen-dependent and androgen-related conditions. The following review describes the history, chemistry, and factors governing the intestinal bacterial formation of equol. J. Nutr. 140: 1355S–1362S, 2010.

Introduction

It is now 57 years since the first report appeared describing a new phenolic compound in an estrogenic fraction of pregnant mare urine (1). It was suggested that the compound be given the name equol, after the equine source of the material. Efforts to obtain large-scale quantities of the compound led to the recognition that it was also present in appreciable amounts in the urine of stallions and nonpregnant mares and the conclusion that it was not associated with the presence of high estrogen states. During the autumn months, the amounts of equol declined and by winter it was impossible to isolate it from urine. The authors concluded that, “so far as can be determined, no dietary factor was the cause of this (seasonal) variation…” (2). It later became apparent that this was not the case when in SW Australia reports emerged of a catastrophic “failure to breed” associated with uterine abnormalities and endometriosis in sheep grazing on Trifolium subterraneum clover (3). Reductions in sperm counts and motility were also documented in ewes (4). This clover disease, as it was so-called, was found to be the result of extremely high circulating concentrations of equol, formed by rumen bacteria from the ingestion of large amounts of the methoxyxylated isoflavone, formononetin, abundant in several indigent species of clover (5–7). Equol was even found as a component in urinary calculi of sheep and cattle (8). Equol has since been reported to be present in the urine and/or plasma of many other animal species, including cows (9), hens (10–14), monkeys (15,16), chimpanzees (17,18), dogs (19), mice (20), rats (20–22), and pigs (16,23), but there are marked differences in the extent of metabolism of isoflavones into equol by these species. Rodents, e.g., very efficiently convert daidzin/daidzein to equol (24), whereas pigs and humans have been reported to do this less efficiently (16,24). In the decades leading to 1970, a great deal of work was performed defining the metabolism of isoflavones and biological actions of equol (6,25–28). While its estrogenic effects were well documented based upon field observations and classical bioassays, it was not until after the discovery of the first estrogen receptor (ER) in the mid-1960s (29) that the relative affinity of equol for the ER could be

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⁵ Abbreviations used: BBM, brush border membrane; ER, estrogen receptor; ISP, isolated soy proteins; RMB, relative molar binding.
Equol [7-hydroxy-3-(4’-hydroxyphenyl)-chroman], an isoflavone, belongs to the general class of compounds referred to as nonsteroidal estrogens. It has a molecular composition of C_{15}H_{14}O_{3} and a molecular weight of 242.27 Daltons. The heterocyclic structure contains 2 reactive hydroxyls and 1 relatively inert and unreactive oxygen in the central furan ring. Physicochemically, it is nonpolar and relatively insoluble in solution, something that should be considered when conducting in vitro experiments, particularly at high concentrations. It is also extremely acid-labile and can readily be destroyed (>60%) in the general work-up of samples, particularly if acidic hydrolytic steps are used (39). Despite having 2 phenolic rings, it exhibits poor UV absorption characteristics, meaning that HPLC with UV detection is unsuitable for its measurement in most biological fluids. As a result of a chiral carbon at position C-3 of the molecule, equol exists in 2 enantiomeric forms, R-(+)-equol and S-(-)-equol, and the latter is the natural diastereoisomer produced by intestinal bacteria in the intestine of humans and rats (40). This makes it distinct from its precursor isoflavone, daidzein, and the 2 other major isoflavones of soy, genistein and glycitein (41). Equol can be readily synthesized from daidzein by catalytic hydrogenation, but this yields the (±)-equol form (42) and it is the form that has been commercially available and mostly utilized in studies of its biological potency and properties. Indeed, unless otherwise stated, it can be assumed that all previously reported experiments used (±)-equol and not the individual enantiomers. It cannot always be assumed that the racemate will behave in an identical manner to that of the individual enantiomers and this was recently shown to be the case for its pharmacokinetics (43). It is probable that biological effects may be underestimated when testing with the racemate and this may particularly hold true for binding affinities to receptors. The racemic mixture can be readily separated by chiral chromatography and the earliest studies used this approach to isolate sufficient amounts of each enantiomer to determine the estrogen binding affinities (40,44) and the pharmacokinetics (43). More recently, methods for the selective synthesis of S-(-)-equol (45,46) and R-(+)-equol (45) have been described. Methods for the synthesis of [^{13}C]labeled isoflavone analogs (47–50) have been described that can represent suitable starting points for the preparation of stable-labeled [^{13}C]equol for use as tracers in metabolic studies or for internal standards in stable-isotope dilution mass spectrometric assays (43). The synthesis of S-(-)-equol and R-(+)-equol by chiral chemistry (45) now affords the large-scale production of enantiomeric pure compounds for use in clinical and animal studies. Finally, the
production of S(-)-equol from daidzein-rich soy germ by a specific equol-producing bacterium, Lactococcus garvieae (51), offers an alternative biological means to producing specifically S(-)-equol (52). With these breakthroughs, it is now possible to study in some detail the effects of equol in animals and humans and such studies will likely shed further light on the relevance of this metabolite to the clinical outcomes.

**Role of intestinal bacteria in the formation of S(-)-Equol**

The early evidence in support an intestinal bacterial origin for equol in humans and animals was as follows: 1) germ-free animals fed a soy diet do not excrete equol in urine (30); 2) S(-)-equol is not excreted in the urine or found in the plasma of either newborn infants that lack a developed microflora (53) or in infants up to the age of 4-mo fed exclusively soy infant formula from early life (54,55); 3) incubation of soy, or daidzein with human fecal flora from adults that produce equol, leads to the formation of S(-)-equol (36,40); 4) some antibiotics will knock-out the production of equol (18,56,57).

Even though it was known for decades that intestinal bacteria were responsible for the production of S(-)-equol, it is only in recent years that specific bacteria capable of converting daidzin/daidzein to S(-)-equol have been isolated and identified (Table 1). Interestingly, whereas it was reported that 1.59% of injected [14C]genistein was recovered as [14C]equol in domestic fowl (77), metabolic and pharmacokinetic studies in humans administered [13C]daidzein and [13C]genistein tracers show conclusively that in humans, S(-)-equol is formed from daidzein and not genistein (78). Although the major degradative pathway for genistein leads to p-ethylphenol, a phenol first found in goat urine (79) and 4-hydroxyphenyl-2-propionic acid in rats (80), recently it was shown that an anaerobic bacterium from mouse intestine could produce 5-hydroxy-equol from genistein by analogous reactions to those that yield equol from daidzein (66,74). All of these conversions are time dependent and slow, and in humans it takes 12–36 h for the appearance of [13C]equol in plasma after oral administration of [13C]daidzein (78), which is consistent with a colonic origin for its formation.

Biotransformations that take place after oral administration of soy isoflavones are summarized in Figure 2. The production of S(-)-equol from daidzin requires 3 key steps. Daidzin first undergoes hydrolysis to split the glucoside moiety and effect release of the bioavailable aglycon, daidzein. This step is crucial to all soy isoflavones, because the conjugated forms (glucosides) do not cross the enterocyte and are consequently not bioavailable (81). Hydrolysis is very efficient and begins in the proximal intestine by the action of brush border membrane β-glucosidases (82). Bacterial β-glucosidases are also capable of performing this hydrolysis and many of the common bacteria that reside in the intestinal tract do this (62,63,83). The efficiency of this initial hydrolytic step by brush border membrane glucosidases is also exemplified by the very high plasma concentrations of daidzein.

### Table 1: List of intestinal bacteria that cultured in vitro have been found to biotransform isoflavones to S(-)-equol or related intermediates

<table>
<thead>
<tr>
<th>Reference</th>
<th>Bacterium strain</th>
<th>Source</th>
<th>Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maruo et al., 2008 (58)</td>
<td>Adlercreutzia equolifaciens</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Minamida et al., 2006 (59)</td>
<td>Asaccharobacter celatus AHU1763</td>
<td>Rat</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Minamida et al., 2006 (60)</td>
<td>Asaccharobacter celatus gen,nov.sp. nov strain do03</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Ueno and Uchiyama, 2002 (61)</td>
<td>Bacteroides ovatus</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Tsangalis et al., 2002 (62)</td>
<td>Bifidobacterium</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Tsangalis et al., 2002 (62)</td>
<td>Bifidobacterium animalis</td>
<td>Pure culture</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Raimondi et al., 2009 (63)</td>
<td>Bifidobacterium sp</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Hur et al., 2000 (64)</td>
<td>Clostridium sp HGH6</td>
<td>Bovine</td>
<td>Daidzein → Dihydrodaidzein</td>
</tr>
<tr>
<td>Tamura et al., 2007 (65)</td>
<td>Clostridium-like bacterium</td>
<td>Human</td>
<td>Daidzein → Dihydrodaidzein</td>
</tr>
<tr>
<td>Matthies et al., 2008 (66)</td>
<td>Coriobacteriaceae sp MT189</td>
<td>Mouse</td>
<td>Daidzein → S-Hydroxy-equol</td>
</tr>
<tr>
<td>Matthies et al., 2008 (66)</td>
<td>Coriobacteriaceae sp MT189</td>
<td>Mouse</td>
<td>Daidzein → S-Hydroxy-equol</td>
</tr>
<tr>
<td>Wang et al., 2005 (67)</td>
<td>Eggerthella sp Julong 732</td>
<td>Human</td>
<td>Dihydrodaidzein → Equol</td>
</tr>
<tr>
<td>Kim et al., 2009 (68)</td>
<td>Eggerthella sp Julong 732</td>
<td>Human</td>
<td>Dihydrodaidzein → Equol</td>
</tr>
<tr>
<td>Yokoyama and Suzuki, 2008 (69)</td>
<td>Eggerthella sp YY7918</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Decroos et al., 2005 (70)</td>
<td>Enterococcus faecium</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Tamura et al., 2007 (71)</td>
<td>Escherichia coli (HSH21 and HGH6)</td>
<td>Human</td>
<td>Daidzein → Daidzein</td>
</tr>
<tr>
<td>Yu et al., 2008 (72)</td>
<td>Eubacterium sp D1 and D2</td>
<td>Pig</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Decroos et al., 2005 (73)</td>
<td>Finegoldia magna</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Decroos et al., 2005 (73)</td>
<td>Lactobacillus mucosae</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Wang et al., 2006 (74)</td>
<td>Lactobacillus sp Niu-016</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Ishimi et al., 2008 (75)</td>
<td>Lactobacillus garvieae (Lc 20-92)</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Ueno and Uchiyama, 2002 (76)</td>
<td>Ruminococcus productus</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Matthies et al., 2009 (77)</td>
<td>Slackia sp HE8</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Matthies et al., 2009 (77)</td>
<td>Slackia sp HE9</td>
<td>Human</td>
<td>Genistein → S-Hydroxy-equol</td>
</tr>
<tr>
<td>Jin et al., 2009 (78)</td>
<td>Slackia equolifaciens (Strain DZE)</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Jin et al., 2008 (79)</td>
<td>Strain PUE</td>
<td>Human</td>
<td>Purarin → Daidzein</td>
</tr>
<tr>
<td>Ueno and Uchiyama, 2002 (79)</td>
<td>Streptococcus intermedius</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Decroos et al., 2005 (80)</td>
<td>Veillonella sp</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
<tr>
<td>Decroos et al., 2005 (80)</td>
<td>Mixture of Lactobacillus mucosae EP12, Enterococcus faecium EP11, Finegoldia magna EP13, and Veillonella sp</td>
<td>Human</td>
<td>Daidzein → Equol</td>
</tr>
</tbody>
</table>

1 In most cases the definitive structure of the equol product was not determined, but it can be assumed that in all cases the product is the S(-)-equol enantiomer.
and genistein in infants fed soy infant formula (54, 55) that have immature and undeveloped gut microflora (53). Daidzein is reduced to \(S\-(\text{+})\text{equol}\) through the intermediate dihydrodaidzein then converted by deoxygenation to yield \(S\-(\text{-})\text{equol}\). Daidzein is also metabolized to O-desmethylangolensin as a result of cleavage across the hetercyclic ring (84), but this metabolite appears to be of little interest in that it has no known biological activity.

Bacteria are enantioselective in metabolizing daidzein to exclusively \(S\-(\text{+})\text{equol}\) and not \(R\-(\text{-})\text{equol}\) (40, 67, 72). It is not completely clear whether the conversion of daidzein to \(S\-(\text{+})\text{equol}\) is performed by a single bacterium or whether there are distinctly different bacteria that execute these reactions, or both. The large variability in the levels of dihydrodaidzein and \(S\-(\text{+})\text{equol}\) in human urine (85) would indicate that there is more than a single bacterium responsible for producing \(S\-(\text{+})\text{equol}\). Furthermore, the finding that certain antibiotics selectively inhibit the formation of equol but not dihydrodaidzein when human feces from equol-producers are incubated with daidzein also supports this contention (56). The list of intestinal bacteria that can produce equol in culture is ever increasing (Table 1); a number of strains have been isolated that perform only conversion of daidzein/daidzein to dihydrodaidzein whereas others appear to be able to completely convert daidzein to \(S\-(\text{-})\text{equol}\) (Table 1). One in particular, Lactococcus garvieae, that is found in some Italian cheeses (51) and has been isolated from human feces (61, 73) was shown to efficiently convert daidzein to \(S\-(\text{-})\text{equol}\) and has been used to produce the first natural \(S\-(\text{-})\text{equol}\)-containing nutraceutical (52, 86). Whether demonstrating formation of \(S\-(\text{-})\text{equol}\) in culture can be considered representative of intraluminal colonic formation of \(S\-(\text{-})\text{equol}\) remains uncertain. It may, e.g. under specific conditions be possible to demonstrate conversion of daidzein to equol in vitro, yet such conditions may not necessarily be reflective of the intraluminal milieu in the human intestinal tract. For example, culturing human fecal flora from equol-producers under conditions that enhance fermentation, such as a high nonstarch polysaccharide medium, enhances conversion of daidzein to equol (87), as do hydrogen gas, butyrate, and propionate (59, 70). Despite the ability to manipulate equol production in vitro, human dietary intervention studies using prebiotics or probiotics have had little impact on its formation (88–92). Therefore, some caution is required in relying on in vitro fecal cultures from adults as a means of confirming equol-producer status (93). Such approaches should always be coupled with specific measurement of equol in urine (94, 95). In the future, it is likely that molecular techniques in bacteriology may help to more accurately define equol-producer status.

### Frequency of equol-producers

All animal species tested produce equol in response to consumption of isoflavones whether from soy protein or clover (16, 23, 24). Rodents in particular have very high plasma \(S\-(\text{-})\text{equol}\) concentrations, in part because most commercial rodent diets are formulated with soy protein (20, 96). For this reason, careful consideration is needed when using rodents, particularly if the primary endpoints being examined are in any way influenced by estrogens, either directly or indirectly, through upstream signaling pathways with estrogen response elements (20, 97–99). Frequently, there is a lack of awareness on the part of investigators of the type and composition of the diets being used by their animal facilities or by the vendors providing rodents for research studies. A high batch-to-batch variability in the isolateflavone content of commercial rodent unpurified diet makes it impossible to control for the background level of these phytoestrogens (97).

When the association between soy isoflavones and equol was first made, it was noted that not all healthy adults produced equol when challenged with soy protein (36). The first reported dietary intervention study of the 6 healthy adults fed 40 g of textured vegetable protein for 7 consecutive days found only 4/6 excreted equol in urine; the term equol-producers was thus coined. Many other studies of larger sample sizes have provided a consensus that only 25–30% of the adult population of Western countries produce \(S\-(\text{-})\text{equol}\) when fed soy foods containing isoflavones (94, 100, 101). This is significantly lower than the reported 50–60% frequency of equol-producers in adults from Japan, Korea, or China (102–105) or in Western adult vegetarians (95). The reasons for these differences are unclear but are important to understand if the hypothesis that the ability to produce equol when consuming soy foods (equol hypothesis) is advantageous in terms of enhancing health benefits can be clearly demonstrated (24, 106). Thus far, the data are inconclusive, but this is partly because, to our knowledge, none of the clinical studies have preselected participants on the basis of equol-producer status but rather have retrospectively subanalyzed data from equol-producers, and most are underpowered. Significant differences in gene expression between equol-producers and equol nonproducers have been demonstrated in postmenopausal women exposed to an isoflavone supplement, with the most notably significant alterations in expression of a number of estrogen-responsive genes (107).

It would appear that equol-producer status is a relatively stable phenomenon, as evidenced from repeat testing over prolonged periods of time in adults (24, 89, 95, 108). There have been many studies looking at associations between equol-producer status and dietary components, including fat and carbohydrate composition (93, 101), PUFA (109), dairy intakes (110), lactose (111), green tea consumption (112), seaweed (113), and soy food intake (103, 105, 110), but no clear conclusions can be made. Prolonged soy food consumption appears not to be a factor driving equol formation (114). One possible explanation for the differences in the frequency of equol-producers among populations, we speculate, may be related to the type of soy foods consumed (115). There are marked differences in the isoflavone composition of Western and Asian soy foods (Fig. 3) (41). Asians consume a high proportion of isoflavone aglycons, because fermented soy foods account for
Western World

25-30% Equal-producers

Soy isoflavone intake from soy foods predominantly Glycosides

Clinical studies use mostly purified protein-based foods

Soy food intake high in Aglycons

Asia 50-60% Equal-producers

Aglcylons may facilitate Equol production? Does Equol increase clinical efficacy of soy?

FIGURE 3 Differences in the type of soy foods consumed by Western and Asian populations may account for differences in the frequency of equol-producers.

about one-third of the total intake of soy foods (116,117). Based upon the typical 20–50 mg/d intake of total isoflavones by Asians, we estimate that 10–30 mg are ingested in the form of aglycons, which in most adults are absorbed faster than glycosides (43,102,118–121) and may be more easily converted to equol than glycosides. In a recent cholesterol-lowering dietary intervention study of a soy germ-enriched pasta containing predominantly isoflavones in the aglycon form, it was found that 69% of the patients were equol-producers (115), which is considerably higher than the 20–30% expected frequency for Westerners (95). Most dietary intervention studies of soy have used foods or products made from isolated soy proteins as the source of isoflavones (122) or soy isoflavone supplements that contain almost exclusively isoflavone glucosides (119). Isolated soy proteins are not commonly consumed in the Asian diet and this may explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods (24,106), then this could explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods, then this could explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods, then this could explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods, then this could explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods, then this could explain the lower frequency of equol-producers in Western adults. Furthermore, if equol production does enhance the efficacy of soy foods, then this could explain the lower frequency of equol-producers in Western adults. 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38. Messina M, Watanabe S, Setchell KDR. Report on the 8th Interna-


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