

## Pharmacokinetics of Dietary Isoflavones

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### Abstract

Dietary isoflavones are reported to have significant influences on human health. The beneficial effects reported include reduced risk of cancers, decreased menopausal symptoms, reduced osteoporosis etc. Most of these benefits have been deduced from epidemiological studies involving soy bean as the source of dietary isoflavones, since soy bean is an important food crop in several parts of the world. Over the last 30 years, considerable progress has been made in understanding the fate of dietary isoflavones in humans. Now we understand that the pharmacokinetics of dietary isoflavones is a complex phenomenon and involving multifaceted biological processes. The role of gut micro flora in deciding the bioavailability of isoflavones is quite significant. This review examines various pharmacokinetic aspects of dietary isoflavones and factors influencing the systemic bioavailability of isoflavones. This review also attempts to identify important factors which may contribute to the inter-person differences in the effects of isoflavones.

**Keywords:** Dietary isoflavones; Genistein; Equol; Gut microflora; Pharmacokinetics

### Introduction

Isoflavones are polyphenolic compounds found in many plant families, but especially in some members of the *Fabaceae* family. It is reported in several agriculturally important legumes such as soy, peanut, green peas, chick peas and alfalfa [1,2]. Soy (*Glycine max*) beans are exceptionally rich in isoflavones, with an average content of 1-2 mg/gram [3] and constitute the major source for dietary isoflavones. The main isoflavones in soy beans, present in glycosylated form, are genistin, daidzin and glycitein [3,4]. The glycosylation is on the 7<sup>th</sup> position of Ring A in the isoflavone ring (Table 1). The aglycone form of these isoflavones known as genistein, daidzein and glycitein respectively, are biologically active [1,5]. Biochanin A and formononetin are other isoflavones present in legumes, which can be converted by 4'-O-demethylation to the more potent genistein and daidzein [6]. Red clover (*Trifolium pretense*) contains Biochanin A and formononetin, in addition to other isoflavones. Kudzu (*Pueraria lobata*), root used as a condiment in East Asian cuisine and in hangover remedies, contains Puerarin (daidzein 8-C-glucoside) in significant amount [1,7].

Soy products are consumed in a variety of forms including whole beans, flour, soy protein isolates, textured soy protein, etc. [1,8]. Fermented soy products like *miso*, *tempeh* and soy sauce are used regularly as part of East Asian cuisine [1,3]. Although the starting raw material is soy bean, the isoflavone content in these foods varies according to the preprocessing and cooking procedure [1,9]; for example, microbial fermentation converts the glycosylated isoflavones to aglycones and prolonged fermentation leads to complete loss of isoflavones [1]. An elaborate database of isoflavone content in unprocessed and processed soy products is available from United States Department of Agriculture (<http://www.nal.usda.gov/fnic/foodcomp/Data/isoflav/isoflav.html>).

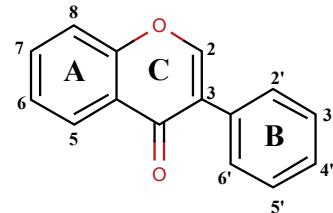
Several epidemiological investigations on health benefits of isoflavone-rich diets, especially soy based food regimes, showed lower incidences of colonic cancer [10], prostate cancer [11], coronary disease [12], breast cancer [12,13] and osteoporosis [14]. As the benefits of dietary isoflavones became evident, tremendous interest was created in investigating the pharmacokinetics and pharmacodynamics of these compounds, especially soy isoflavones. While pharmacodynamics (the molecular mechanisms) of isoflavones are now well understood and

reproducible, the data on pharmacokinetics of dietary isoflavones often appears inconsistent [15]. This review discusses the pharmacokinetics of isoflavones and about the factors that may influence the systemic bioavailability of dietary isoflavones.

### Fate of Dietary Isoflavones in the Gastrointestinal Tract

Dietary isoflavones are absorbed into systemic circulation from gastrointestinal tract. It appears that glycosylated soy isoflavones are not absorbed intact from the gastrointestinal tract [16,17], and are absorbed only after deglycosylation to the aglycone form [18,19]. But puerarin (daidzein-8-C-glucoside), the major bioactive isoflavone of kudzu root, does not undergo significant de glycosylation and is thought to be absorbed intact via intestinal glucose transporters [7,20].

A. Isoflavone ring system showing the ring nomenclature and numbering



B. Structures of Isoflavones discussed in this article

	R1	R2	R3
Genistein	-H	-OH	-OH
Daidzein	-H	-H	-OH
Glycitein	-OCH <sub>3</sub>	-H	-OH
Formononetin	-H	-H	-OCH <sub>3</sub>
Biochanin A	-H	-OH	-OCH <sub>3</sub>

Table 1: Position of Ring A in the isoflavone ring.

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The conversion of glycosylated isoflavones to de glycosylated isoflavones begins in the oral cavity, wherein oral microflora and oral epithelium exhibit  $\beta$ -glucosidase activity [21]. In the upper small intestine, conversion to aglycone form continues by the action of intestinal lactase phlorizin hydrolase [18,22], enterocytic  $\beta$ -glucosidase [19] and by microbial  $\beta$ -glucosidases [23,24].

Lactase phlorizin hydrolase, commonly known as lactase (E.C=3.2.1.108), is a membrane bound enzyme on the luminal side of the intestinal brush border and hydrolyses the glycosylated isoflavones to aglycones that diffuses into the enterocytes [18]. In absence or reduced activity of intestinal lactase phlorizin hydrolase, the glycosylated isoflavones reach the large intestine, where they are converted to the respective aglycone form by the resident intestinal microflora.

The anaerobic condition in the large intestine also favors reductive reactions on the isoflavones by the microbial flora [1,23]. Under the anaerobic, reductive conditions of the colon, genistein is reduced to dihydrogenistein and further to 5-hydroxyequol [25], while daidzein is reduced to dihydrodaidzein and equol [26]. Further, microbial cleavage of the Ring-C of isoflavones produces deoxybenzoin metabolites (DOBs), which are passively absorbed and have biological activity similar to isoflavones [27,28].

Inter-individual and racial variations exist in the level and activity of intestinal lactase phlorizin hydrolase [29-32]. Lactase persistence or continued production of lactase into adulthood is common in individuals of European descent, while its frequency is low in East-Asian populations [30,31]. Therefore in individuals with reduced lactase activity, larger proportion of dietary isoflavones is subjected to microbial metabolism in the intestine, reducing the amount of intact isoflavone absorbed and consequently increasing the amount of microbial metabolites absorbed.

A biologically significant product from microbial metabolism of isoflavone is equol [26,33]. Daidzein on metabolism by specific bacterial consortia in the large intestine produces S(-)equol and O-desmethylangolensin (O-DMA) which are absorbed into systemic circulation by passive diffusion [4,34]. Significantly, S(-)equol is more estrogenic than daidzein itself [34,35]. Considerable variability exists in the effectiveness of these specific bacterial consortia, and approximately 30%-50% of human population can produce equol following a soy based diet, and approximately 80%-90% can produce O-DMA [36]. Similarly, the ability to metabolize daidzein to equol appears to be higher in populations who routinely included soya based foods in their regular diet [26].

A recent study suggests that specific interactions between the human host and the intestinal microflora may exist in equol producing individuals, which may explain the variability between "equol producers" and "equol non-producers" in a given population [37]. Several species of bacteria isolated from fecal matter of "equol producers" have shown ability to convert daidzein to equol, under *in vitro* conditions [35]. The equol production status of an individual may vary over a period of time, subject to events such as antibiotic therapy and diet which may alter the nature and population of equol producing microflora in the gut [38,39]. Genistein can be converted to 5-hydroxyequol by microbial metabolism, but evidence for production 5-hydroxyequol in human subjects is yet to be reported [40].

Although microbial production of equol remains an important

field of interest, DOBs such as O-DMA from daidzein and 6'-hydroxy-O-desmethylangolensin (6'-O-DMA) from genistein are biologically significant due their weak estrogenic effect [41]. Several bacterial isolates from human gut have shown to anaerobically cleave the Ring-C of the isoflavones to produce O-DMA and 6'-O-DMA [25,27,28,42]. Further microbial metabolism of the O-DMA does not occur, as it does not possess a hydroxyl group on position 6' (position 5 on daidzein Ring-A), while in case of 6'-O-DMA, the *methyl ethanone* bridge is hydrolyzed between position 1 and 1' to produce 4-hydroxyphenyl-2-propionic acid and 1,3,5-trihydroxybenzene [25,28,43]. Microbial metabolism of genistein and daidzein is represented in figure 1.

Intestinal microflora is also reported to perform 4'-O-demethylation of Biochanin A and formononetin to produce genistein and daidzein respectively, but to a lesser extent than liver microsomes [6]. The structure of the isoflavone appears to influence the susceptibility to microbial metabolism. The isoflavones with hydroxyl groups at 5,7 or 4' positions appears to be more susceptible to microbial metabolism than those without hydroxyl substitutions at these positions [20].

Therefore, the availability of a particular dietary isoflavone in the gut of an individual appears to be influenced by i) lactase persistence ii) the nature and population of the gut microbial flora of the individual. Both these factors influence the amount of intact isoflavone aglycone available for absorption by passive diffusion into intestinal epithelium. Infants and neonates may not have fully developed microflora and are therefore the role of microbial de-glycosylation and further metabolism of dietary isoflavones in the intestinal lumen appears to be limited [44,45].

In addition, *deglycuronidation* of isoflavone conjugates can be carried out by intestinal microflora, and relevance of this is discussed below.

## Oral Bioavailability of Isoflavones

Bioavailability of nutrients is defined as the "the proportion of a nutrient capable of being absorbed and available for use or storage" [46] and depends upon the factors affecting its absorption, distribution, metabolism and elimination kinetics.

After consumption, glycosylated isoflavones are rapidly deglycosylated, absorbed and metabolized in intestinal enterocytes and liver, entering the systemic circulation predominantly as conjugates with limited bioavailability. For example, "free" genistein aglycone typically represents only 1-3% of total plasma genistein [47]. The mean time to attain peak plasma concentrations ( $t_{max}$ ) for the total (conjugated + unconjugated) genistein and daidzein is approximately 5-6 and 6-8 hours in humans [48,49]. In humans, the systemic bioavailability, as measured in terms of Area Under Curve (AUC), of genistein (mean AUC = 4.54  $\mu\text{g}/(\text{mL.h})$ ) is greater than that of daidzein (mean AUC = 2.94  $\mu\text{g}/(\text{mL.h})$ ) [49]. Other pharmacokinetic studies [50,51] have reported similar values.

The extent of isoflavone absorption appears to be similar, irrespective of the glycone or aglycone nature of the isoflavone source [23,24,52,53], although a slight delay in the onset of absorption is expected due to microbial deglycosylation required for glycosylated sources [19]. In addition to the status of glycosylation, the absorption is reported to be affected by other contents of diet, especially the dietary fiber content [54-56]. Bioavailability is increased by a rapid gut transit time and by low fecal digestion rates and is decreased by a fiber-rich diet [54,57,58].

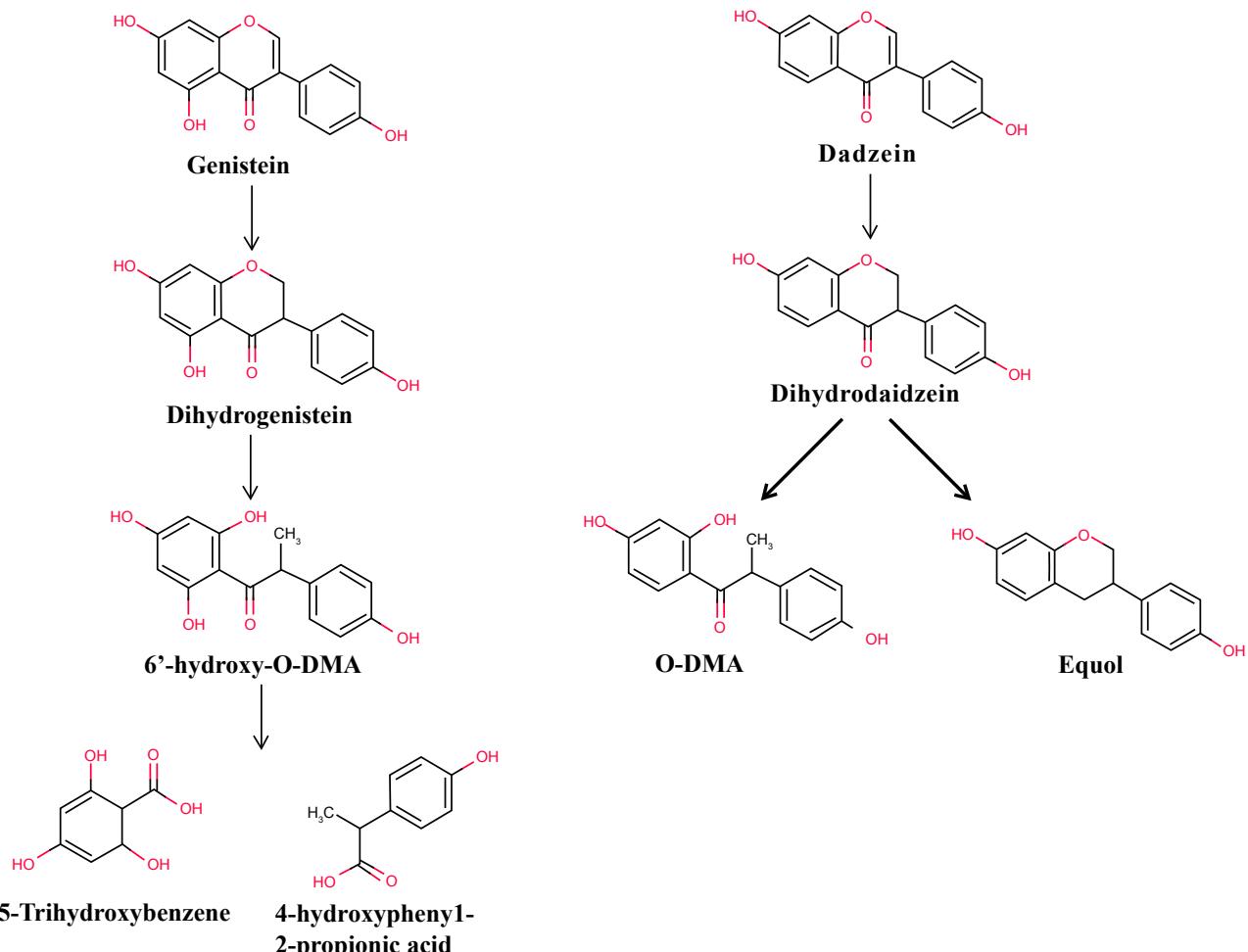


Figure 1: Metabolism of genistein and daidzein by gut microflora.

## Distribution

Isoflavones are rapidly distributed to all tissues and crosses placental barrier and blood brain barrier [59,60]. The volume of distribution ( $V_d$ ) of daidzein is found to be greater than that of genistein [48,55]. In a human study involving radiolabelled isoflavones, it was found that the mean volume of distribution normalized to bioavailability ( $V_d/F$ ), clearance rate, and half-life of [ $^{13}\text{C}$ ] daidzein were 336.25 L, 30.09 L/h, and 7.75 h, respectively; the corresponding values for [ $^{13}\text{C}$ ] genistein were 258.76 L, 21.85 L/h, and 7.77 h [48]. Similar values have been reported in several other pharmacokinetic studies [50,51].

Humans consuming three meals containing soy milk on a daily basis may have serum genistein concentrations up to  $4.6 \mu\text{M}$  [56], and human infants fed soy-based infant formula may have plasma genistein levels between 1.5 and  $4.4 \mu\text{M}$  [45]. Postmenopausal women consuming soy isoflavone supplements as an alternative to hormone replacement therapy can show serum levels in the range of 5-10  $\mu\text{M}$  [49,50].

Isoflavones are also distributed to the extra-vascular compartments. Placental transfer of isoflavones from dietary sources has been demonstrated in animal models [59,61-63] and human volunteers [64,65]. Isoflavones are also reported in the amniotic fluid, in expectant mothers on soy based diet [64,66]. Prostate is reported to achieve

higher-than-serum concentration of isoflavones in males consuming soy rich food [67].

## Metabolism

The metabolism of isoflavones closely mimic the metabolism of endogenous estrogens, with phase-II conjugative reactions predominant than phase-I reactions. The isoflavone aglycones, including equol, which passively diffuses into the intestinal cells are rapidly conjugated into sulfate or glucuronide conjugates, such that only 1-3% of isoflavones in the aglycone form reaches the systemic circulation [47,68,69].

UDP glucuronosyltransferase (UGT) and sulfotransferase (SULT) are the key enzymes involved in the phase-II conjugative reactions with isoflavones [70]. These reactions occurs mainly in the intestinal microsomes, concurrent with the absorption, but hepatic isoforms are also active [71,72]. Therefore, the extent of first-pass metabolism is very high (>90%) for isoflavones like genistein and daidzein before they enter into the general circulation.

UGT mediated glucuronidation seems to be the predominant phase-II conjugative reaction, and the glucuronide conjugate levels are higher than the sulphate conjugates [70,73,74]. Several isoforms of UGTs (1A1, 1A3, 1A4, 1A5, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B10,

2B11, 2B15, and 2B17) exist [70,71,75]. Most of the UGT isoforms are present in several organs, including intestine, kidneys and liver, but their distribution and levels shows variation [75]. UGT1A1 is expressed in all the organs although its expression in the liver appeared to be more pronounced than that in the intestine, UGT1A9 is only expressed in liver whereas UGT1A8 and UGT1A10 are mostly expressed in the small intestine [75].

UGT isoforms are reported to catalyze glucuronide conjugation at the 7 and 4' position of genistein and daidzein [70,71]. UGT1A1, 1A8, 1A9 and 1A10 were identified to be the major isoforms responsible for glucuronide conjugation of genistein, glycinein, biochanin A, prunetin, formononetin and daidzein [72]. Polymorphisms in UGT has also been reported, which may result in inter-individual differences in isoflavone conjugation rates and extents [76,77].

Sulphation of isoflavones are catalyzed by the SULT isoforms, especially SULT 1A1\*2, 1E, and 2A1 in intestine and liver [70,78]. SULT1A1 and SULT1E1 are reported to be important in regioselective mono- and di-sulfation reactions of isoflavones [79]. Sulphoglucuronide conjugates of isoflavones are also produced, by a combined or sequential action of UGTs and SULTs [73].

Isoflavones undergo phase-I metabolism too, although to a lesser extent than the phase-II conjugative reactions [5,73]. Hydroxylation reactions appears to be the main Phase-I reaction of isoflavones occurring in the liver [80,81].

The conjugated isoflavones are secreted in the bile and are released into the upper small intestinal tract, wherein microbial deconjugation and subsequent reabsorption of the isoflavones occurs. This process, known as entero-hepatic recycling, can significantly increase the residence time of the isoflavones in the body [82,83]. In addition to the entero-hepatic recycling, enteric recycling - wherein the intestinal enterocytes excrete the isoflavone conjugates back into the intestinal lumen may also significantly influence the disposition and bioavailability of isoflavones [82,84].

Efflux transporters such as multidrug resistance proteins (MRP1 and MRP2) and breast cancer resistance proteins (BCRP) are involved in entero-hepatic recycling and enteric recycling of isoflavones [77,85,86] and can be subject to genetic polymorphisms [77,87]. A recent study with BCRP knock-out (-/-) mice have shown that mice lacking BCRP show significantly reduced intestinal and biliary excretion of isoflavone conjugates, when compared to the wild-type mice [88]. A similar study with MRP2 deficient mutant mice reported a higher plasma concentration of genistein and daidzein following oral administration, partly due to reduced biliary excretion [87]. The inter-person variations in the efflux transporter expression and activity may cause marked variations in the intestinal disposition of dietary isoflavones [86,87]. A single nucleotide polymorphism (rs12762549) in MRP2 gene, was reported to be associated with inter-individual variation of plasma level of isoflavone metabolites in humans [87].

## Elimination

Approximately 10-60% of the dietary isoflavones is excreted in urine and constitutes the main route for elimination of isoflavones. The urinary excretion proportions varies with the isoflavone nature; for example, the urinary excretion of daidzein is higher than that of genistein and glycinein [51,89]. Glucuronide conjugates account for the majority (70-90%) of the isoflavone content in urine, followed by sulphate conjugates (10-25%) and aglycone forms (1-10%) [89]. The peak urinary elimination appears to be 7-8 hours after a isoflavone rich

meal [51] and majority of the elimination occurs within 24 hours of the meal, with an elimination 8-10 hours [90].

Fecal elimination is a minor route, accounting for 1-4% of the dietary isoflavone consumption [51], with the aglycone form accounting for the majority (>80%) of the fecal isoflavone content [91]. Isoflavones from the diet appears in the breast milk [45,92], amniotic fluid [64] and prostatic fluid [93].

The biological fate of dietary isoflavones is schematically summarized in figure 2.

## Biological Activities of Isoflavones

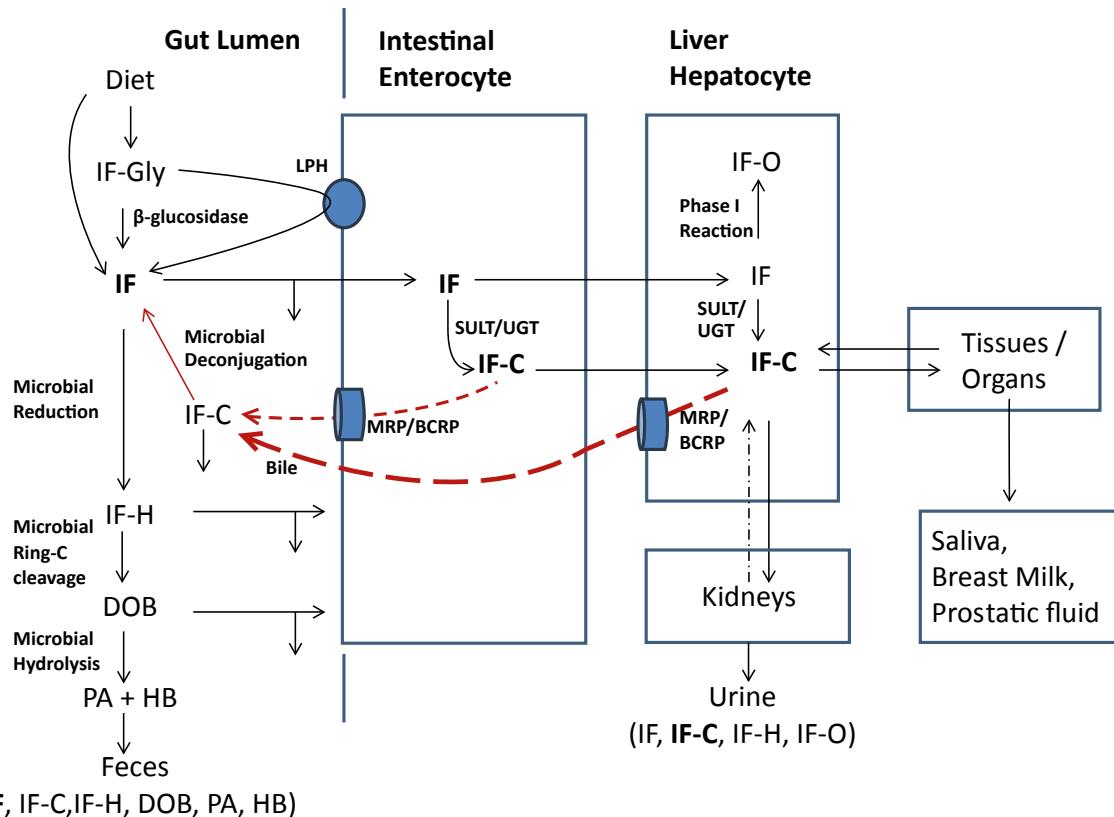
Isoflavones can produce both potentially beneficial and deleterious effects in humans by interacting with various cellular receptors, metabolites and enzymes. Isoflavones possess structural and functional features which resembles estrogens, namely, the terminal phenolic groups and therefore can act as estromimetics in metazoans [94]. Isoflavones are weak to moderate phytoestrogens, and can potentially modulate estrogenic responses through interaction with estrogen receptors [95]. As estromimetics, they can act as agonists on cellular estrogen receptors and thereby modulate estrogen-mediated cellular functions such as proliferation and apoptosis in cells abundant in estrogen receptors such as breast and prostate.

Two major subtypes of estrogen receptors are reported in humans, *viz.* estrogen receptor-alpha (ER $\alpha$ ) and estrogen receptor-beta (ER $\beta$ ). Agonists of ER $\alpha$  generally causes cell proliferation (for example, in breast cells), while ER $\beta$  agonists causes cell cycle arrest (for example, in prostate cells) and apoptosis [95,96]. This estromimetic effect of isoflavones, especially soy isoflavones, are therefore reported to be correlated to lower incidences of cancers, such as prostate cancer, in populations which consumes regular quantities of isoflavone-rich food [97,98].

In addition to the estrogenic effects, isoflavones may also have effects on other physiological systems. Isoflavones and their oxidative metabolites are reported to have anti-oxidant and free radical scavenging properties at physiological concentrations [99-101]. Isoflavones may reduce low-density lipoprotein (LDL) cholesterol in serum and thereby provide beneficial effects to overall cardiac functioning, presumably due their estrogenic effects on lipid peroxidation.

In addition to the above mentioned beneficial biological effects, isoflavones may also show potentially deleterious effects on cells, by virtue of their ability to inhibit key enzymes such as topoisomerases and kinases. Genistein is reported to be a potent inhibitor of topoisomerase II [102,103]. Inhibition of Topoisomerase II is reported to cause cleavage of MLL (myeloid-lymphoid leukemia) genes *in utero* and thereby cause an increased risk of acute myeloid leukemia and of acute lymphoid leukemia in infants [104-106]. Soy isoflavones, especially genistein, is a potent inhibitor of tyrosine kinases [107,108]. Soy isoflavones are reported to interfere with thyroid peroxidase involved in the formation of thyroid hormones [109,110]. Soy based foods were reported to increase the risk of hyperthyroidism [111], but this effect can be prevented with concurrent intake of Iodine [112,113].

These physiological effects, both beneficial and deleterious, of isoflavones are therefore dependent upon the plasma concentration and persistence of isoflavones (as aglycones) at the target organ [114]. The conjugated isoflavones do not easily diffuse across the cell membrane and therefore possess only weak cellular activities when compared to aglycone forms [74]. Therefore, the factors modifying



**Figure 2:** Fate of dietary isoflavones in human body. In each compartment, the most predominant component is indicated in bold format. Enteric recycling and enterohepatic recycling are represented by broken arrows. Abbreviations used in this figure; isoflavone glycoside (IF-Gly), Isoflavone aglycone (IF), isoflavone conjugate (IF-C), reduced isoflavone (IF-H), oxidized isoflavone (IF-O), deoxybenzoins (DOB), propionic acid derivative (PA), hydroxyl benzene derivative (HB), lactase phlorizin hydrolase (LPH), sulfotransferase (SULT), UDP glucuronosyltransferase (UGT), multidrug resistance protein (MRP) and breast cancer resistance proteins (BCRP).

pharmacokinetics (absorption, distribution, disposition, metabolism and elimination) of the oral isoflavones are important in maintaining the balance between beneficial and adverse effects of the isoflavones.

## Challenges and Conclusion

Extrapolating the effect of isoflavones from *in vitro* studies to humans is often complicated. For example, genistein aglycone produces rapid cell arrest and apoptosis of prostate cancer lines at micromolar concentration [115,116], but these effects are difficult to reproduce in metazoans because the serum levels of aglycones are in nanomolar levels [11,117]. The high rates of conjugative metabolism and resultant low levels of systemic aglycones leads to reduced pharmacological effects of isoflavones [23].

Studies with animal models provide valuable pharmacokinetic data, especially information about the metabolism and disposition patterns of a test compound. Rodent models have been used extensively for understanding the pharmacokinetics and pharmacodynamics of isoflavones [78,83,115]. But some studies [118,119] have shown that rodents (and other species) show marked differences in the metabolic pattern of isoflavones, which may have implications on selecting a suitable animal model for such studies [119].

Meta-analysis and interpreting the outcomes from multiple studies involving benefits (and risks) of dietary isoflavones is a challenge for researchers and regulatory authorities. For example, European Food Safety Authority recently rejected a number of beneficial claims on

soy products, including reduction of serum LDL concentrations, menopausal symptoms, cardiovascular health and hair growth, citing lack of substantial correlation between the consumption of soy and the study outcomes [120,121]. In 1999, United States Food and Drug Administration gave approval for labeling foods with soy proteins as being protective against coronary heart disease, based on outcomes of 38 clinical studies showing that consumption of at least 25 grams of soy per day lowered total and LDL cholesterol [122]. Further studies have confirmed this LDL lowering effect [123], while other studies have challenged the significance of the extent of LDL lowering and coronary risk [124]. Similarly, the extent of beneficial effects provided by dietary soy isoflavones on prostate cancer [97,98] is disputed by some studies [125,126]. These variations in study outcomes indicate that significant inter-individual variations exist in the pharmacokinetics and pharmacodynamics of isoflavones from dietary sources.

In summary, from a pharmacokinetic point of view, the bioavailability of isoflavones is subject to several factors that contributes to the inter-person variability observed i) variability in the isoflavone content in the food ii) availability of isoflavones from the food matrix iii) lactase persistence status of the test population iv) variations in the gastrointestinal microflora v) inherent variations in the gastric transit times vi) genetic variations in the systemic metabolic rates. Therefore including these factors into analysis of the study outcomes may help in better interpretation of such studies.

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