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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- $\beta$ . 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 methoxylated 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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Soy, and Menopause Research Leadership Conference”, held in Washington, DC, June 16, 2009. The supplement coordinator for this supplement is Kara Lewis, Life Sciences Research Organization (LSRO) Senior Staff Scientist. The supplement is the responsibility of the guest editors to whom the Editor of The Journal of Nutrition has delegated supervision of both technical conformity to the published regulations of The Journal of Nutrition and general oversight of the scientific merit of each article. Publication costs for this supplement were defrayed in part by the payment of page charges. This publication must therefore be hereby marked “advertisement” in accordance with 18 USC section 1734 solely to indicate this fact. The Guest Editor for this supplement is Neil Shay. Guest Editor disclosure: Neil Shay declares no conflict of interest. Supplement Coordinator disclosure: Kara Lewis is currently under contract with and receives compensation from the supplement sponsor. She was also compensated for attending and organizing the Equol, Soy, and Menopause Research Leadership Conference and for organizing, writing, editing, or reviewing, and collection of supplemental manuscripts. The opinions expressed in this publication are those of the authors and are not attributable to the sponsors or the publisher, Editor, or Editorial Board of The Journal of Nutrition.

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5 Abbreviations used: BBM, brush border membrane; ER, estrogen receptor; ISP, isolated soy proteins; RMB, relative molar binding. © 2010 American Society for Nutrition. 1355S First published online June 2, 2010; doi:10.3945/jn.109.119776. by guest on October 1, 2017 jn.nutrition.org Downloaded from

quantified. When the relative molar binding affinities of a number of phytoestrogens for sheep uterine ER were compared, equol was found to have much higher affinity than its precursor daidzein in competing with radioactive estradiol for binding to the cytosolic receptor (27), supporting the theory that it may be advantageous to be able to convert daidzein to equol (24). There was little interest in equol for several decades until the chance discovery in 1980 of high concentrations of an unknown estrogen-like compound in rat urine (30) accompanying the mammalian lignans, enterolactone and enterodiol (31–33). At the time, it was referred to as compound 386/192, a notation for the molecular ion and base peak in the mass spectrum of its trimethylsilyl ether derivative. In common with most endogenous steroid hormones, including estrogens, it was conjugated predominantly to glucuronic acid and a lesser extent to sulfuric acid (34). Its presence in such high concentrations in rat urine fortuitously afforded a means of isolating sufficient quantities for structural elucidation studies by infrared spectroscopy, NMR, and GC-MS (35) and the subsequent confirmation that it was identical in chemical structure to the equol first isolated from pregnant mare urine in 1932 by Marrian et al. (1,2). This confirmation was made possible because one of us (K.D.R.S.) was gifted from the curator of the UK Medical Research Council’s Steroid Reference Collection (the late Professor D.N. Kirk) the original 4.0 mg sample of equol

isolated from pregnant mares urine by Marrian et al in 1932. Equol was also found to occur as a minor constituent in the urine of many adults. The link between equol and soy came about after a series of studies in which different plant-based foods were fed to rats maintained on a purified diet. The introduction of soy protein led to a huge increase in the urinary excretion of equol and following this observation, the soy isoflavone daidzin was isolated and shown to be a precursor to equol (35). It was also found that the introduction of soy protein to the diet led to an increased excretion of equol in some but not all adults (36), whereas in vitro incubation of cultured fecal flora from equol-producing individuals with either daidzein or soy protein resulted in the formation of equol (36). The finding of high concentrations of equol in the urine of adults consuming soy foods prompted the hypothesis that this nonsteroidal estrogen may be beneficial in the prevention and treatment of many hormone-dependent conditions (36). Progress in research studies of equol was hampered by the lack of sufficient amounts of the compound for biological and clinical testing and by the divergent interest and focus on genistein, the other soy-derived isoflavone that was shown to be a potent inhibitor of tyrosine protein kinases (37) and a compound that was readily available in bulk. Almost 20 y after the finding of equol in human urine, it was proposed that the efficiency with which adults convert daidzein to equol when consuming diets containing soy foods could enhance the clinical effectiveness of soy-based diets—the so called equol-hypothesis (24)—and this has driven a resurgence of interest in equol, as is evident from the almost exponential increase since 1980 in the number of publications cited by a PUBMED search of this as a keyword (Fig. 1). At the recent 8th International Soy Symposium held in Tokyo, Japan, for the first time an entire session was devoted to equol (38). This overview will focus on some of the key areas related to this unique molecule and is not intended to be a comprehensive review of the topic. Chemistry Equol [7-hydroxy-3-(49-hydroxyphenyl)-chroman], an isoflavan, belongs to the general class of compounds referred to as nonsteroidal estrogens. It has a molecular composition of C<sub>15</sub>H<sub>14</sub>O<sub>3</sub> 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.

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