PERGAMON

Phytochemistry 60 (2002) 205–211

PHYTOCHEMISTRY

www.elsevier.com/locate/phytochem

Molecules of Interest

# Genistein

Richard A. Dixon[a,*], Daneel Ferreira[b]

[a]*Plant Biology Division, Samuel Roberts Noble Foundation, 2510 Sam Noble Parkway, Ardmore, OK 73401, USA*
[b]*NCNPR, School of Pharmacy, The University of Mississipi, University, MS 38677, USA*

Received 10 March 2002; accepted 26 March 2002

**Abstract**

Genistein (4′,5,7-trihydroxyisoflavone) is a common precursor in the biosynthesis of antimicrobial phytoalexins and phytoanticipins in legumes, and an important nutraceutical molecule found in soybean seeds. Genistein is a phytoestrogen with a wide variety of pharmacological effects in animal cells, including tyrosine kinase inhibition, and dietary genistein ingestion has been linked, through epidemiological and animal model studies, with a range of potential health beneficial effects. These include chemoprevention of breast and prostate cancers, cardiovascular disease and post-menopausal ailments. In spite of an extensive literature on the effects of dietary genistein, questions still exist as to its potential overall benefits as a component of the human diet. Genistein can be synthesized chemically via the deoxybenzoin or chalcone route. Genistein is synthesized in plants from the flavanone naringenin by a novel ring migration reaction catalyzed by the cytochrome P450 enzyme isoflavone synthase (IFS). *IFS* genes have recently been cloned from a number of plant species, and production of genistein can be now achieved in non-legumes by recombinant DNA approaches. 

*Keywords:* Genistein; Isoflavone; *Glycine max*; Leguminosae; Phytoestrogen; Antioxidant; Cancer chemoprevention

## 1. Introduction

Genistein (**1**) is biosynthetically the simplest of the isoflavonoid compounds of the Leguminosae. It is a central intermediate in the biosynthesis of more complex isoflavonoids with roles in establishment or inhibition of interactions between plants and microbes. Its many biological activities have made it a subject in over 3600 published studies (listed in Biological Abstracts) in the last 10 years. Most of these studies have focused on the pharmacological activities of genistein as a tyrosine kinase inhibitor, its chemoprotectant activities against cancers and cardiovascular disease, and its phytoestrogen activity. Genistein is a major subject of discussion in the context of nutraceuticals and functional foods, and may soon provide a case study for evaluating the delivery of health-promoting compounds through genetically modified plants. We here review the biological activities of genistein in relation to its effects on plant and animal health, its chemical and biological synthesis, and the first attempts to genetically engineer this compound in transgenic plants.

## 2. Distribution of genistein and its metabolites

The isoflavonoids enjoy a restricted distribution in the plant kingdom, and are mostly limited to the subfamily Papilionoideae of the Leguminosae. Their structural variation is surprisingly large and involves not only the number and complexity of substituents on the 3-phenylchroman framework, but also different oxidation levels of the heterocycle and the presence of additional heterocyclic rings. The number of known isoflavone glycosides, e.g. genistin (genistein 7-*O*-β-D-glucopyranoside) is, however, small when compared to the vast range of known flavonoid glycosides. *O*-Glycosides predominate but a considerable number of *C*-glycosides has also been documented. Natural sources from which isoflavonoids have been isolated, including genistein and closely related analogs like biochanin A (**3**) and their glycosides are listed in an excellent review by Dewick (1994).

* Corresponding author. Tel.: +1-580-224-6601; fax: +1-580-224-6692.

*E-mail address:* radixon@noble.org (R.A. Dixon).

0031-9422/02/$ - see front matter 
PII: S0031-9422(02)00116-4

## 3. Genistein and plant health

Many isoflavonoids exhibit broad-spectrum antimicrobial activity and are therefore believed to help the plant fight microbial disease. Antimicrobial isoflavonoids can be classified as pre-formed "phytoanticipins" or inducible "phytoalexins". Genistein may function both as a phytoalexin and as a phytoanticipin. Derivatives such as the prenylated genisteins of lupin, which are synthesized during seedling development, may also act as phytoanticipins. The best-characterized isoflavonoid phytoalexins are the pterocarpans, isoflavans and isoflavanones of bean, alfalfa, pea and soybean. Most have the A-ring substitution pattern of daidzein (4′,7-dihydroxisoflavone) (**2**), and genistein is therefore not an intermediate in their biosynthesis. However, a small number of 5-hydroxyisoflavonoid-derived phytoalexins derived from genistein have been reported in the Leguminosae, the prenylated isoflavanone kievitone from *Phaseolus vulgaris* perhaps being the most studied example.

## 4. Genistein as a phytoestrogen

Genistein shares structural features with the potent estrogen estradiol-17β (**4**), particularly the phenolic ring and the distance (11.5 A) between its 4′- and 7- hydroxyl groups (Fig. 1). These features confer ability to bind estrogen receptors and sex hormone binding proteins, and genistein can thus exert both estrogenic and antiestrogenic activity, the latter by competing for receptor binding by estradiol. Structural similarities have also been noted between genistein and tamoxifen (**5**) (Fig. 1), a synthetic anti-estrogen that has been clinically tested as a chemopreventive agent in women with high risk of breast cancer. The potent estrogen equol (**6**) (a major metabolite of dietary isoflavonoids formed by the gastrointestinal flora) (Fig. 1) and genistein can displace bound estrogen and testosterone from human sex steroid binding protein. Thus, genistein and other phytoestrogens could potentially affect clearance rates of androgens and estrogens and therefore the availability of the hormones to target cells. It should be noted that genistein binds differentially to human α and β estrogen receptors (Barnes et al., 2000), and this should be carefully considered when extrapolating the results of phytoestrogen administration experiments in animals to hormone-related diseases in humans.

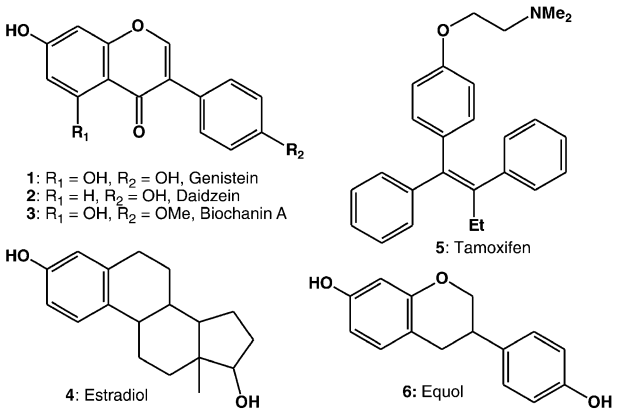



Fig. 1. Structures of isoflavone phytoestrogens in relation to estradiol and tamoxifen.

The major dietary sources of isoflavonoids for humans are soy products. One gram of powdered soybean chips contains nearly 800 μg of daidzein and over 500 μg of genistein (primarily as glycosides), whereas one gram of soy protein has approximately 150 μg of daidzein and 250 μg of genistein. Highly processed soy products such as miso and soy sauce contain lower levels of genistein than does tofu, the major source of isoflavones in the Asian diet. In humans eating a soy-rich diet, ingested isoflavone levels can be very high, as determined by urinary excretion. Their levels of urinary equol can be approximately 100-fold higher than those observed in adults who consume little soy products in their diet. A high dietary consumption of genistein has been linked to a number of potential health benefits, as summarized in Fig. 2 and discussed below.

## 5. Genistein as a cancer chemopreventive agent

Significant correlations exist between an isoflavone-rich soy-based diet and reduced incidence of breast cancer or mortality from prostate cancer in humans. An early epidemiological study of Singapore Chinese women that included 420 healthy controls and 200 with histologically confirmed breast cancer indicated that soy consumption was directly correlated with reduced risk of cancer (Lee et al., 1991), and the effects appeared to be dietary rather than genetic. Similar observations have been reproduced in many, but not all, subsequent studies undertaken up the present day. Based on knowledge of diet and urinary excretion levels of daidzein, genistein, and equol in Japanese as compared to American or European subjects, the isoflavonoids found in soy products were proposed to be the agents responsible for reduced cancer risk.

When administered neonatally, genistein effectively protects against chemically-induced mammary tumors in rats (Fritz et al., 1998). The protective effects include increased latency, reduced tumor incidence and multiplicity, and more rapid maturation of undifferentiated end buds to differentiated lobules. Biochanin A (4′-methoxygenistein) (**3**), a major isoflavone component of chickpea, is likewise active as a cancer chemopreventant in animal model systems. Genistein may

induce early mammary gland differentiation resulting in a less active epidermal growth factor signaling pathway in adulthood that, in turn, suppresses development of mammary cancer (Lamartiniere, 2000). Although no clinical trials have been reported documenting effects of controlled dietary supplementation with genistein on breast cancer incidence in humans, a high soy diet containing up to 45 mg of isoflavones per day can cause changes in the menstrual cycle that may help reduce cancer risk.

In addition to effects on breast cancers, genistein and related isoflavones also inhibit cell growth, or development of chemically induced cancers, in stomach, bladder, lung, prostate, and blood. Inhibition of the growth of human stomach cancer cell lines in vitro by genistein and biochanin A apparently involves stimulation of a signal transduction pathway leading to apoptosis (Yanagihara et al., 1993). When these cancer cells were transplanted into mice, biochanin A, but not genistein, significantly inhibited tumor growth. Genistein strongly inhibits growth of leukemia cells when targeted to them by linkage to a monoclonal antibody (Uckun et al., 1995), and a prenyl isoflavone derivative (ipriflavone) has been developed as an oral treatment for acute leukemias.

In spite of the large number of studies supporting cancer chemoprevention by genistein, some studies have suggested a potential for opposite effects. These include increased numbers of carcinogen-induced aberrant crypt foci in the colons of rats fed genistein and induced structural chromosome aberrations in human peripheral lymphocytes.

## 6. Genistein and cardiovascular disease

Results of epidemiological studies have suggested that high dietary intake of isoflavones and/or flavonols may contribute to a low incidence of heart disease in Japanese women. These effects may result from inhibition of low density lipoprotein oxidation by isoflavones, an effect that may be enhanced by food sources rich in vitamim C (Hwang et al., 2001). Genistein also appears to improve plasma lipids, resulting in lowered LDL cholesterol, the ratio of total cholesterol to HDL cholesterol, and the ratio of LDL to HDL cholesterol, in pre-menopausal women (MerzDemlow et al., 2000). In rats, the hypocholesterolemic effect of a soy diet may involve interactions between the isoflavones and soy protein (Peluso et al., 2000), whereas, in cholesterol fed rabbits, attenuation of atherosclerosis by isoflavones does not require the presence of soy protein.

## 7. Genistein and post-menopausal problems

Estrogen deficiency in post-menopausal women can lead to unpleasant symptoms such as hot flushes and vaginal dryness, with a long-term increased risk of bone loss in addition to cardiovascular disease. Soy isoflavones positively help maintenance of bone mass in ovariectomized rodents, although daidzein may be more efficient than genistein in this respect. One study has indicated that isoflavone-rich soy protein may attenuate bone loss in the lumbar spine of post-menopausal women, and that this effect is due to isoflavones rather

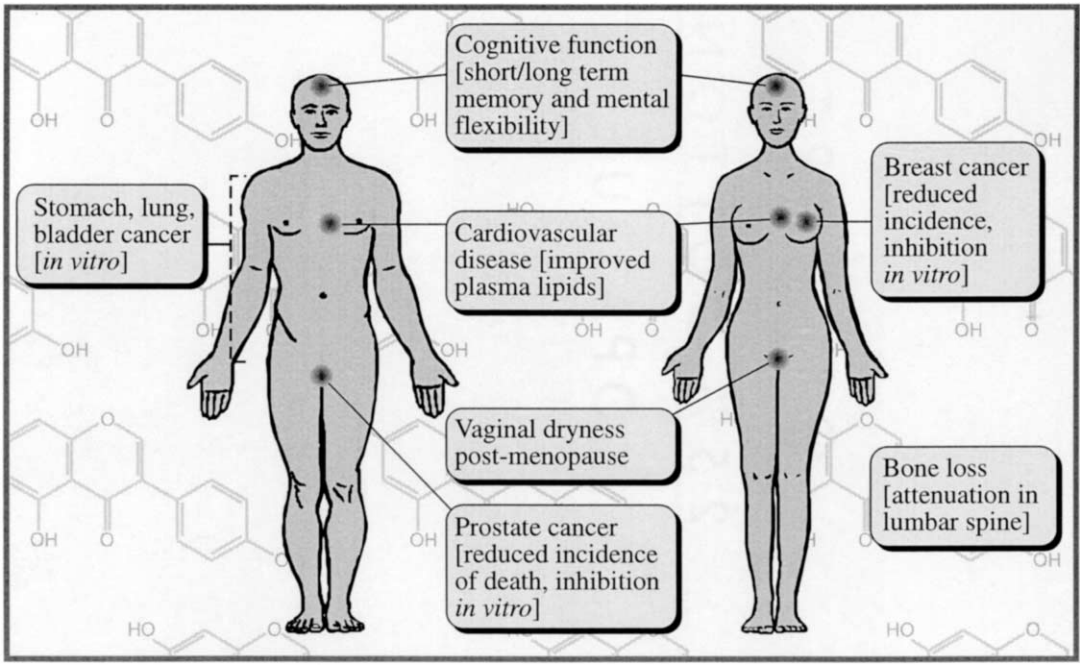



Fig. 2. Proposed targets for beneficial effects of dietary genistein or a high soy diet on human health.

than to soy protein (Alekel et al., 2000). An isoflavone-rich diet may help approximately two thirds of post-menopausal women to better cope with hot flushes, in addition to potentially reducing the risk of cardiovascular disease, which is elevated post-menopause.

Estrogen replacement therapy has been shown to improve episodic and semantic memory in post-menopausal women and, remarkably, a high soy diet improves memory within weeks in both young male and female volunteers (File et al., 2001). Understanding how phytoestrogens affect cognitive function will be an exciting goal for the future.

## 8. Pharmacological activities of genistein

Not all the effects of isoflavones on human health are necessarily associated with their estrogenic activity. Genistein also inhibits DNA topoisomerase and tyrosine protein kinase (Akiyama et al., 1987), as well as possessing antioxidant and cell cycle inhibitor activity. Kinase inhibition is generally regarded as being specific for tyrosine kinases, such as epidermal growth factor (EGF) receptor, although at higher concentrations genistein also inhibits protein histidine kinase. Other isoflavones such as daidzein do not inhibit tyrosine kinase activity, and are therefore used as controls in pharmacological experiments utilizing genistein.

Genistein blocks EGF-mediated tyrosine phosphorylation in vivo in human epidermal carcinoma cells. When specifically targeted to the B-cell-specific receptor CD-19 by conjugation to a monoclonal antibody, genistein selectively inhibited CD-19-associated tyrosine kinase activities, resulting in death of human B-cell precursor leukemia cells (Uckun et al., 1995). However, in several cell systems in which genistein inhibits growth, it does not appear to induce phosphorylation of EGF receptors or other tyrosine kinase substrates; in such cases, it has been suggested that the isoflavone might inhibit cell growth by modulating transforming growth factor (TGF) β1 signaling pathways.

Unlike other isoflavonoids, genistein exerts toxicity only at concentrations greatly in excess of those at which it first exerts its biological and pharmacological effects, making it a potentially important molecule for dietary cancer chemoprevention.

## 9. Bioavailability of dietary genistein

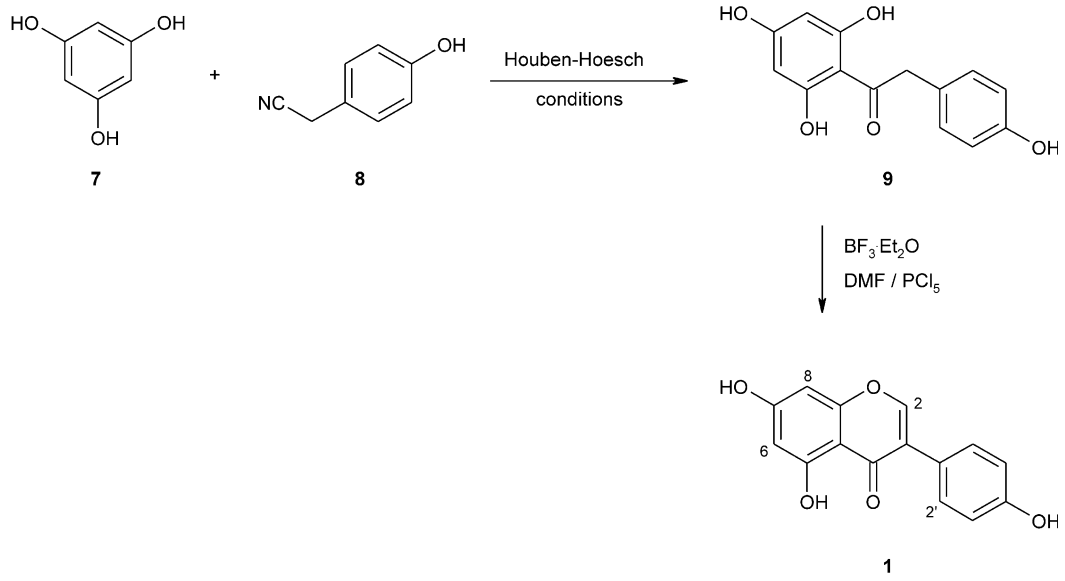
Most flavonoids exist in the plant as glycosidic conjugates, generally located in the cell vacuoles. Bioavailability of these dietary components depends on relative uptake rates of conjugated and free forms, hydrolysis of glycosides by gut bacteria or gut wall enzymes, further metabolism, for example to glucuronides within the liver, and excretion rate. The malonyl glucosides of daidzein and genistein found in soybean are labile and readily degraded to the non-acylated glucosides following cooking. The free aglycones, but not the glycosides, are absorbed from rat stomach. However, once in the small intestine, brush border lactase phlorizin hydrolase can effectively hydrolyze isoflavone glucosides. Nevertheless, in humans, isoflavones appear in blood plasma at a more rapid rate, and at higher levels, following oral administration of aglycones as compared to glycosides, and genistein and daidzein, but not their glycosides, are readily transported across human intestinal epithelial cell monolayers (Steensma et al., 1999).

## 10. Chemical synthesis of genistein

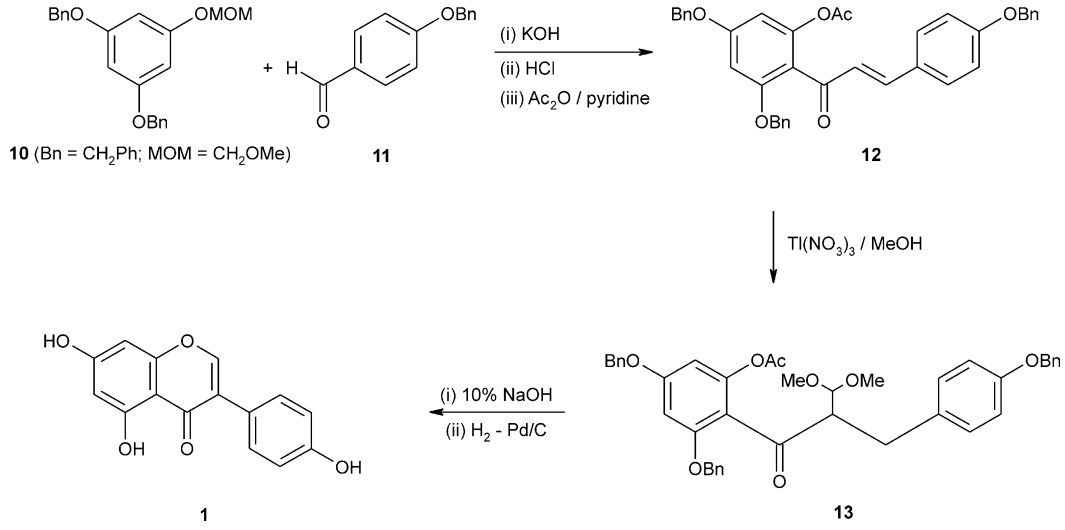
The synthesis of isoflavones remains an important adjunct in the classical sense of structural elucidation of natural analogs. Isoflavones are typically the primary synthetic targets due to the potential of their facile conversion into most of the other classes of isoflavonoids. Recently the emphasis of the synthetic protocols has shifted to increasingly address the needs of the chemistry-biology interface, i.e. the stereoselective syntheses of enantiopure derivatives [e.g. isoflavone epoxides (Waldemar et al., 2002), isoflavanones (Vicario et al., 2000), isoflavans (Versteeg et al., 1999), and pterocarpans (Van Aardt et al., 2001)], and the synthesis of isotopically labeled isoflavonoid estrogens (Whalley et al., 2000).

The two traditional approaches to the synthesis of isoflavones involve the deoxybenzoin (2-hydroxyphenyl benzyl ketone) and chalcone routes. Other methods like rearrangement of flavanones, rearrangement and cyclization of chalcone epoxides, palladium catalyzed cross coupling of 3-halochromones with arylboronic acids, organolead-mediated arylation of chroman-4-ones, etc. are less general and were reviewed by Dewick (1994) and Balasubramanian and Nair (2000).

The deoxybenzoin route involves the base catalyzed condensation of the 2-hydroxyphenyl benzyl ketone with a reagent containing an activated C1-unit. This approach is still routinely employed and uses a plethora of C1-reagents under a variety of reaction conditions (Dewick, 1994; Balasubramanian and Nair, 2000). Its utility is demonstrated in Scheme 1 for a recent synthesis of genistein (**1**) (Balasubramanian and Nair, 2000). Thus, treatment of deoxybenzoin (**9**), available via Houben–Hoesch acylation of phloroglucinol (**7**) with p-hydroxyphenylacetonitrile (**8**), with *N*,*N*-dimethyl (chloromethylene)ammonium chloride [$(Me_2N^+{=}CHCl)Cl^-$], in situ prepared by reaction of *N*,*N*-dimethylformamide (DMF) and $PCl_5$, gives genistein in 90% yield. This method is high yielding, may be used under mild conditions in a "one pot" procedure, and is suitable for scale-up to ton quantities.




Scheme 1. Synthesis of genistein via the deoxybenzoin route employing $DMF/PCl_5$ as source of $(Me_2N' = CHCl)Cl'$.

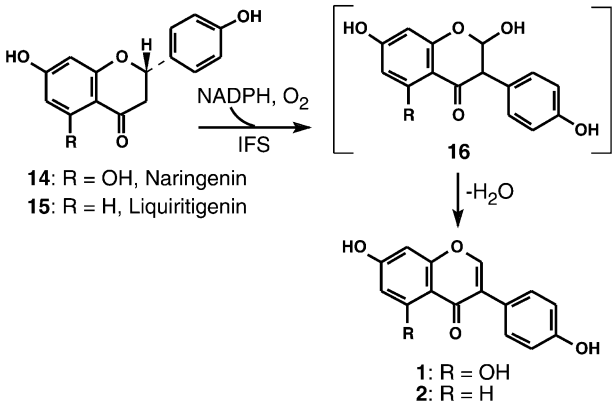



Scheme 2. Synthesis of genistein via the chalcone route.

In the other main approach, isoflavone synthesis is achieved by oxidative rearrangement of chalcones. Chalcones are readily accessible via base catalyzed condensation of acetophenones and aromatic aldehydes, and are hence more readily obtainable than deoxybenzoins, particularly where complex substitution patterns are involved. The principles underpinning these metal catalyzed chalcone rearrangements are illustrated in Scheme 2 which is adapted from the method for the synthesis of alkylpolyhydroxy- and alkoxycoumaronochromones recently published by Tsukayama et al. (2001). Thus, base catalyzed aldol condensation of the *O*-protected acetophenone (**10**) and aldehyde (**11**) followed by the relevant deprotection/reprotection of the 2′-hydroxyl group, afford the protected chalcone (**12**) in ca. 70% yield. Oxidative rearrangement of (**12**) with thallium(III)trinitrate in methanol affords an intermediate acetal (**13**) via a biogenetic-type aryl migration mechanism (Ollis et al., 1970). The acetal may then be transformed into the isoflavone derivative by either base of acid catalyzed treatment, thus permitting considerable flexibility when acid- or base-sensitive groups are present. Genistein (**1**), is then generated by deprotection under appropriate conditions, e.g. debenzylation using hydrogenation over a Pd/C catalyst.

## 11. Biosynthesis of genistein

Isoflavonoids are formed by a branch of the flavonoid biosynthetic pathway, and originate from a central flavanone intermediate [naringenin (**14**) in the case of




Scheme 3. Enzymatic formation of isoflavones from flavanones via the isoflavone synthase reaction.

genistein] that is ubiquitously present in plants. For entry into the isoflavonoid pathway, the flavanone first undergoes abstraction of hydrogen radical at C-3 followed by B-ring migration from C-2 to C-3 and subsequent hydroxylation of the resulting C-2 radical. This reaction requires NADPH and molecular oxygen, and is catalyzed by a microsomal cytochrome P450 enzyme (2-hydroxyisoflavanone synthase or 2-HIS, loosely termed isoflavone synthase or IFS). IFS is stereoselective, and (2*R*)-flavanones are not substrates. The resulting 2-hydroxyisoflavanone (**16**) is unstable and undergoes dehydration to yield genistein or daidzein [the latter is formed by IFS from liquiritigenin [4′,7-dihydroxyflavanone] (**15**)], as shown in Scheme 3. The dehydration reaction can take place non-enzymatically in vitro, although the reaction may be enzyme catalyzed in vivo.

Because of the lability and low abundance of IFS, it eluded molecular characterization for many years. However, cDNAs encoding IFS have now been cloned from soybean and other species (Jung et al., 2000; Steele et al., 1999), largely aided by functional genomics approaches. One form of the enzyme from soybean, CYP93C1v2, converts liquiritigenin or naringenin directly to daidzein or genistein, respectively, in the presence of NADPH when expressed in insect cells (Steele et al., 1999). It is not clear whether dehydration of the putative 2-hydroxyisoflavanone intermediate occurs on the enzyme, or results from an endogenous dehydratase activity present in the insect cell microsomes. In contrast, when IFS from licorice (*Glycyrrhiza echinata*) or soybean is expressed in yeast, the 2-hydroxyisoflavanone intermediate can be recovered.

## 12. Engineering genistein synthesis in transgenic plants

IFS is the entry point enzyme of isoflavonoid biosynthesis, and therefore the key step for engineering isoflavone production into plants (non-legumes) that lack the pathway. To demonstrate proof of principle for the genetic manipulation of isoflavonoid natural products for human health enhancement, IFS has been introduced into *Arabidopsis thaliana*, corn and tobacco (Jung et al., 2000; Yu et al., 2000). Free genistein does not accumulate in *Arabidopsis* expressing soybean IFS. Rather, the isoflavone is converted to glucose-rhamnose-genistein, rhamnose-genistein, and a yet to be characterized genistein glucoside (Liu et al. 2002). This glycosylation pattern reflects that of the endogenous leaf flavonols of *Arabidopsis*, kaempferol and quercetin, although the genistein appears to be conjugated through the 7-hydroxyl of the A-ring whereas the flavonols are glycosylated at the 3-position. It is not known whether the same glycosyl transferases are involved in glycosylation of endogenous flavonols and the "foreign" isoflavone.

The level of genistein conjugate production in transgenic *Arabidopsis* is in part dependent on the IFS activity level (Liu et al., 2002), but may also be determined by substrate availability, substrate channeling, or product turnover. Glycosylation does not appear to be rate limiting. Up-regulation of flavonoid synthesis in maize BMS cell cultures expressing soybean IFS by expression of a chimeric transcription factor containing the maize C1 and R coding regions leads to low levels of genistein production, from undetectable levels in the absence of CRC expression (Yu et al., 2000). Over-expression of chalcone isomerase in *Arabidopsis* expressing IFS leads to a 3-fold increase in flavonols, but to no increase in genistein conjugates. Likewise, genistein production is not increased in the *pap1-D* genetic background in which anthocyanin production is strongly up-regulated (Liu et al., 2002). Thus, there appears to be metabolic channeling through the endogenous pathways of flavonoid biosynthesis in *Arabidopsis* that results in limitations to flux through the introduced IFS. It is clear that we do not yet understand how to engineer high levels of genistein, such as will be required for potential disease chemoprevention, in transgenic plants. Solving this problem will require a better understanding of the regulatory architecture of the flavonoid pathway in the various target plants.

## Acknowledgements

We thank Cuc Ly and Desmond Slade for artwork. Work in the authors' laboratories was supported by the Samuel Roberts Noble Foundation and the United States Department of Agriculture, Agricultural Research Service Specific Agreement No. 58–6408–7-012.

## References

Akiyama, T., Ishida, J., Nakagawa, S., Ogawara, H., Watanabe, S., Itoh, N., Shibuya, M., Fukami, Y., 1987. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J. Biol. Chem. 262, 5592–5595.

Alekel, D.L., StGermain, A., Pererson, C.T., Hanson, K.B., Stewart, J.W., Toda, T., 2000. Isoflavone-rich soy protein isolate attenuates bone loss in the lumbar spine of perimenopausal women. Am. J. Clin. Nutr. 72, 844–852.

Balasubramanian, S., Nair, M.G., 2000. An efficient "one pot" synthesis of isoflavones. Synthetic Communications 30, 469–484.

Barnes, S., Kim, H., DarleyUsmar, V., Patel, R., Xu, J., Boersma, B., Luo, M., 2000. Beyond ER alpha and ER beta: estrogen receptor binding is only part of the isoflavone story. J. Nutr. 130, 656. S-657S.

Dewick, P.M., 1994. The isoflavonoids. In: Harborne, J.B. (Ed.), The Flavonoids, Advances in Research Since 1986. Chapman and Hall, London, pp. 117–238.

File, S.E., Jarrett, N., Fluck, E., Duffy, R., Casey, K., Wiseman, H., 2001. Eating soya improves human memory. Psychopharmacology 157, 430–436.

Fritz, W.A., Coward, L., Wang, J., Lamartiniere, C.A., 1998. Dietary genistein: perinatal mammary cancer prevention, bioavailability and toxicity testing in the rat. Carcinogenesis 19, 2151–2158.

Hwang, J.L., Hodis, H.N., Sevanian, A., 2001. Soy and alfalfa phytoestrogen extracts become potent low-density lipoprotein antioxidants in the presence of acerola cherry extract. J. Agric. Food Chem. 49, 308–314.

Jung, W., Yu, O., Lau, S.-M.C., O'Keefe, D.P., Odell, J., Fader, G., McGonigle, B., 2000. Identification and expression of isoflavone synthase, the key enzyme for biosynthesis of isoflavones in legumes. Nature Biotechnol. 18, 208–212.

Lamartiniere, C.A., 2000. Protection against breast cancer with genistein: a component of soy. Am. J. Clin. Nutr. 71, 1705. S-1707S.

Lee, H.P., Gourley, L., Duffy, S.W., Esteve, J., Lee, J., Day, N.E., 1991. Dietary effects on breast-cancer risk in Singapore. Lancet 337, 1197–1200.

Liu, C.-J., Blount, J.W., Steele, C.L., Dixon, R.A., 2002. Production of isoflavone glycoconjugates in transgenic *Arabidopsis* disproportionately reduces antioxidant flavonoid levels. Plant J., submitted.

MerzDemlow, B.E., Duncan, A.M., Wangen, K.E., Xu, X., Carr, T.P., Phipps, W.R., Kurzer, M.S., 2000. Soy isoflavones improve plasma lipids in normocholesterolemic, premenopausal women. Am. J. Clin. Nutr. 71, 1462–1469.

Ollis, W.D., Ormand, K.L., Redman, B.T., Roberts, R.J., Sutherland, I.O., 1970. Oxidative rearrangement of olefins by thallium(III) acetate. II. Synthesis of isoflavones. J. Chem. Soc. C 125–128.

Peluso, M.R., Winters, T.A., Shanahan, M.F., Banz, W.J., 2000. A cooperative interaction between soy protein and its isoflavone-enriched fraction lowers hepatic lipids in male obese Zucker rats and reduces blood platelet sensitivity in male Sprague–Dawley rats. J. Nutr 130, 2333–2342.

Steele, C.L., Gijzen, M., Qutob, D., Dixon, R.A., 1999. Molecular characterization of the enzyme catalyzing the aryl migration reaction of isoflavonoid biosynthesis in soybean. Arch. Biochem. Biophys. 367, 147–150.

Steensma, A., Noteborn, H.P.J.M., van der Jagt, R.C.M., Polman, T.H.G., Mengelers, M.J.B., Kuiper, H.A., 1999. Bioavailability of genistein, daidzein, and their glycosides in intestinal epithelial Caco-2 cells. Env. Toxicol. Pharmacol. 7, 209–211.

Tsukayama, M., Oda, A., Kawamura, Y., Nishiuchi, M., Yamashita, K., 2001. Facile synthesis of polyhydroxycoumaronochromones with quinones: synthesis of alkylpolyhydroxy- and alkoxycoumaronochromones from 2′-hydroxyisoflavones. Tetrahedron Lett. 42, 6163–6166.

Uckun, F.M., Evans, W.E., Forsyth, C.J., Waddick, K.G., Ahlgren, L.T., Chelstrom, L.M., Burkhardt, A., Bolen, J., Myers, D.E., 1995. Biotherapy of B-cell precursor leukemia by targeting genistein to CD19-associated tyrosine kinases. Science 267, 886–891.

Van Aardt, T.G., Van Rensburg, H., Ferreira, D., 2001. Synthesis of isoflavonoids. Enantiopure *cis*- and *trans*-6a-hydroxypterocarpans and a racemic *trans*-pterocarpan. Tetrahedron 56, 455–460.

Versteeg, M., Bezuidenhout, B.C.B., Ferreira, D., 1999. Stereoselective synthesis of isoflavonoids. (*R*)- and (*S*)-isoflavans. Tetrahedron 55, 3365–3376.

Vicario, J.L., Badia, D., Dominguez, E., Rodriquez, M., Carrillo, L., 2000. The first stereocontrolled synthesis of isoflavanones. Tetrahedron Lett. 41, 8297–8300.

Waldemar, A., Rao, P.B., Degen, H-G., Levai, A., Patonay, T., Saha-Moeller, C.R., 2002. Asymmetric Weitz-Scheffer epoxidation of isoflavones with hydroperoxides mediated by optically active phase-transfer catalysts. J. Org. Chem. 67, 259–264.

Whalley, J.L., Oldfield, M.F., Botting, N.P., 2000. Synthesis of [4-$^{13}$C]-isoflavonoid phytoestrogens. Tetrahedron 56, 455–460.

Yanagihara, K., Ito, A., Toge, T., Numoto, M., 1993. Antiproliferative effects of isoflavones on human cancer cell lines established from the gastrointestinal tract. Cancer Res. 53, 5815–5821.

Yu, O., Jung, W., Shi, J., Croes, R.A., Fader, G.M., McGonigle, B., Odell, J.T., 2000. Production of the isoflavones genistein and daidzein in non-legume dicot and monocot tissues. Plant Physiol. 124, 781–794.