Isoflavonoids

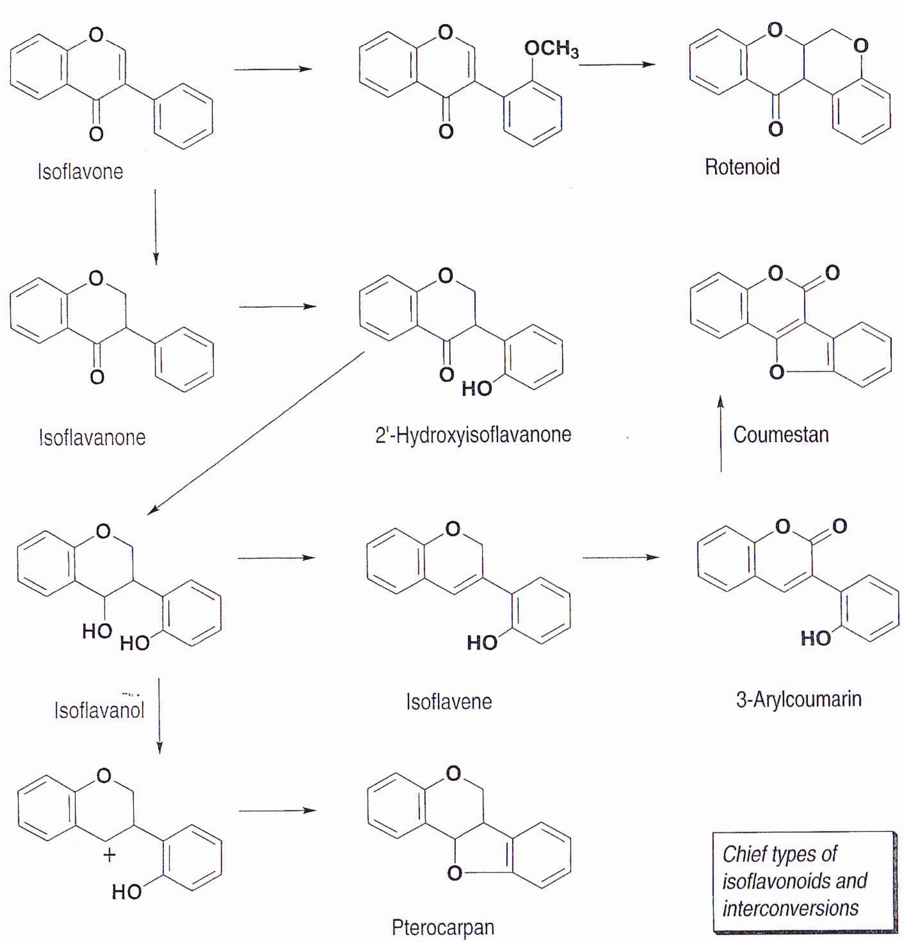
Isoflavonoids are characterized, like flavonoids, by a C_{15} skeleton of the Ar-C_3-Ar type, but one which is now rearranged to be a 1,2-diphenylpropane: all molecules in this group can be related to the skeleton of 3-phenylchromane. The distribution of these flavonoids is rather limited: although they have been characterized in two Gymnosperm genera (*Podocarpus*, *Juniperus*) and in scattered Angiosperm genera (*Iris* spp., *Wyethia* sp.), they are in fact almost specific to the Fabaceae. This specificity is probably linked to that of the enzyme responsible for the rearrangement of 2-phenylchromane to 3-phenylchromane (the rearrangement of a flavanone to an isoflavone).

The narrow botanical distribution does not preclude structural diversity: 870 isoflavonoids were known in 1990 (240 more than in 1985). They can be classified into a dozen structural types differentiated by their degree of oxidation and by the existence of added heterocycles. In all types, we can note the high frequency of isoprenylated derivatives, and consequently, of furan-, dihydrofuran-, and pyran-type structures.

The most common compounds are isoflavones, which occur in the free state, or, less commonly, as glycosides (*O*-glycosides, or exceptionally *C*-glycosides). Related structures are less numerous and include isoflavanones, isoflavenes, and isoflavanes. Fairly often, isoflavonoids have an additional ring, which as a general rule, arises from the cyclization of a 2'-hydroxylated derivative: such is the case of pterocarpans and their derivatives (pterocarpenes and 6a-hydroxypterocarpans), and also of coumaranochromones.

Other isoflavonoids have a coumarinic structure resulting from the oxidation of an isoflav-3-ene: consider the 3-arylcoumarins (= isoflav-3-en-2-ones) of *Glycyrrhiza* spp. and the cyclization products of a 2'-hydroxy-3-arylcoumarin, in other words coumestans (i.e., oxidized pterocarpans).

Some polycyclic compounds have an additional carbon atom, for example



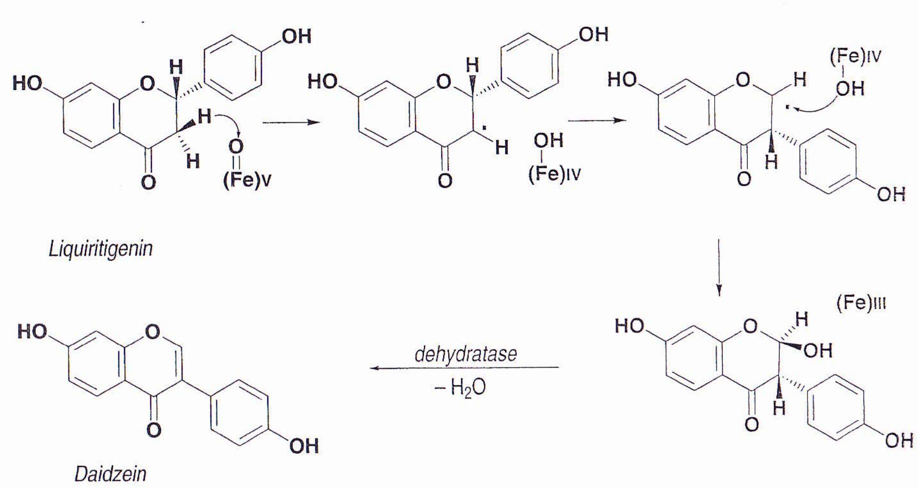
Chief types of isoflavonoids and interconversions

One last group of compounds is, on the contrary, characterized by the loss of a carbon atom: the benzofurans which, biosynthetically, are neither neolignans, nor cyclization products of a stilbene, but rather isoflavonoids formed (maybe?) by the loss of the C-6 of coumestan.

Like flavonoids, isoflavonoids can form dimers and oligomers (e.g., bis-isoflavanes, isoflavane-flavanone,) as well as adducts with cinnamic acids (isoflavano-lignans).

1. BIOSYNTHESIS

The mechanism proposed to explain the formation of isoflavonoids consists of two steps. The first one is the oxidation of a flavanone and its rearrangement, the second one is the elimination of a water molecule, which yields isoflavone (e.g., (2*S*)-liquiritigenin —> daidzein). The first step is catalyzed by isoflavone-synthase (a cytochrome P450-dependent mono-oxygenase) in the presence of NADPH and oxygen



Likely origin of isoflavones

and leads to a 2-hydroxyisoflavanone. The mechanism is thought to involve a radical, with hydroxylation taking place at the same time as aryl migration. The mechanism that was initially postulated, namely the formation of an epoxide, followed by its protonation and opening to form a spirodienone intermediate on the pathway to isoflavone, is now considered improbable because the derivative hydroxylated at C-2 has been isolated.

The interconversions within the series are fairly well understood (see table p. 348) based on labeling experiments or the isolation of the relevant enzymes. Isoprenylation is frequent and always takes place after the basic skeleton has been formed.

2. BIOLOGICAL ACTIVITY

In plants, a good number of isoflavonoid structures are phytoalexins, in other words substances produced by the plant in response to an infection by a pathogenic agent, most often fungal in nature. They may be considered as the natural defense products of the organisms that produce them.

The pharmacological properties of isoflavonoids are seldom known. The sole activity which has found an application is the insecticide activity of rotenoids. Estrogenic properties are also known: isoflavonoids cause infertility in sheep that ingest massive quantities of clover; cows seem less susceptible, perhaps because of a difference in metabolism.

Estrogenic activity of isoflavonoids. The occurrence of isoflavones in food raises the question of their potential impact on human health. In the soybean, the concentration of daidzein (7,4'-dihydroxyisoflavone), genistein (5,7,4'-trihydroxyisoflavone) and their glycosyl derivatives (glucosides- and 6''-*O*-malonylglucosides) can reach 3 g/kg. The same compounds are also found in all of the derived products (soybean powder, milk, fermented products), at concentrations that vary depending on the industrial manufacturing process.

These isoflavones and their intestinal metabolites (equol, demethylangolensin) bind to estrogen receptors, and most often, they have a weak estrogenic activity. They are also tyrosine-kinase inhibitors which may have a role in the transformation and cell proliferation phenomena. In animal models, a soybean-based diet decreases mammary and prostate carcinogenesis. Pure genistein is also an anticarcinogen (mammary tumors of the female rat during the neonatal period, colon microadenomas). These data confirmed the many results obtained, *in vitro*, on different cultured cell lines. In humans, epidemiologic studies strongly suggest that the low incidence of (or, in some cases, the lower mortality from) hormone-dependent diseases that is observed in Asia is correlated with the high consumption of soybean which is common in those cultures. The soybean isoflavones, and maybe other constituents as well, seem to have a preventive effect on breast and prostate cancer, as well as colorectal cancer.

Several recent studies suggest that isoflavones and soybean decrease the symptoms of menopause (hot flashes and others) and reduce the risk of osteoporosis.

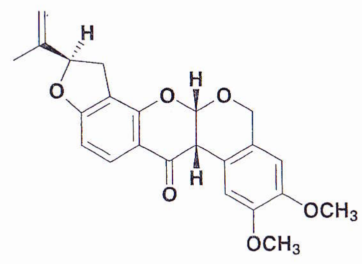
Is a soybean-based diet harmless for very young children? This is a topic of controversy: although it is known that such a diet results in very high plasma levels of phytoestrogens—which is a risk in theory—no clinical effects have been observed.

3. ROTENOIDS

These compounds, biogenetically related to isoflavonoids, have in common a four-ring structure: a chromanochromanone. The two oxygenated cycles are *cis* fused, and the biological activity is maximal for those derivatives that possess a dihydrofuran ring. The chief representative of the group is rotenone, the major active principle in the roots of various tropical Fabaceae of the genera *Derris*, *Lonchocarpus*, *Milletia*, *Mundulea* and *Tephrosia*.

• DERRIS, *Derris* sp., Fabaceae

Derris are vines growing in southeast Asia. *D. elliptica* (Roxb.) Benth is a species from Malaysia and Burma, also introduced and cultivated in Africa. Other species are used, particularly *D. malaccensis* (Benth.) Prain. In their area of origin, the roots of these vines are traditionally used as insecticidal and ichthyotoxic agents. The drug consists of the root, and on the market, an extract is frequently found which is enriched and titrated to contain about 30% rotenone. The rotenoid level of *Derris* powder ranges from 3 to 10%. The roots of South American *Lonchocarpus* (*L. urucu* Killip & Smith, *L. utilis* A.C. Smith) are used in the same forms and for the same purposes.



Rotenone

$R_1 = CH_3$, $R_2 = H$: *Formononetin*
$R_1 = R_2 = H$: *Daidzein*
$R_1 = H$, $R_2 = OH$: *Genistein*

Rotenone is responsible for the insecticidal properties; active upon contact as well as by ingestion, it inhibits mitochondrial respiration at the very first steps (inhibition of NADH-dependent dehydrogenase).

The main market outlet for rotenoids-containing Fabaceae (powder, extracts rotenone) is phytopharmacy (treatment of house plants, and, sometimes, of vegetable gardens) and the extermination of ectoparasites of domestic animals.

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