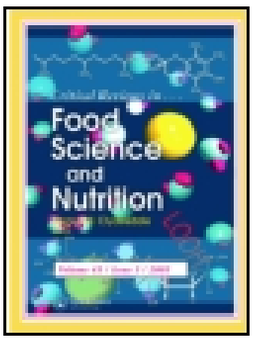

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REVIEW

Isoflavones derived from plant raw materials: bioavailability, anti-cancer, anti-aging potentials, and microbiome modulation

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ABSTRACT

Isoflavones are secondary metabolites that represent the most abundant category of plant polyphenols. Dietary soy, kudzu, and red clover contain primarily genistein, daidzein, glycitein, puerarin, formononetin, and biochanin A. The structural similarity of these compounds to β-estradiol has demonstrated protection against age-related and hormone-dependent diseases in both genders. Demonstrative shreds of evidence confirmed the fundamental health benefits of the consumption of these isoflavones. These relevant activities are complex and largely driven by the source, active ingredients, dose, and administration period of the bioactive compounds. However, the preclinical and clinical studies of these compounds are greatly variable, controversial, and still with no consensus due to the non-standardized research protocols. In addition, absorption, distribution, metabolism, and excretion studies, and the safety profile of isoflavones have been far limited. This highlights a major gap in understanding the potentially critical role of these isoflavones as prospective replacement therapy. Our general review exclusively focuses attention on the crucial role of isoflavones derived from these plant materials and critically highlights their bioavailability, possible anticancer, antiaging potentials, and microbiome modulation. Despite their fundamental health benefits, plant isoflavones reveal prospective therapeutic effects that worth further standardized analysis.

KEYWORDS

Aging; bioavailability; cancer; equol; isoflavones; microorganisms; phytoestrogen

Introduction

Over the past 30 years, there have been >45,000 publications related to isoflavones from different sources, out of them, >7000 for their anticancer effect, >1000 publications concerned their anti-aging, >1000 for microbiome modulation. Botanicals, being safe because of their natural origin, are linked to influential health concerns owing to their isoflavones-rich content (Hajirahimkhan, Dietz, and Bolton 2013). Isoflavones as plant-origin secondary metabolites are formed to defend against environmental stress such as ultraviolet (UV) radiation, mechanical damage, or any other attack from the surroundings (Serra, Almeida, and Dinis 2018; Tidke et al. 2018). Soy, red clover and kudzu were articulated significantly in the medical field. This is clearly because each of these botanicals contains a unique profile with a considerable quantity of isoflavones. The safety evaluation of isoflavone-containing botanicals depends mostly on their ability to enhance the metabolism of estrogen. However, this evaluation can be only achieved precisely if a proper characterization of the isoflavone profiles is applied (Sakthivelu et al. 2008). Importantly, these isoflavones were shown to possibly exhibit a variety of biological functions e.g. anti-aging, anti-cancer, and microbiome modulations when consumed in considerable amount (Szeja, Grynkiewicz, and Rusin 2017). The complete understanding of therapeutic effect of each of these compounds is largely complex. Also, their bioavailability and metabolism widely differ according to the chemical structure of isoflavone ingested. In addition, the precise mechanisms of action to demonstrate these multifactorial biological potentials remain obscure.

Recent reviews paid attention to identifying and analyzing the data linked to isoflavones and their role in the pharmaceutical field. For instance, Wu et al. (2020) built a baseline for understanding the antiaging properties of various polyphenols, but yet did not extensively contribute to a debate concerning the plant-derived isoflavones. In addition, Křížová et al. (2019) addressed the isoflavones health benefits in both human and animals. Besides, Domínguez-López et al. (2020) enumerated the effect of phytoestrogens hormone-related health concerns. However, these findings illustrated the magnitude of phytoestrogen with a limited scope

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covering the AMDE studies and prospective anti-aging potentials of the above-mentioned botanicals. Moreover, they have not made a substantial contribution to the significant effect of isoflavones on microbiome modulation. Also, as previously stated there is no recorded literature critically surveying the potential pharmaceutical activities of isoflavones derived from soybean, red clover, and kudzu. As a sequence, our current review outlined the controversial evidence of the previously published data regarding the relevant potential activities of botanicals'-derived-bioactive compounds and highlighted their safety concerns.

This current review extensively navigated the relative published articles, papers, and books indexed in Scopus, Web of Science, PubMed, Springer, and google scholar databases. The investigations reported using the abovementioned keywords were approximately 1066, out of which 781 was excluded and 285 studies met the eligibility criteria. Hence, this review was grouped into 7 groups: introduction, historical background, plant characteristics and identification, physicochemical properties, bioavailability and pharmacokinetics, general metabolism, and pharmacological actions of isoflavones. In addition, the review surveyed the pharmaceutical effect of isoflavones from soybean, red clover and kudzu, critically exploring their bioavailability and scrutinize their pharmacological potentials with their diverse mechanism of action. The present findings report the extracted information from the review papers and articles including epidemiological, preclinical, and clinical studies to bring out the current status on the topic.

Historical background

The history of isoflavones dates back to 1932 when Marrian and Haslewood discovered the chemical structure of equol as a fundamental metabolite in the urine of horses (Gampe et al. 2020). Any historical background of isoflavones should refer to Reinsch in the 1840s when ononins were isolated from the root of a herbal plant named "*Ononis spinosa*" and recognized as a glycoside (Pace et al. 2006).

The name "equol" interestingly reflects its equine origin. By that time, researchers mistakenly associated equol with the high concentration of estrogen during the pregnancy. In addition, equol was isolated in large quantities in the urine during summer and absent in winter. Subsequently, it was again incorrectly concluded that the estrogen imbalance occurred due to the seasonal variations. Interestingly, equol was found in the urine on both non-pregnant mares and stallions. Therefore, the previous theory of an association between equol and the large concentration of estrogen was disapproved (Gampe et al. 2020). Building on these limited findings, the occurrence of the first biological significance of isoflavones was discovered in 1946 when sheep grazing pastures seeded with *Trifolium subterraneum* until they manifested "clover disease" (Moorby et al. 2004). The manifestation of veterinarian fertility and reproductive problems in sheep has arisen the attention toward isoflavones derived from clover. Thus, the etiology of that disease was eventually reported to be due to a dietary source namely "formononetin"—plant-derived isoflavones (Moorby et al. 2004). The investigation of isoflavones and its metabolites then were straightforward and received much interest. Besides, it was a good starting point to explore isoflavones in many species such as domestic animals (Křížová et al. 2019), primates (Blair et al. 2003), felines (Bell, Rutherfurd, and Hendriks 2006), and laying hens (Setchell, Brown, and Lydeking-Olsen 2002). Afterward, soybean isoflavone metabolites (equol) were experimentally recognized in the human urine for the first time in the 1980s by Axelson M. (Setchell and Clerici 2010). By that decade, an extensive survey was presented by JL Ingham who immensely summarized over 100 years of data published in respect to naturally occurring isoflavones (Wang et al. 2020). Since then, the term phytoestrogen or phytoestrogenic isoflavones coined in that sense reflects a potential biological hallmark in the medial application. Recently, EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) issued a review of over 340 printed pages where the safety of isoflavones from food supplements (soybean, red lover, and kudzu) in menopausal women was widely dealt with.

Plant characteristics and identification

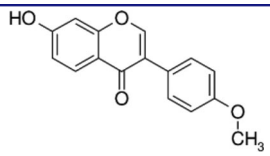
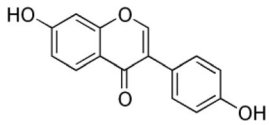
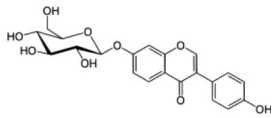
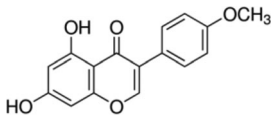
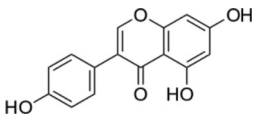
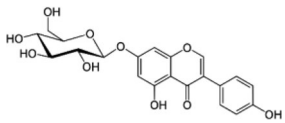
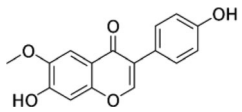
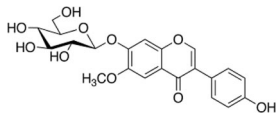
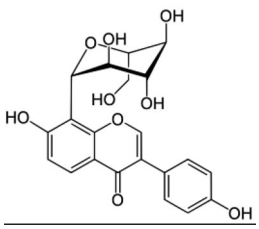
Isoflavones are phytochemicals that exist mainly in a variety of plants, seeds, and are widely distributed in many species belonging to *Leguminosae* family (Dixon and Sumner 2003). Isoflavones including glycosides and aglycones are considered the most remarkable compounds of the botanical sources: soybean, red clover, and kudzu. These botanicals contain a considerably large quantity of phytochemicals (flavonoids and non-flavonoids). Besides, they constitute the most substantial part of flavonoids that are predominantly synthesized in these plants (Boyle et al. 2003). Each group of the above-mentioned plants typically constitutes a characteristic isoflavone profile. Also, their structural isoflavones either occur in aglycons or glycosides forms (Burdette and Marcus 2013; Delmonte, Perry, and Rader 2006; Steller et al. 2013). The abundant representative aglycones and glycosides chemotypes are presented in Table 1 below. The data is provided as described by the U.S. Department of Agriculture, Natural Resources Conservation Service (Faulkner et al., 2011).

Soy isoflavones comprise three main isoflavones in their profile: daidzein, genistein, and to a lesser extent glycitein (isoflavone aglycones) as described in Table 2. These also exist in glucoside forms (e.g. daidzin, genistin, glycitein). Interestingly, the majority of isoflavones in nature exist as glycoside conjugates. Upon extraction of soybean, isoflavones maintain their different forms (Duru, Kovaleva, and Glukhareva 2017; Lante et al. 2018). Regarding red clover, it was found to contain formononetin and biochanin A, which primarily occur in aglycone form (Lemežienė et al. 2015). The glycosylated form of formononetin is also named ononin. In kudzu (*Pueraria lobata*), the abundant isoflavone is puerarin (Zeng et al. 2012). Besides puerarin, *Pueraria lobata* also comprises daidzein and then genistein (Son et al. 2019). Interestingly, researchers tend to count equol among the isoflavone classification (Boyle et al. 2003). Nevertheless,

Table 1. Description of the botanical sources of isoflavones in soybean, red clover, and kudzu (Lemežienė et al. 2015; Faulkner et al. 2011; Son et al. 2019).

Variables	Soybean	Red clover	kudzu
Botanical family	*Fabaceae/Leguminosae*—Pea family	*Fabaceae/Leguminosae*—Pea family	*Fabaceae/Leguminosae*—Pea family
Scientific name (species)	*Glycine max*	*Trifolium pratense*	*Pueraria montana*
Synonyms	*Dolichos soja* L.	*Trifolium pratense* L. var. *frigidum auct*. non Gaudin	*Dolichos lobatus* Willd
	Glycine gracilis	*Trifolium pratense* L. var. *sativum* Schreb	*Pueraria hirsuta* (Thunb.); C.K. Schneid.
	Glycine hispida		*Pueraria lobata* (Willd.) Ohwi
	Glycine soja Merr., non-Siebold, and Zucc., reseeding soybean or wild soybean		*Pueraria lobata* (Willd.) Ohwi var. thomsonii (Benth.) Maesen;
	Glycine ussuriensis		*Pueraria thunbergiana* (Siebold, and Zucc.) Benth
	Phaseolus max L.; Soja hispida Moench		
	Soja max Piper		

Table 2. Chemical structure, names and formula of isoflavones in soybean, red clover and kudzu (Jun et al. 2003; Munro et al. 2003; Occhiuto et al. 2007).

Isoflavone	Chemical structure	CAS registry	Chemical formula	Chemical name
Formononetin		485-72-3	$C_{16}H_{12}O_4$	7-hydroxy-3-(4-methoxyphenyl)–4-benzopyrone (biochanin B)
Daidzein		486-66-8	$C_{15}H_{10}O_4$	7-Hydroxy-3-(4-hydroxyphenyl)-4-benzopyrone
Daidzin		552-66-9	$C_{21}H_{20}O_9$	4H-1-Benzopyran-4-one,7-(β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)-(daidzein 7-O-glucoside)
Biochanin A		491-80-5	$C_{16}H_{12}O_5$	5,7-Dihydroxy-3-p-methoxyphenyl-4H-chromen-4-one
Genistein		446-72-0	$C_{15}H_{10}O_5$	5,7-Dihydroxy-3-(4-hydroxyphenyl)-4-benzopyrone
Genistin		529-59-9	$C_{21}H_{20}O_{10}$	4H-1-Benzopyran-4-one, 7-(β-D-glucopyranosyloxy)-5-hydroxy-3-(4-hydroxyphenyl)-(genistein 7-O-glucoside)
Glycitein		40957-83-3	$C_{16}H_{12}O_5$	7,4′-Dihydroxy-6-methoxyisoflavone (glycitin aglycone)
Glycitin		40246-10-4	$C_{22}H_{22}O_{10}$	4H-1-Benzopyran-4-one, 7-(β-D-glucopyranosyloxy)-3-(4-hydroxyphenyl)–6-methoxy-(glycitein 7-O-glucoside)
Puerarin		3681-99-0	$C_{21}H_{20}O_9$	4H-1-Benzopyran-4-one, 8-β-D-glucopyranosyloxy-7-hydroxy-3-(4-hydroxyphenyl)-(daidzein 8-C-glucoside)

the other group refused to rank it among the estrogenic compounds. Equol was, accordingly, classified as a metabolic product resulted from the action of intestinal microflora (Setchell et al. 2001; Setchell, Brown, and Lydeking-Olsen 2002).

Physicochemical properties

There are three molecules of aglycone isoflavones in soy isoflavones: daidzein, genistein and glycitein (isoflavone aglycones). There are also (e.g. daidzin, genistin, glycitin) as their corresponding glucosides. Most of the isoflavones exist in foods as glycoside conjugates which could be attributed to the extraction conditions. In soybean, the naturally occurring glycosylated and its derived forms , usually, maintain their structural forms in the extracts . The primary isoflavones in red clover are formononetin and biochanin A (Spagnuolo et al. 2014), the latter being present in the form of aglycone. The formononetin glycosylated form is also called ononin. In kudzu, puerarin is the primary isoflavone (Zeng et al. 2012), besides puerarin, daidzein, and genistein as the main isoflavones.

The extraction process or subsequent action after ingestion of intestinal microorganisms could alter the constitution of isoflavones in different plants (Piao and Eun 2020). Various techniques of plant pretreatment, such as soaking, boiling, and fermentation or extraction processes, using organic or green extraction assisted extraction techniques, may help to extract or recover isoflavones. These pretreatment or extraction conditions could effectively enhance and improve the bioavailability of isoflavones possibly via deactivating anti-nutritional components. However, physicochemical changes may also significantly impact the stability of nutrients and bioactive compounds specifically after the harsh conditions of either pretreatment or extraction (Akande et al. 2010).

Pharmacokinetics, ADME profiling and bioavailability

Although there is a shortage of data on pharmacokinetics, individual isoflavones of soybeans as bioactive ingredients were investigated for bioavailability. These isoflavones including daidzein and genistein, and their corresponding β-glycosides, methoxylated isoflavones; glycitin, formononetin, and biochanin A were extensively examined. Moreover, the dietary range of isoflavone in the food supplements was analyzed using several analytical methods (Lund et al. 2001).

In pharmacology, the perspective idea of adding protective groups to molecules is standard practice. This approach was typically adopted in the isoflavone-therapy thereby enhancing its absorption. Cassidys's study was a good starting point when 50 mg of isoflavone (genistein, and daidzein) and 25 mg of 3 methoxylated isoflavones (glycitein, formononetin, and biochanin A), respectively, were administrated to 19 healthy, medication-free women and a healthy man. The blood samples over 24–48 h, and 2 weeks, respectively, were collected for the GC-MS analysis (Cassidy et al. 2006). It has been found that isoflavone absorption in healthy adults was rapid and efficient. This was achieved in the case of daidzein, genistein, and their corresponding β-glycosides fates. In most adults, it took 4–7 h to reach peak plasma concentrations (Tmax) after aglycones ingestion. However, this pattern was shifted to 8–11 h when glycosides were ingested, indicating that the sugar moiety hydrolysis was considered the primary step for absorption.

Also, other findings demonstrated that isoflavones have comparatively long elimination half-lives (t1/2). The elimination time was found to be quite regular among adults and relatively long after the ingestion of pure compounds than soy-containing foods (Cassidy et al. 2006; Halm, Ashburn, and Franke 2007). The daidzein and genistein t1/2 were calculated to be 9.34 and 7.13 h, respectively. Thus, the early rise in isoflavone plasma concentration could be interpreted by the early absorption of some aglycone in the gastrointestinal tract (stomach, duodenum, and proximal jejunum) (Lund et al. 2001). Yet, when the glycosides were ingested, the plasma curve was further prominent, suggesting the existence of certain limitations of hydrolysis in the proximal part of the gastrointestinal tract (GIT). In this regard, daidzein or genistein was noticed to easily appear in the plasma. Afterward, similarities in their plasma profiles were evident, mostly like those which were found after the ingestion of relative aglycones. The systemic bioavailability which was estimated by comparing the area under curves (AUCs) in dose-normalized conditions was higher for the β-glycosides than for the relative aglycones.

Conversely, there are numerous β-glucosidases situated along with the whole length of human intestines that reserve enough quantity of isoflavone glycosides engaged in the hydrolysis process. β-Glucosidase activity broadly exhibited a developmental expression pattern particularly in an early stage of life. Also, it has pivotally helped in the isoflavones absorption from soy infant formula, resulting in high titers in the plasma of infants (Setchell, Brown, and Lydeking-Olsen 2002; Yang and Tsai 2019). Although β-glucosidase (EC 3.2.1.21) was isolated from human feces, there were predominantly , membrane-bound (Dai et al. 2021; Li et al. 2009). Distinctly the highest activity of these enzymes against flavonoids was articulated in the jejunum. In addition, isoflavones such as estrogens have been reported to go through enterohepatic recycling and shortly detected in bile when orally administered (Yang and Tsai 2019; Zeng et al. 2016). Thus, isoflavones are actively metabolized in the humans' intestines generating a range of metabolites (Figure 1) (Murota, Nakamura, and Uehara 2018; Yang and Tsai 2019).

Recent studies using Caco-2 TC7 monolayers have elucidated that genistin cannot easily infiltrate the enterocyte. While the corresponding aglycone, genistein, is permeable (Liu and Hu 2002). Subsequently, latest evidences suggest that the bioavailability of isoflavones was jointly associated with the hydrolytic stage of the glycosidic moiety. The superior bioavailability of AUC-determined isoflavones was evident in the subjects consuming the isoflavone glycosides, acting as a protective factor that would hinder the

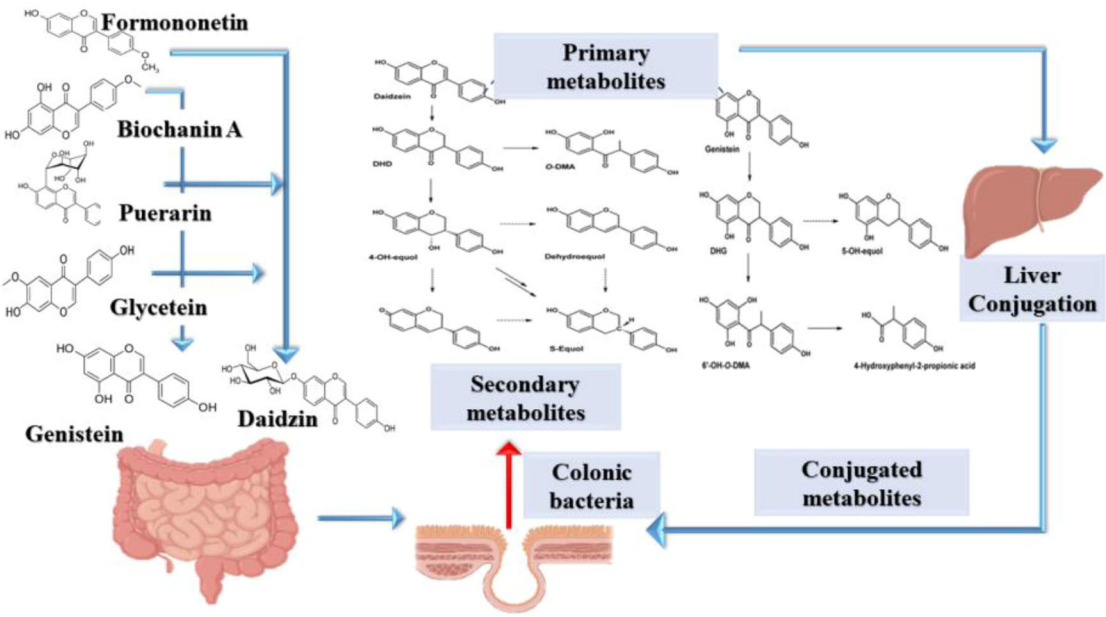


Figure 1. The production and metabolism of different isoflavones in humans. Isoflavones are metabolized extensively by intestinal microbiota into small molecule derivatives. Isoflavones are metabolized extensively by intestinal microbiota into small molecule derivatives. The red arrow indicates the bioconversion of isoflavones in the colon into secondary metabolites, and blue arrows indicate the reactions.

biodegradation of isoflavones. The quite a small portion of the aglycone that appeared in plasma, even after comparatively large doses were consumed, is an outstanding feature of pharmacokinetic studies. While the rise in unconjugated plasma levels of daidzein and genistein, aglycones were found to be 8.42% ± 0.89% and 3.71% ± 1.06% of total isoflavones after the first 2 hours of isoflavones administration, respectively.

The unconjugated daidzein reported as plasma profiles were identical to what was previously investigated when 125 g soybeans were consumed by three adults . These findings revealed that, higher the isoflavone intake, the peak concentrations in plasma were higher (Yang and Tsai 2019). The results obtained from plasma conjugated isoflavones were in harmony with numerous past and recent studies revealing that glucuronides is the main circulating form of all phytoestrogens (Islam et al. 2015; Legette et al. 2014; Yang and Tsai 2019; Zeng et al. 2016). When phytoestrogens were studied in the plasma, it was found to be comprising , exclusively glucuronide conjugates , in the portal venous blood of rats (Zeng et al. 2012). The first-pass conjugation uptake by the enterocyte of the Caco-2 TC monolayers tested was verified by the use of the everted intestinal sacs technique in rats (Liu and Hu 2002; Parsa et al. 2013). This elucidated that the intestine is the key factor for glucuronidation of isoflavone-active ingredients, in case of steroid hormones and not the liver.

The precise catalyzing conjugation of Uridine 5′-diphospho-glucuronosyltransferase (UDP-glucuronyl transferase) is yet to be fully investigated. In addition, it does not render them biologically inactive, although, daidzein and genistein circulate primarily in plasma as glucuronides and, to a lesser range, as sulfates (Soukup et al. 2016). It also significantly helps to preserve their intact form in the enterohepatic circulation. Probably, the intestinal hydrolysis of glucuronidases offered the persistent appropriate levels of unconjugated isoflavones.

Equol is isoflavandiol estrogen basically metabolized from its original form “daidzein” in the intestines by the action of bacterial microflora (Figure 1). Despite being steroids, endogenous estrogenic hormones like estradiol, equol (a non-steroidal isoflavones) was firstly recognized in the urine and blood of human samples. Importantly, its discovery resulted in declaring soy as a potential rich source of isoflavones (Setchell and Clerici 2010; Yang and Tsai 2019). In prior experiments, two-thirds of people who consumed soy-containing foods were observed to be capable of transforming daidzein into equol (Setchell and Clerici 2010). This ability has represented an opportunity to recognize individuals who have the bacterial enzymes or intestinal conditions required for this biotransformation.

Many of the previously analyzed supplements were recorded to have a high level of 6-O-methoxylated isoflavone glycoside. Compared with other isoflavones, there were scanty reports on the biological features or bioavailability of glycitin . On the other hand, based on its chemical properties it was predicted that the glycitin would have less estrogenic activity than daidzein, and genistein. To elucidate this prediction, feeding experiments were conducted in humans using a soy germ with a high glycitin concentration. It became clear that glycitein would build up in the plasma in about 24 hours (Dai et al. 2015; Yuan et al. 2012).

There are notable variations between the kinetics activity of methoxylated isoflavones, glycitin, formononetin and biochanin A, which depends on the function of the methoxyl group in the molecules. Glycitin, that is present in more than one phytoestrogen supplement, underwent hydrolysis of the β-glycoside moiety but without advanced

biotransformation, resulting in high plasma concentrations of glycitein. While biochanin A and formononetin, were efficiently and rapidly demethylated, resulting in high plasma concentrations of genistein and daidzein that were normally detected after the ingestion soy-containing food. Once a healthy individual ingested pure glycitin as a single bolus dose, his aglycone glycitein, was easily found in plasma at peak pla sma concentrations in about 4 hours. Additionally, glycitin tends to undergo minimal further biotransformation, apart from hydrolysis of the sugar moiety. Usually, the levels of plasma daidzein showed a slight increase 12 hours after glycitin ingestion, suggesting mild demethylation that is probably occurring in the colon (Figure 1). The steric obstacle of 7-hydroxyl to the structure of glycitein in the 6-methyoxyl group was assumed to account for the absence of intestinal bacterial conversion to daidzein. On the other hand, the methoxylated B-ring isoflavones of clover, formononetin and biochanin A showed no structural steric obstruction. Therefore, they were easily and effectively demethylated in humans, giving a boost to both daidzein and genistein. According to the literature data, only about 5% of the methoxylated isoflavones remained unchanged and the isoflavones that characterize soy proteins were effectively rendered bioavailable.

The fate of isoflavones of red clover derivatives such as Promensil is consistent in sheep and many other animal species with well-known metabolism, particularly formononetin and biochanin A (Beck, Rohr, and Jungbauer 2005; Fritz et al. 2013; Fugh-Berman 2007). An extremely low affinity for the estrogen receptor was observed when investigating the mechanism of action of formononetin and biochanin A (Murota, Nakamura, and Uehara 2018; Silva 2021). Molecular modeling studies showed that 7 and 4'-hydroxyl on the β-ring of isoflavones is the binding location for the estrogen receptor (Murota, Nakamura, and Uehara 2018; Silva 2021). Thus, the incidence of a methyl group greatly decreased the estrogenic potency. It can be assumed beneficial to turn clover isoflavones into soy-typical isoflavones that directly were recognized when the red clover supplement was consumed. This is plausible as it is extremely difficult to comprehend the physiological benefits of consuming methoxylated isoflavones as well as utilizing them as a form of genistein and prodrug delivery daidzein as a precursor.

All supplements have been studied as over-the-counter products which are commercially available. Because these products drop below the 1994 Dietary Supplement Health and Education Act scrutiny, there is currently no supplement industry legislation. The fact that there is virtually no proof of pharmacokinetics, phytoestrogen supplement safety, or pharmacology, the issue is more challenging. Besides, numerous statements driving the sales as health supplement rely currently on the clinical and nutritional evidence rather than supplements from phytoestrogen-rich foods, such as soy. These studies on pharmacokinetics have a bearing on the clinical trials since all isoflavones cannot have uniform absorption and bioavailability.

General metabolism of isoflavonoids

Some dietary flavonoids are found in their glycosidic forms wherein one or more sugar moieties are bound at position C-3 to the phenolic or hydroxyl groups. The fundamental structure of flavonoids, i.e. the aglycon shape structure and the type of sugar moiety to which they are attached, influences their bioavailability (Manach et al. 2004).

The glycoside forms of dietary flavonoids are mostly present conjugated as a sequence of the physiological role of phase enzymes. However, it was not the case in plasma, where glycosides are scarce (Morand et al. 2000; Sesink, O'Leary, and Hollman 2001). Deglycosylation, based on the type of sugar moiety, occurs in the small intestine and even in the large intestine. For this purpose, two different enzymes were known to act as β-glucosidases against monoglucosides of flavonoids in the digestive tract (Day et al. 2003). The first enzyme was lactase-phlorizine hydrolase (LPH) which was reported to act as an associated brush border that LPH hydrolyzes lactose to glucose and galactose. LPH efficiently hydrolyzes both genistin and daidzin in isoflavone metabolism. Thus, the aglycons formed in the intestinal lumen could be quickly absorbed (Tamura, Tsushida, and Shinohara 2007). In order to manifest a lactase deficiency, the plasma concentrations of isoflavone metabolites are only inhibited at the initial phase of absorption. This metabolic action is comparable to those of individuals who are capable of producing lactase, probably because the lower hydrolysis potency is balanced by the intestinal microbiota. In case of human intestine and liver cell-free extracts, hydrolysis of isoflavone glucosides is mainly carried out by the other enzyme—cytosolic-β-glucosidase (CBG), with a lower LPH contribution than in rats (Islam et al. 2014).

A methylated isoflavone, calycosin-7-O-glucoside, has recently been documented to be a novel substrate for sodium-glucose transport proteins (SGLT1) in rats, but not for LPH. Therefore, deglycosylation in the intestinal tract may be required in order to enhance the bioavailability of flavonoid monoglucosides, even though the subsequent action of microbiota might be sufficient to compensate for the absence of this phase (Shi et al. 2016). Once flavonoid aglycons reach their destination in the intestinal epithelial cells, phase II enzymes generate the corresponding conjugated metabolites. Flavonoids, uridine-5-diphosphate-glucuronosyltransferases (UGT), sulfotransferases (SULT), and catechol-O-methyltransferases (COMT) have been also articulated to be metabolized by three groups of phase II enzymes (Van Der Woude et al. 2004).

UGT were considered important enzymes which conjugate both flavonoids , and glucuronic acid in the small intestine of rats (Krych et al. 2013; Van Der Woude et al. 2004). UGT and SULT were, in addition, recorded to take a major part in the production of monoglucuronide and sulfate in human (Mullen, Edwards, and Crozier 2006; Van Der Woude et al. 2004). Liver is another crucial location of phase II metabolism. For example, absorbed flavonoids following intestinal conjugation are transferred to the portal vein or even the lacteal veins. Further conjugation occurs in the liver, including methylation or sulfation, leading to the

formation of multiple conjugates. These metabolites are subsequently deconjugated and reabsorbed by the intestinal microbiota. This enterohepatic circulation leads to an increase in the level of plasma flavonoids and their half-life in both humans and rats (Che et al. 2005; Yang and Tsai 2019).

Intestinal microbiota's importance in isoflavones metabolism

Bioavailability represents the proportion of molecule's absorbed doses, and ultimately its metabolites, that reach its physiological activity sites. GIT is centric to metabolic processes In case of bioavailability of ingested bioactive compounds certainly, the liver and kidneys play a significant role. Effective phenolic conjugation primarily occurs in all three organs (gut, liver, kidney), mainly via the action of O-methyltransferases, UDP glucuronosyltransferases, and sulfotransferases. This conjugation basically takes place to increase water solubility and subsequent excretion (Manach et al. 2004).

There is insufficient data to completely understand the fate and function of polyphenols in the upper parts of the GIT. However, in the context of oral cancer prevention, influence of polyphenols have been widely discussed (Petti and Scully 2009). Although their fate has not been systematically examined in the stomach yet, there is satisfactory evidence that isoflavones (an important category of polyphenols) can be deglycosylated in the jejunum and quickly absorbed into the membrane of enterocytes through lactase-phlorizin hydrolase activity (Németh et al. 2003; Petri et al. 2003). These mechanisms may raise the impact of the chewing process on the bioavailability of polyphenols through both indirect and direct pathways, such as salivary hydrolysis (Walle et al. 2005).

Equol is primarily meant to be formed in distal sections of the intestinal tract. Consequently, it can be explained that the GIT transport mechanisms are not region-specific. It is well-known that a large percentage of ingested polyphenols enter the colon, where decreased transit time helps the bacterial conversion. This is process is regardless of what exactly happens in the upper part of GIT. It was previously reported that the peaks of phenolic metabolites in plasma samples were observed 6–8 h postprandial after consuming the plant substrates (Franke, Custer, and Hundahl 2004).

Indeed, a large proportion of the phenolics absorbed are effectively conjugated in the enterocytes and later was observed in the liver by the action of bile (enterohepatic circulation) before being secreted back into the small intestine (Yang and Tsai 2019). Enterohepatic circulation thus leads to bacterial nourishment as different bacterial species can hydrolyze the bulk of glucuronidated and sulfated phenolic metabolites produced in the bile (Ridlon, Kang, and Hylemon 2006). Bacterial hydrolysis thus makes it possible to reabsorb the conjugated phenolics before being lost in feces and thus postponing the presence of phenolic metabolites (second plasma peak) in the blood. It was previously demonstrated that the phenolic compounds are associated with the alteration that occur in the intestinal microbial population after treatment with an antibiotic. Therefore, the decrease in phenolic concentrations in plasma, and kidneys, is another significant evidence. This evidence suggested that distal gut microorganisms mainly function in the metabolism of phenolic compounds (Kilkkinen et al. 2002).

The utilization of germ-free mice, i.e. mice that have been bred in isolators under controlled sterile conditions and living microorganisms free-diets, has given valuable insights into the crucial aspect of intestinal microbial populations in shaping the host physiology, such as the ability to metabolize food substrates such as phenolics. Recent molecular studies have highlighted the presence of few thousands of different species of bacteria in the human GIT and, consequently, of more individual strains (Qin et al. 2010). In brief, our intestinal microbiome concealed several primary and significant roles for the transformation of nutritional dietary phenolic compounds. However, each organism (in the sense of a personalized fingerprint) has its own characteristic intestinal microbiota, regardless of the presence of the core microbiome and the persistence of the gut microbial ecosystem over time with insignificant changes in dietary habits. Indeed, there are broad inter-individual variations between intestinal bacterial composition, and diversity together. There are also noticeable quantitative differences and little similarity indexes between the gut specimens of various persons, even for most dominant microbial species (Clavel et al. 2005; Clavel and Mapesa 2013; Křížová et al. 2019)

Role of intestinal microflora in the bioavailability and metabolism of isoflavones/or/metabolic pathways of isoflavone metabolites

A sequence of dominant core mechanisms that contribute significantly in a wide panel of phenolic compounds metabolism, including isoflavones, are catalyzed by gut bacteria which are: (Selma, Espín, and Tomás-Barberán 2009) 1. Esterified and conjugated boundary hydrolysis, 2. Deglycosylation (sugar moiety removal), 3. Demethylation (methyl hydroxyl group replacement), and 4. Dehydroxylation (hydroxyl group reduction). Recent studies have shown that the therapeutic effectiveness of isoflavones may be due to their ability to be transformed into other types of metabolites, e.g. dihydrodaidzein (DHD), tetrahydrodaidzein (THD), equol, and O-Desmethylangolensin (O-DMA) in the intestines (Peirotén et al. 2020). In addition, significant attention has recently been paid to Equol (7-hydroxy-3-(4-hydroxyphenyl)-chroman), a metabolite of daidzein, as its biological activity, differs from that of its precursor (Setchell, Brown, and Lydeking-Olsen 2002; Subedi et al. 2017). The metabolites of genistein and glycitein are basically present in human urine (for genistein: dihydrogenistein, 6-OH-O-DMA (Heinonen et al. 2003), 4-hydroxyphenyl-2-propionic acid and phloroglucinol; (for glycitein: dihydroglycitein, 5-methoxy-DMA and 6-methoxy-equol) (Coldham et al. 2002; Hur et al. 2000). These metabolites' physiological functions remain obscure.

Table 3. Bacterial strain able to convert the isoflavone daidzein OR/genera of equol-producing bacteria.

Bacterial strain	End metabolite	Origin	References
Adlercreutzia equolifaciens FJC-B9	Equol	Human feces	Maruo et al. 2008
Asaccharobacter celatus	Equol	Rat cecum	Minamida et al. 2006
do03	—	—	Minamida et al. 2008
Eggerthella sp. YY7918	Equol	Human feces	Yokoyama and Suzuki 2008
Enterorhabdus mucosicola	Equol	Mouse ileal	Matthies et al. 2008
Mt1-B8	—	mucosa	Clavel et al. 2009
Eubacterium ramulus wK1	*O*-desmethylangolensin	Human feces	Schoefer et al. 2002
Lactococcus sp. 20–92	Dihydrodaidzein	Human feces	Shimada et al. 2010
Slackia equolifaciens	Equol	Human feces	Jin et al. 2008
DZE	—	—	Jin et al. 2010
Slackia isoflavoniconvertens HE8	Equol	Human feces	Matthies, Blaut, and Braune 2009
Slackia sp. NATTS	Equol	Human feces	Tsuji et al. 2010
Strain D1 and D2	Equol	Pig feces	Yu, Yao, and Zhu 2008
Strain HGH6	Dihydrodaidzein	Human feces	Hur and Rafii 2000
Strain HGH136	*O*-desmethylangolensin	Human feces	Hur et al. 2002
Strain Julong 732	Equol[b]	Human feces	Wang, Hur, et al. 2005
Strain Niu-O16	Dihydrodaidzein	Bovine rumen	Wang, Shin, et al. 2005; Zhao et al. 2011
Strain SY8519	*O*-desmethylangolensin	Human feces	Yokoyama et al. 2010
Strain TM-40	Dihydrodaidzein	Human feces	Tamura, Tsushida, and Shinohara 2007

Equol was documented to exhibit higher estrogenicity level, feasible antioxidative potency and antiandrogenic properties compared to that of daidzein (Atkinson, Frankenfeld, and Lampe 2005; Setchell, Brown, Zimmer-Nechemias, et al. 2002). Interindividual variability in equol production may be specific to humans, all animals tested up to date, as well as rats, mice, and chimpanzees, which systematically manifested equol excretion (Atkinson, Frankenfeld, and Lampe 2005; Subedi et al. 2017). Though O-Desmethylangolensin (O-DMA) is present in 80%–90% of the human population, equol was found only in 30%–50% of the population (Atkinson, Frankenfeld, and Lampe 2005). The variations in the gut microbial population have resulted in interindividual variance in the capacity to generate equol. Accordingly, the intestinal microbiota responsible for the development of equals can vary from one person to another (Setchell and Clerici 2010).

Equol production

From the fecal sample of an equol-producing human subject, a stable mixed culture that transforms daidzein into equol was obtained. It was reported that it constitutes *Lactobacillus mucosae*, *Finegoldia magna*, *Enterococcus faecium* and *Veillonella* sp. The capacity to generate equol was provided by the addition of this bacterial consortium to a fecal culture that could not metabolize daidzein (Decroos et al. 2005). Interestingly, it was revealed that biochanin A, formononetin, and glycitein, could be metabolized by *Eubacterium limosum*, which can produce O-demethylation products of multiple methylated compounds (Hur and Rafii 2000). Demethylated drugs, genistein, daidzein and 6,7,4′-trihydroxyisoflavone, respectively, were also found in cultures after bacterial cells incubation. However, the same metabolites were not recognized with spent culture medium, suggesting the presence of cell-associated demethylase activities. It was surprisingly identified that *E. coli* strain, HGH21, and the gram-positive bacterial strain, HGH6, after screening a healthy person's fecal bacteria, develop daidzein and genistein under anaerobic environments, respectively, from their precursors, daidzin and genistin (Hur et al. 2000). An anaerobic gram-positive bacterium classified as HGH136 has been identified (Hur et al. 2002). The 16S rRNA analysis of this strain was reported to be closely associated with *Clostridium* species. In order to generate O-DMA under anaerobic conditions, this bacterium splits the C-ring of daidzein. O-DMA was, in addition, generated by incubation of strain HGH136 with synthetic dihydrodaidzein. By combining either daidzein or dihydrodaidzein to the incubation medium of strain HGH136, no further metabolites were eventually detected (Hur et al. 2002).

Later, one more strain of *Clostridium-like bacteria*, named TM-40, was discovered to metabolize daidzine (Tamura, Tsushida, and Shinohara 2007). The strain was demonstrated to be able to convert dihydrodaidzein into both daidzin and daidzein (Table 3). The 16S rRNA sequence of this strain was largely similar to the *Clostridium* species but has a 93% resemblance to that of *Coprobacillus catenaformis* (Tamura, Tsushida, and Shinohara 2007).

Equol-producing bacteria

Numerous strains of bacteria with sequences similar to *Eggerthella* species are considered a major part of the intestinal colonic bacteria connected to the production of equol. Nine strains of bacteria with 16S rRNA genes 93% similar to that of *Eggerthella sinensis*, were identified to have the ability to metabolize isoflavones by producing daidzein equol, known as *Adlercreutzia equolifaciens*, a new type of species (Maruo et al. 2008). Among them, a strain defined as, A. *DSM 19450, equolifaciens*, was sequenced (Maruo et al. 2008). With approximately 92.8% similarity to *Eggerthella hongkongensis* HKU10, a strain, *Julong 732*, was isolated from colonic bacteria in humans by which was able to transform dihydrodaidzein to equol, but not daidzein (Wang, Shin, et al. 2005).

Eggerthella sp., another fecal bacterial strain YY7918, which was isolated from a human, was reported to transform daidzein and dihydrodaidzein to S-equol (Yokoyama and Suzuki 2008). The genome of this strain was also

sequenced (Yokoyama et al. 2011). Another strain of do03 T bacteria, identical to *Eggerthella* and capable of producing daidzein equol via the production of dihydrodaidzein, was obtained from the rat intestine. Similarly, both butyric acid, and arginine improve strain do03 T's capacity to yield more than four times the amount of equol (Minamida et al. 2008). It was recognized as *Asaccharobacter celatus* because of its distinctive biochemical properties (Minamida et al. 2008).

Isoflavones are also metabolized by certain strains of the genus *Slackia*. A non-spore-forming, gram-positive, *NATTS*-designated bacterial strain was collected from an equol-producing person's fecal bacteria. In a sorbose containing cultures as a source of carbon, daidzein was transformed to equol. The strain has been determined to belong to *Slackia*, using the 16S RNA sequence (Tsuji et al. 2012; Tsuji et al. 2010). From this bacterium, the genes converting daidzein to dihydrodaidzein, and dihydrodaidzein to equol have been cloned and categorized as (*Orf 1-3*). It was also showed that a protein produced by *orf3*, which belongs to the NADH flavin oxidoreductase family can convert daidzein to dihydrodaidzein (Tsuji et al. 2010). Dihydrodaidzein was subsequently transformed by the action of orf2-encoded protein, that belongs to superfamily of short-chain dehydrogenase/reductase, to cis and trans-tetrahydrodaidzein (THD). A protein encoded by orf1 that has an amino acid sequence identical to succinate dehydrogenase (Tsuji et al. 2010) was highlighted to convert cis and trans-THD to equol. Besides, A DZE-designated strain of bacteria that is able to convert daidzein to equol was reported to possess 89% and 88% similar to *Slackia faecicanis* CCUG 48399 and *Slackia exigua AF101240*, respectively, and 87% similar to *Slackia heliotrinireducens* (Jin et al. 2008). An equol-producing strain 20–92 was isolated from the human digestive tract and identified by 16S rRNA analysis as *Lactococcus garvieae* (Uchiyama, Ueno, and Suzuki 2007). It's been shown after genetic analysis that this microbe has an open reading frame, Orf US2, which encodes a reductase of dihydrodaidzein that transforms daidzein into dihydrodaidzein [88].

Of the 22 strains characteristic to human *Bifidobacterium* strains investigated 12 of them efficiently transformed daidzin to daidzein (Raimondi et al. 2009). Though, none of these strains could transform daidzein to equol. *Bifidobacterium animalis*, *B. longum* and *longum-a*, and *B. pseudolongum* were claimed to deconjugate the malonyl-, acetyl- and β-glucoside conjugates of daidzin to generate daidzein in soy milk (Tsangalis et al. 2002). These strains have been identified as a mix of *Lactobacillus mucosae* EPI2, *Enterococcus faecium* EPI1, *Finegoldia magna* EPI3 and *Veillonella* sp. in soy milk. Furthermore, EP generated equol from daidzein in pure culture, but none of these strains could generate equol (Decroos et al. 2005).

Potentiation of gut microbiota

The natural product administration to humans has revealed a meaningful contribution to avoid or treat many serious diseases. Because of the significance counted for phenolic bioavailability and associated effects on health, dietary strategies that enable gut microbiomes implied significant implications in the dietary strategies to develop active and potential metabolites. The utilizing of antibiotics is the main evidence of the concept that it intends to influence metabolites production by targeting intestinal microbial populations (Franke, Custer, and Hundahl 2004; Milder et al. 2007). To date, however, the concept of diet-driven optimization of microbial phenolic conversion has still not been corroborated by the relevant evidence. The relation between the consumption of specific constituents of the diet and the development of phenolic metabolites is still undefined. Hence, as for most of the polyphenols, there are no known producers of microbial metabolites in the human gut. In the same research agenda, soy—and their isoflavone content—is considered one of the pioneering examples of this challenge-led approach due to the lack of microbial contribution in metabolite production. Nevertheless, the increased equol excretion has been linked to increased fat, meat, and fruit consumption (Gardana, Canzi, and Simonetti 2009).

Probiotics are categorized as live microorganisms that serve potential health benefits to the consumer if administered in sufficient quantities (Duru et al. 2019). Based on the logical basis that by increasing the concentration of aglycones of probiotic lactic acid bacteria (primarily *lactobacilli* and *bifidobacteria*), glucosidases could then able to improve the phenolic bioavailability. Based on that logic, their use has drawn much attention to enhancing phenolic activation in the GIT. It is suggested that deglycosylation is not a limiting step for the in vivo production of active metabolites in the intestine. Moreover, although many pieces of research on soy product fermentation using probiotic bacteria have been conducted in clinical trials, no beneficial effects of probiotic bacteria were demonstrated in all ten soy-based and probiotic treatments (Greany et al. 2004).

More interestingly, researchers at University of Ghent have effectively used human intestine phenolic-transforming bacteria such as demethylation-catalyzing *Eubacterium limosum* to improve the activation of both isoflavone and isoxanthohumol in vitro continuous culture systems and in vivo in rats (Possemiers et al. 2008). Functional foods such as prebiotics e.g. fructooligosaccharides (FOS) and inulin, non-digestible nutrition additives, were documented to exhibit a beneficial impact on the host by selectively improving the production and/or action of one or a small number of species of bacteria existing in the colon (Roberfroid 2007).

Pharmacological actions

Isoflavones as anticancer

Cancer was defined as a deadly uncontrolled growth of the cells due to genetic or epigenetic defects and signaling alterations in the cell (Khan et al. 2016). Currently, over 60% of anticarcinogenic drugs are secondary metabolites derived from plant sources (Dall'acqua 2014).

Soybean, red clover, and kudzu are leguminous plants linked to a decreased incidence of cancer, indicating a potential possible role of these plants in cancer control and prevention (Figure 2). Although the scientific data are yet

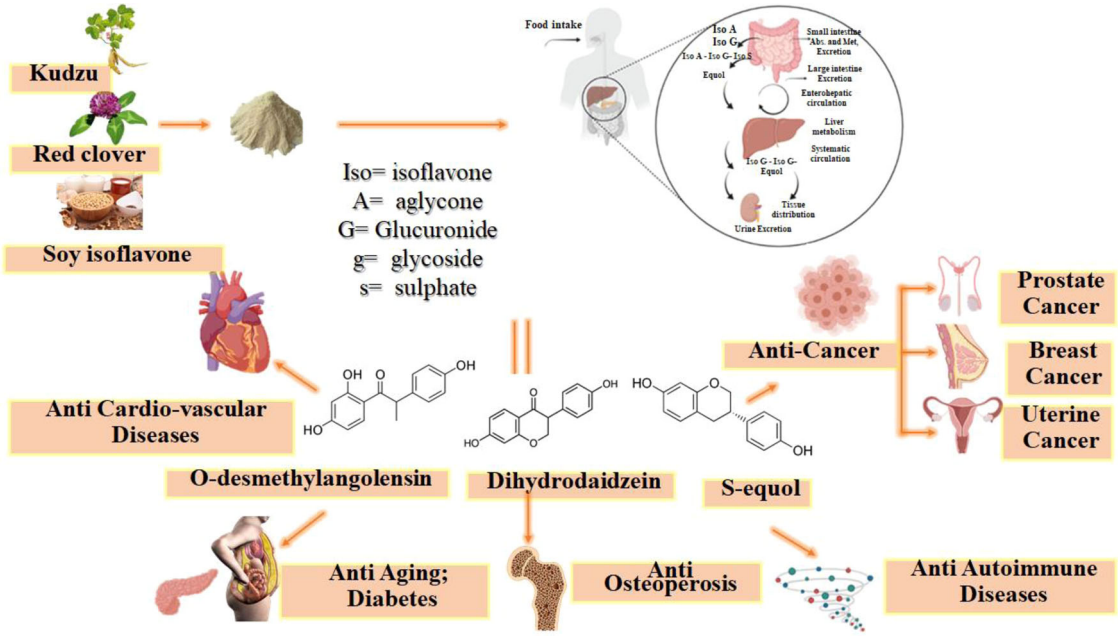


Figure 2. The black arrows indicate the ingestion, metabolism, and systematic circulation of isoflavones thought the body until final extraction in urine. The orange arrows indicate the different pharmacological actions of isoflavones metabolites.

scattered, some evidence highlighted the significance of isoflavones in improving the efficacy of chemotherapy or decreasing its adverse effects. Furthermore, a combination of a variety of isoflavones' bioactive compounds has exhibited a significant role in this regard. These legumes are largely consumed in the eastern countries e.g. Japan and China more than the non-Asian countries (Tidke et al. 2015). Therefore, the incidence of cancer cases has been reported to be higher in western populations (He and Chen 2013). Needless to say, that lifestyle, diet and other environmental conditions are also crucial factors that contribute to the etiology of a variety of cancer. Isoflavones tend to possibly have an anticancer effect due to their antioxidant and anti-inflammatory activities particularly if consumed in an appropriate amount. Beside their ability to modulate the signaling pathways and cell proliferation (Hosseinzadeh et al. 2020). For instance, Glycine max (genistein, daidzein and glycitein) has been reported to likely exhibit multipurpose anticancer potentials e.g. gallbladder (Ono et al. 2020), prostate (Shafiee et al. 2020), breast (Yuliani, Istyastono, and Riswanto 2016), and bladder carcinomas (Park et al. 2019). Interestingly, the synergism of daidzein and genistein soy isoflavones improves the apoptotic effects on C4-2B prostatic cell lines. Genistein as the most abundant isoflavones in soy was suggested to enhance apoptosis, inhibit angiogenesis and metastasis (Sahin et al. 2019). Also, *glycine max* isoflavones were recorded to inhibit SHH signaling, expression of SMO, and GLI1 in clinical nasopharyngeal cancer stem cells (Zhang et al. 2019). In addition, NF-κB inhibition and DNA methylation and enhancement of histone acetylation are molecular mechanisms recorded in the in vitro and in vivo studies that were found to be linked to cancer control and prevention (Sarkar and Li 2003).

Similarly, these multiple effects were demonstrated when red clover and kudzu extracts were preclinically or clinically investigated. For instance, formononetin battles cancer growth by inducing apoptosis, retarding cell growth, and impeding metastasis by targeting different pathways. These pathways were normally modulated in a variety of cancers such as breast (Zakłos-Szyda and Budryn 2020), prostate, nasopharyngeal bladder, lung, cervical carcinomas. In addition, osteosarcoma, multiple myeloma (Kim et al. 2018), glioma (Liu et al. 2015) has been inhibited by formononetin. The metabolic pathways that fight the progression of carcinomas were suggested to be due to the activation of MAPK and inactivation of PI3K/AKT Pathway, inhibition of JAK/STAT or BCR-ABL/STAT5 signaling pathways (Jiang et al. 2019).

The anticancer properties of biochanin A have been also documented against hepatic, breast, colon and ovarian carcinomas, leukemia and smooth muscle proliferation. These therapeutic effects were demonstrated through different mechanisms of action. Apoptotic effect in PC-3 and LNCaP and TRAIL in prostatic cancer, anti-angiogenic and genotoxic effects in breast cancer (MCF-7), improvement of ERα-positive cell proliferation, inhibition of epidermal growth factor receptors and antifibrotic effect and liver injury were also mechanisms of actions documented in previous studies (Breikaa et al. 2013; Raheja et al. 2018).

Puerarin's possible anticancer potentials although less investigated s shown to offer protection in hepatic, breast, colon and ovarian carcinomas, leukemia and smooth muscle proliferation. Puerarin as an anticarcinogenic agent showed multiple mechanisms of action in different models. It was investigated to restore hepatic injury and regulate Bcl-2 mRNA expression, activate pulmonary PKC signaling pathway, regulate JNK signal pathway in acute promyelocytic leukemia, retard human oophoroma cells HO-8910, inhibit of MDR phenotype in breast cancer, suppress NF-κB activity, inhibit colon cancer (HT-29 cellular growth, suppress c-myc

Table 4. Anti-cancer effect of isoflavones and their molecular mechanisms of action.

Bioactive component	Model/oncological manifestation	Drug administration, and duration	Effect/molecular mechanism	References
Formononetin	Preclinical 4T1 breast cancer in tumor-bearing BALB/c	100, 200, and 400 mg/kg mice, 6 days/week for 5 consecutive weeks	↑ apoptosis in 4T1 cells, ↑T-cell cytokines production (IL-12 and IFN-γ), ↓ 17-β-estradiol (E2) synthesis,	Akbaribazm, Khazaei, and Khazaei 2020
Daidzein	Preclinical multiple myeloma	50, 75, and 100 μM FMN for 6 h/20–40 mg FMN/kg mice i.p. thrice/week for 20 days	ROS-regulated ↓ STAT3 and STAT5 signaling cascade	Kim et al. 2018
	In vitro human breast cancer cell lines MDA-MB-231 and MCF-7 cells.	1–15 mg/mL for 48 h	↓ROS generation; regulation of MMP-9, N-cadherin and E-cadherin; or VEGF secretion	Zakłos-Szyda and Budryn 2020
	In vitro osteoblastic OCT1	(1, 5, 10, 30, and 60 μg/mL) of daidzein for 48 h	↑ Col I, Runx2, and ALP expression, ↑ BMP-2/Smads pathway	Hu et al. 2017
	In vitro human prostate cancer	Dz (25–200 μM), Gt (25–200 μM) or their combinations (25 or 50 μM of each) for 48 h	↓ LNCaP and C4-2B cells.	Dong et al. 2013
Biochanin A	Prostate cancer cells	Biochanin A (20–100 μM) for 48 h	Regulate NF-kB activity, ↑TRAIL-mediated apoptosis, TRAIL-induced apoptosis	Szliszka et al. 2013
	In vitro non-small cell lung cancer (NSCLC) cell lines	NI	↑ antiproliferative activity against cancer cell lines	Ambrosio et al. 2016
	Melanogenesis (B16 melanoma cells)	0.1 g of 2% biochanin A twice daily for 3 weeks	↓ tyrosinase, ↓ melanogenesis in cultured B16 melanoma cells and skin of zebrafish embryos and mice	Lin et al. 2011
Genistein	In vitro murine and human breast, ovarian and prostate carcinomas	GenLip (10–80 μM)	↓ tumor-promoter, 12-O-tetradecanoylphorbol-13-Acetate, ↑ apoptosis cascades	Phan et al. 2013
	Clinical nasopharyngeal cancer stem cells	(0–100 μM) of Gen for 5 days	↓SHH signaling, ↓ expression of SMO, and GLI1	Zhang et al. 2019
	Clinical metastatic colorectal cancer	30–600 mg/day for 7 days every 2 weeks for 3–6 months	Combination of Gen to FOLFOX or FOLFOX–Bevacizumab was safe and efficient	Pintova et al. 2019
	In vitro squamous cell carcinoma cells SK-MEL-28	(0-50 μM) of Gen for 24 h	↓ MEK/ERK and JNK signaling pathway, ↓ MMP-9 and p-JNK expression	Li et al. 2020
Glycitein (Gly)	In vitro nontumorigenic (RWPE-1) prostate epithelial cells	Gly (0–100 μM/L) for 72 h	↑ ERK1/2, ↓ RWPE-1 cell proliferation by 40%	Clubbs and Bomser 2007
	Human DNA topoisomerase II activity and cancer cell proliferation	Dz, Gen, Gly (100 μM each)	Cancer cell cytotoxicity, ↓cellular topo II	Mizushina et al. 2013
	In vitro human T cell leukemia	Genistein, daidzein and glycitein	Regulate MMP-13 activity and MMP-8 expression, ↓ proteintyrosine phosphorylation in Jurkat cells	Kim, Chaves, et al. 2002
Puerarin	In vitro colon cancer (SW480, LoVo and HCT-116)	(4–256 μg/mL) puerarin 6″-O-xyloside for 24 h	Induce mitochondria-mediated intrinsic apoptosis and ↓tumor invasion and metastasis	Zhang, Wang, and Mo 2018
	Vascular smooth muscle cells proliferation	Oxidized low-density lipoprotein (50 μg/mL), then puerarin (0–50 μM)	↓ proliferation of VSMCs, ↓ERK 1/2 phosphorylation and PCNA expression	Hu et al. 2016
	Breast cancer MCF-7/adr cells	20–200 μM for 3–48 h	↓ MDR1 in MCF-7/adr cells, NF-kB activation and CRE transcription-dependent elevation of AMPK	Hien et al. 2010

and Bcl-2 expression, enhance Bax expression and caspase-3 activation), block proliferation of HS578T, MDA-MB-231, and MCF-7 breast cancer (Zhou, Zhang, and Peng 2014). The possible anticancer effect and multiple molecular mechanisms of different isoflavones are elucidated in Table 4.

Effects of isoflavones on thyroid

A single case concerning soy isoflavones that triggered hypothyroidism in a patient with chronic lymphocytic thyroiditis over ten years was documented by Nakamura et al. (Nakamura et al. 2017). Although most research evidence may cause one to believe that soybeans are generally well tolerated by the Asian population, these researchers emphasize that consuming health drinks containing soy isoflavone extracts can lead to severe hypothyroidism. On the other hand, there were valuable reported data after 3 years of research about 389 postmenopausal women taking 54 mg/day of genistein (Bitto et al. 2010). The findings indicated that therapy was not highly affected by serum thyroid hormones and autoantibodies. Despite the obvious evidence, isoflavones' safety, especially in non-Asian ethnic groups still require further research.

Effects of isoflavones on breast cancer

Three studies and one prospective cohort analysis have not supported the hypothesis of possible incidence of breast cancer after the ingestion of isoflavones from dietary supplements for the main organ, mammary gland (Boucher et al.

2013). The study found that neither mammographic breast density (741 women) nor histopathological alterations (75 women) were identified after the consumption of soy isoflavones/soy extracts, soy protein, daidzein-rich isoflavones, genistein, and red clover extracts focused on interventional experiments. The Panel settled that there was no suggestion, based on the evidence reviewed, that isoflavones in postmenopausal women had negative effects on the mammary gland when administered. There is minimal knowledge obtained from this comprehensive study on women with breast cancer. Therefore, the analysis cannot focus on the hazard of estrogenic isoflavone-based dietary supplements in postmenopausal women with a current diagnosis or background of estrogen-dependent cancer.

Additionally, no enhanced effect of isoflavones on mammary gland cell proliferation was observed in animal experiments performed on OVX monkeys at doses up to 35.7 mg/kg body weight/day for approximately 30 days, or at lower therapeutic amounts for 6 months to 3 years. Comparably, when assessed at doses up to 68 mg/kg body weight/day for 1 month or at a smaller concentration of 7.2 mg/kg body weight/day for 6 months, equol did not display a significant impact in monkeys.

In rats, lumen formation and yet no secretion was triggered after treatment with equol at 36 mg/kg body weight/day, and the number of terminal ducts and type II lobules was improved in a 90-day trial. At the same dosage, the proportion of proliferating cell nuclear antigen (PCNA)-positive cells in the terminal ducts and type II lobules increased after treatment with equol. At the lower dose of 4.5 mg/kg body weight/day dose measured, no effect was detected (Rachoń et al. 2008). In addition, the National Toxicology Program (NTP) noted that while sub-chronic genistein therapy in OVX rats led to increased proliferation of mammary gland cells, long-term exposure to genistein by intact rats has resulted in only unclear evidence of carcinogenic activity.

Effects of isoflavones on uterine tissue

There are few pieces of data (Kwun, Kim, and Shin 2009) available on the harmful impact of isoflavones on the uterus in females. Three cases of negative impacts on the endometrium (e.g. excessive uterine bleeding and endometriosis) in women have been documented probably due to excessive soy food intake. Since soy was cleared from their diet, the symptoms were obviously vanished or diminished (Chandrareddy et al. 2008). On the other hand, test materials were administrated to immature female or ovariectomized (OVX) rats or mice, and the uterine excess weight was subsequently recorded. Isoflavones are believed to trigger uterotrophic complications in rats. In an in vitro study, genistein and daidzein mediated the cell proliferation after the induction of uterine cancer cell lines at concentrations of 10 nM to 10 μM in the absence of estradiol (Kayisli et al. 2002; Malloy et al. 2018). Another study with administration of 18 μM, genistein showed apoptosis of HeLa cell (Xiao et al. 2011). However, once existing at concentrations in nanomolar, isoflavones can reduce the proliferative effect of estradiol while triggering a minor induction at 1 μM (Sampey et al. 2011).

EFSA (SciFinder database, online) summarized that no changes in endometrial thickness (studies involving a total of 1484 participants) or exceptional histopathological outcomes (studies involving 677 participants) have been detected for the target organ uterus in any of the clinical interventional studies, with the highest investigated isoflavone dose of 150 mg per day for a 2.5-year period. In rats administrated with doses of different types of isoflavones of between 10 to 100 mg/kg body weight/day on uterine weight was recorded. The report concluded that the consequences after isoflavone administration were not adverse. Based on the evidence from human studies and results of animal studies, the research found that, when given at the above-mentioned menopausal dose and duration, soy isoflavones, soy-based products, daidzein and glycitein-rich isoflavones, genistein, and soy or red clover extract deemed to have no negative impact on the uterus of postmenopausal women. No data has indeed been obtained from such systematic analysis on females with uterine cancer. Therefore, the panel was unable to suggest that postmenopausal women under a bad clinical condition or a history of estrogen-dependent cancer could be always deprived from estrogenic isoflavone-based dietary supplements.

Isoflavones as anti-aging

The antiaging properties are largely associated with antioxidant, anti-cardiovascular diseases, and antihypertensive potentials (Sakthivelu et al. 2008). There are many reasons behind the occurrence of aging, particularly the release of free radicals in the body and hormonal reduction. Isoflavones, in addition to their estrogenic properties, were documented to possess scavenging activities and restore DNA damage (Cassidy 2005; Miquel et al. 2006). The similarity of isoflavones to 17β-estradiol explains their prospective antiaging potentials through the interaction with estrogen receptors (Sator et al. 2004).

Effect on cardiovascular diseases and hypertension

For over five decades, the hypocholesterolemic effects of isoflavones have been established, with positive effects recorded on cholesterol levels, LDL cholesterol, and triglycerides (Lu, Tice, and Bellino 2001; Van Horn et al. 2008). Soy isoflavones were recently concluded to improve the cardiovascular risk markers through the reduction of systolic blood pressure in menopause. Also, soy isoflavones were experimented to reverse the ratio of glucocorticoids/adrenal androgens, lower serum cholesterol, delay the development of atherosclerotic plaque, inhibit platelet aggregation, increase cardiac contractility. However, a precaution, was recommended as they can have various effects on blood viscosity and increase in the levels of triglycerides (Al-Nakkash et al. 2009; Bovell-Benjamin 2010; Liu et al. 2012; Rosenzweig and Barnes 2003). Therefore, Food and Drug Administration (FDA)

started debating the safe intake of isoflavones (Wuttke, Jarry, and Seidlova-Wuttke 2010).

Isoflavones can presumably serve as hermetic factors to modify intracellular redox signaling in the vascular system that helps to increase the health period and decrease the occurrence of a cardiovascular age-associated malfunction via the Nrf2/Keap1 defence cascade (Siow and Mann 2010). Potential beneficial effects of red clover-derived supplementation have been observed on triglycerides and PAI-1 in perimenopausal women and on total and LDL cholesterol in apoE E2/E3 genotype women (Atkinson et al. 2004) . A traditional Chinese medicine containing *Pueraria lobate* extract was demonstrated to minimize the systolic blood pressure and induce concentration-dependent vasodilation in vivo studies (Ng et al. 2011). In addition, puerarin was found to enhance vascular insulin resistance and cardiovascular injury through nf kappa b/jnk and erk1/2 pathway inhibition in salt-sensitive hypertension (Tan et al. 2017).

Isoflavones as antidiabetic and antihyperlipidemic

Diabetes mellitus (DM) could be the most highly growing metabolic disease in the world. DM represents highly serious health concerns in which a defective mechanism of insulin secretion or insulin deficiency is manifested. This results in hyperglycemia which in turn leads to an increase in the formation of free radicals, glucose, and lipid peroxidation autooxidation, as well as antioxidant protection system disturbances. Isoflavones supplementation in this regard helps to lower blood glucose, hyperlipidemia and to possibly improve the antioxidant and anti-inflammatory defence mechanisms (Figure 2) (Ae Park et al. 2006; Lee 2006).

Genistein was revealed to have a dose-dependent protective effect on the toxicity of pancreatic β-cells that in response contribute to regulating insulin and glucose blood levels (El-Kordy and Alshahrani 2015). The underlying mechanisms could be through increasing insulin sensitivity and lower insulin requirement or improving glucose tolerance and insulin homeostasis (Li et al. 2018). Recently, red lover isoflavones were examined to improve SIRT1 expression, insulin sensitivity, and lipid profile in STZ-induced type II diabetes in rodents, and encourage the regeneration of pancreatic and insulin secretion in β-cells in alloxan-induced type I diabetes (Oza and Kulkarni 2020; Qiu et al. 2017). Similarly, the possible antidiabetic effects of *P. lobata* may be related to the inhibition of (protein tyrosine phosphatase 1B) PTP1B, thus enhancing the signaling pathway for insulin (Duru et al. 2018; Duru et al. 2020; Sun et al. 2019). Also, combining both *salvia miltiorrhiza* and *pueraria lobata* resulted in potential lipid-lowering effect and minimized the rise of AST, ALT, and CK in in vivo studies (Cheung et al. 2017).

Isoflavones as anti-osteoporosis and skin aging

Soy isoflavones were suggested to possibly exhibit antiaging properties through improving the metabolism of glucose and bone , and insulin resistance in post-menopausal women if ingested in a considerable quantity (Mori et al. 2008). Also, it helped to protect against in vitro UV-induced skin-aging in hairless mouse (Kim et al. 2004). In addition, glycitin was reported to demonstrate protection against skin aging and wrinkling through enhancing transforming growth factor (TGF) secretion and fibroblast proliferation (Huang et al. 2010; Kim et al. 2015). Recently, genistein was examined as a potential promotor for the recovery of klotho (anti-aging protein synthesized in the kidneys) that shed some light on its role in antiaging and in vivo renal fibrosis (Li et al. 2019).

In addition to *Glycine max*, the combination of red clover and dried pomegranate concentrate has been shown to be promising as a new potent protective agent in menopausal women to alleviate climatic symptoms, especially in terms of estrogen depletion, obesity, hyperlipidemia, hepatic steatosis and osteoporosis (Kang et al. 2016). Furthermore, it exhibited a potential role in enhancing the strength of the tibial metaphysis in preclinical trials (Cegieła et al. 2012) and significantly attenuated loss of bone mineral density due to estrogen deficiency, increased bone turnover, and stimulated equol development in osteopenia postmenopausal women (Lambert et al. 2017).

Formononetin and biochanin A demonstrated a potential use in cosmetic, as it enhances the permeation in the skin and may retain in the epidermis and dermis (Dias et al. 2018). Other results indicated that red clover isoflavones are effective in reducing estrogen deprivation-induced skin aging. The findings revealed uniform skin thickness with a regular level of keratin, collagen, vasculature and elastic fibers (Circosta et al. 2006).

Puerarin was documented to possibly exert an antiosteoporotic effect through modifying anti-oxidative NF-κB signal pathway in the bone marrow (Michihara et al. 2012). Besides, puerarin ameliorated osteoporotic syndromes in ovariectomized mice and substantially increased blood calcium, phosphorus, ALP and OPG concentrations (Li et al. 2016). Interestingly, because of the decreased number of melanocytes in the hair, *P. lobata* extract may prevent the development of new gray hair without any significant negative effects (Jo et al. 2013).

Effect of isoflavones on nervous system

The brain can be regarded as a master organ that controls all our behaviors through neuroendocrine signals, integrates and preserves data in the form of memories, and coordinates the functions of various organs. Diet-brain interactions offer a possible insight into the molecular basis of alteration of dietary brain function and the diet contributing to neurological disorders. Only recently specific effects of diet on the brain and its molecular and cellular bases have been investigated (Mattson 2002).

Phytoestrogens have been extensively researched e.g. soy isoflavones, for their possible health benefits (Gleason et al. 2015; Lephart et al. 2002; Soni et al. 2014; Sumien et al. 2013). The data showed that isoflavones can be either estrogen agonists or antagonists (Cui et al. 2020; Soni et al. 2014; Sumien et al. 2013). No information was available on the effects of phytoestrogens on brain function in 1996, when a

research project investigated the effects of soy isoflavones on brain cognition (Cui et al. 2020; Gleason et al. 2015; Lephart et al. 2002) was initiated. This research also has acknowledged certain biomarkers that are essential for the normal cognitive function of brain. Furthermore the impact of soy isoflavones on brain chemistry, composition, and cognitive function has been receiving attention (Pan 2002).

The effects of soy isoflavones on acetyltransferase (ChAT) and brain-derived neurotrophic factor mRNA levels in rats' frontal cortex. An ovariectomized (OVX) rat estrogen deficiency model was used to analyze if soy isoflavones estrogen are agonists or antagonists in the estrogen-responsive biomarker control (Cui et al. 2020; Lephart et al. 2002). Fifteen bilaterally ovariectomized female rats were randomized into three groups, each of five rats. Within the control group, the casein-lactalbumin-based regimen was supplied to the animal. The estrogen group enriched a control diet of 17-β-estradiol equivalent to the female's 2 mg/day dose. The control diet enriched with soy isoflavone extract was given to rats in the soy-isoflavone group (43% genistein, 21% daidezine and 2% glycitein) equal to the isoflavone additional soybeans. It was shown that levels of ChAT and (BDNF) mRNA were significantly greater in rats' frontal cortex, which were enriched with estradiol or isoflavone diets, than in rats' frontal cortex which were fed a control diet free of soy. Such data showed that isoflavones could be used in the frontal nucleus of adult female rodents as estrogen agonists (Lee, Lee, and Heon 2005; Lephart et al. 2002).

Effects of soy isoflavones on brain aromatase, 50-reductase, the sexually dimorphic region, regulatory, visual-spatial memory, and reproductive behavior. Several studies have been carried out to study the effect of soy isoflavones on the abovementioned enzymes in the brain. No soy isoflavones were affected by amygdala (AMY) and medial basal hypothalamic preoptic area (MBHPOA) (Abdel-Aleem et al. 2019). In adult male rats, soy isoflavones slightly increased 50-reductase activity but significantly in the AMY and slightly decreased but significantly in the MBH-POA (Abdel-Aleem et al. 2019). In adult male rats, not in female rats, soy isoflavones have significantly modified the structure and volume of the sexually dimorphic brain region (Lephart, Adlercreutz, and Lund 2001; Lund et al. 2001). In both male and female rats, soy isoflavones have developed anxiolytic effects (Lund and Lephart 2001). In addition, the effect of soy isoflavones on reproductive activity and estrogen receptor-dependent gene expression was examined in adult male and female Long Evans rats (Patisaul et al. 2001). Isoflavone supplements have increased ER13 mRNA levels by 27% in the paraventricular nucleus, while 1713-estradiol have decreased ER13 mRNA levels by 41%. Furthermore, isoflavone supplements in the hypothalamus ventromedial nucleus were also found to be able to antagonize upregulation of the ERo.-dependent oxytocin receptor. Thus, isoflavones were highlighted to cause a significant decrease in receptive behavior in estrogen- and progesterone-primed female rats. Such data had suggested that estrogen could serve as an antagonist.

Some incidences of feminizing consequences such as lowered libido and erectile malfunction were reported but a few in number. Also, a decreased sperm concentration was recorded, but with no morphological characteristics (Cederroth, Zimmermann, and Nef 2012; Siepmann et al. 2011; Yin et al. 2014). A meta-analysis of clinical data, however, found that soy food or isoflavones did not have an impact on the semen and sperm (Hamilton-Reeves et al. 2010). The possible problems of male fertility and the uncertain long-term health manifestations of consuming heavily processed industrial soy products need a careful framework.

Effect on familial amyotrophic lateral sclerosis and stroke. A progressive, lethal neurodegenerative condition is a characteristic of amyotrophic lateral sclerosis (ALS). There are two types of ALS: intermittent and family ALS (Henry-Vitrac et al. 2010; Ma et al. 2009). In a murine FALS model, male mice have developed the disease and died earlier than female mice. Genistein therapy (at the dose of 16 mg/kg body weight, intraperitoneally injected (i.p., twice/day) delayed onset and mortality in male mice but did not have an influence on female mice with ample endogenous estrogenic properties. (Nabavi et al. 2015). These results showed that genistein defends the protective effects of endogenous estrogen in female mice from male FALS mice and does not antagonize them. In the free-radical stroke model, treatment with genistein (at a dose of 16 mg/kg i.p., every 6 hours from 24 hours before to 24 hours after irradiation) significantly decreased the size of the lesions in both male and female mice (Khan et al. 2020).

Effects on neurodegeneration-relevant modifications of brain proteins; Alzheimer's disease. The hyperphosphorylation of the microtubule-associated tau protein investigated the effect of soy isoflavones on tau phosphorylation in monkey's brains. Ovariectomized female cynomolgus monkeys aged 11 years and fed either an isoflavone diet or an isoflavone-free diet or a three-year isoflavone-free diet were supplemented with equine estrogen conjugates (EEC diet) (Kim et al. 2000). The frontal cortex tissues were extracted and analyzed. The results showed that phosphorylation of the protein tau had only been blocked in the frontal cortex of monkeys fed a steady diet containing isoflavone. It indicates that, via estrogen-independent mechanisms, soy isoflavones could slightly postpone neurodegeneration. Moreover, the impact of soy isoflavones on the brain of mice was examined in a proteomics study (Kim, Chaves, et al. 2002). For a lifetime, C57B6 mice were also fed either an isoflavone diet or a low isoflavone diet. Aged mice were then euthanized, and the proteins were extracted by 2-dimensional electrophoresis in the brain's complete homogenates. Matrix-assisted laser desorption/ionization-time of flight mass spectrometry discovered several proteins after in-gel digestion with trypsin. These proteins were impaired in the brains of the mice fed the isoflavone-based foods.

On the other side, the formation and extension of β-amyloid fibrils were stated to be inhibited by various compounds that possess an antioxidant activity which in turn attenuates Aβ-induced oxidative stress (Ono et al. 2006). Via antioxidation, anti-inflammation, and cell signaling pathways, soy isoflavones were revealed to feasibly protect neurons and prevent nervous system degeneration (Rüfer et al. 2009; Sankar et al. 2015). Vest and Pike (2013 supposed that in case of postmenopausal women, the drop in estrogen levels increased the incidence of AD. In addition to that, Rosario and Pike (2008) performed a meta-analysis and found that estrogen replacement therapy reduced the risk of AD (odds ratio: 0.66, 95% confidence interval: 0.53–0.2), indicating that estrogen prevents cognitive dysfunction. Nevertheless, both the Women's Estrogen-Stroke Study and the Women's Health Initiative study showed that estrogen did not play a protective function and increased the rate of stroke and dementia (Lu et al. 2018).

Effect of multiple sclerosis. Multiple sclerosis (MS) is a dynamic autoimmune condition known in young adults as the most prevalent crippling neurological disease (Togha et al. 2010). An inducible T-cell mediated autoimmune disease, validated as a related MS model (Steinman and Zamvil 2006; Yoshida et al. 2012) refers to a health manifestation namely an experimental allergic encephalomyelitis (EAE). In a number of human autoimmune diseases, including MS, there is a separate female predominance (Whitacre 2001). Estrogens, however, have also been shown to be repressive in T-cell-mediated autoimmune diseases. The influence of genistein on the path of EAE has been investigated in a few recent studies. Genistein injection in ovariectomized mice has been reported to decrease the severity of EAE (De Paula et al. 2008). Oral therapy with 7-O-tetradecanoyl-genistein to enhance EAE signs has also been documented in the literature (Castro et al. 2012).

Nothing, however, has been discussed, about the impact of genistein on the intensity of EAE after disease establishment. Particularly, evidence has shown that the molecular targets of genistein include enzymes, cytokines, cell proliferation, gene regulation, transcription factors, and apoptosis. As previously investigated, the protection against and strengthening the signs of EAE could be potentiated by genistein (Ravindranath et al. 2004). In some trials, at the initial stage of the disease, mice were given genistein (8–9) and the results showed that, unlike in the early phase, late-phase EAE genistein administration was not efficient in regulating clinical symptoms. The observed discrepancy may be because inflammation and demyelination begin to worsen in the progressive stage of EAE (Costa et al. 2003). Nevertheless, genistein was not capable of inducing an alteration to the cytokine pattern in the case of the advanced stage of disease, the proliferation of lymphocyte, and cytotoxicity percentage. Both of which, at the early stage of the disease, could make genistein potent enough in improving EAE severity (Razeghi Jahromi et al. 2014). But, in the initial phase of EAE, genistein gavaging lowered the activation indexes of lymphocytes, which primarily reflects CD4 memory + T-cell proliferation, minimized IFN-γ secretion, and significantly reduced the percent of cytotoxicity, which mostly expresses CD8+ operation (Sun et al. 2001). EAE is typically determined by the entry into the central nervous system of myelin-auto reactive CD4+ and CD8+ T cells (Oyebamiji et al. 2013). In MS plaques, CD8+ T-cells were detectable and recorded in EAE and MS to mediate the inflammation which were activated to express IFN-γ (Sun et al. 2001). IFN-γ has the primary regulatory role among the many cytokines tangled in MS and EAE pathogenesis, guiding the development of chemokines, involving the proliferation of T cells and subsequently influencing the initiation and disease progression (Tran, Prince, and Owens 2000). In addition, the findings explained that treating mice with genistein significantly inhibits IL-12 development in the spleen immediately after the onset of clinical signs (Ghanaatian et al. 2019). When genistein was given to mice with advanced EAE, no comparable effect on the level of IL-12 was observed. One of the major proinflammatory cytokines altered in EAE/MS is IL-12 have indicated an improvement in the secretion that may result in increased demyelination.

Brain-gut link. The importance of the gut microbiota in MS has also been substantially researched in its experimental autoimmune encephalomyelitis (EAE) animal model. Inactivation of EAE disorder in germ-free (GF) mice due to HC fecal transfer and increasing the incidence of disease due to MS patients' fecal transmission potentially confirms the vital function of gut microbiota in MS (Berer et al. 2017; Cekanaviciute et al. 2017). Several metabolic mechanisms, like short-chain fatty acids (Fan and Zhang 2019; Melbye et al. 2019), tryptophan (Freedman, Shahi, and Mangalam 2018; Rothhammer et al. 2016) and phytoestrogen metabolism (Rothhammer et al. 2016) were shown to influence the severity of disease. As discussed by Freedman, Shahi, and Mangalam (2018), the depletion of microorganisms present in phytoestrogen metabolism may provide a key function in the maintenance of inflammation by all these microbes (Cady et al. 2020).

Effect as neuroprotective agents. By reducing microglial-mediated inflammatory responses, phytoestrogens can exhibit neuroprotection. It was revealed that formononetin, daidzein, pratensein, calycosin, and irilone stimulated microglia LPS-induced pro-inflammatory cytokine output (Chen et al. 2008). In several in vivo experiments, neuroprotective benefits of phytoestrogens in the foods were reported. In treated rats either daidzein- plus genistein-based formula or a soy-enriched food, the synaptic density was also significantly higher on either standard chow or soy-free diets (MacLusky, Thomas, and Leranth 2017). In addition, a comparison between rats on a control diet and rats fed a steady diet including soy-derived phytoestrogens demonstrated improved learning and memory (Lee et al. 2009). Furthermore, pretreatment with phytoestrogens protected mice from CNS neurotoxicity following Parkinson's disease

Table 5. In vivo effects of isoflavones on the immune system.

Species	Compound	Dose (day)	OVX	Effects	Reference
Mouse	Genistein	8–200 mg/kg	+	⇓number of peripheral lymphocytes ⇓Ag-specific Ab titer ⇓Thymus weight ⇑thymocyte apoptosis	Yellayi et al. 2002
Mouse	Genistein	8–80 mg/kg 1000–1500 ppm	+	⇓DTH response ⇓number of LN CD4+ and CD8+ T cells	Verdrengh et al. 2003
Mouse	Genistein	4–20 mg/kg	+	⇓Ag-specific T cell response ⇓Ag-specific Ab titier ⇓Ag-specific cytokine production ⇒dendritic cell function ⇒CD 4+ CD 25+ T cell function	Sakai et al. 2006
Mouse	Genistein	30 mg/kg	–	⇓Anti-collagen II Ab ⇓DTH response	Yellayi et al. 2003
Mouse	Genistein	4–20 mg/kg	–	⇑IFN-γ and IL-4 production ⇑Thymus weight	Sakai et al. 2006
Mouse	Genistein	2–20 mg/kg	–	⇑cytotoxic T cell and NK cell activity ⇑resistance to B16F10 tumor	Guo et al. 2001
Mouse	Genistein	4–20 mg/kg	–	⇓inflammatory dermatitis in NC mice ⇓IFN-γ and ⇑IL-4 production	Sakai et al. 2006
Guinea pig	Genistein	15 mg/kg	–	⇓Ag-induced asthma	Duan et al. 2003
Mouse	Daidzein	10–40 mg/kg	–	⇑Thymus weight ⇑phagocytic activity ⇑Ag-specific IgM Ab	Sakai and Kogiso 2008

(PD) triggered by 1-methyl-4-phenyl1,2-,3,6-tetrahydropyridine (MPTP) (Liu et al. 2008).

Estrogen replacement treatment (ERT) was shown to boost CNS activity through avoiding oxidative stress and developing amyloid plaques, mainly in Alzheimer's disease (Simpkins et al. 2009). Admittedly, transcription of ER alpha- and ERβ-dependent genes containing estrogen response elements (EREs) (Schreihofer 2005) were stimulated by genistein, daidzein, and zearalenone. By their promoters, phytoestrogens, furthermore, were shown to be 100–1000 times less efficient than 17β-estradiol. However, it can also hit G protein-coupled estrogen receptor-30 (GPR-30), a plasma membrane GPER of cells in a large number of tissues (Prossnitz, Arterburn, and Sklar 2007).

Effects of isoflavones on infant's health

In addition to the preferences and beneficial effects supported by serious research-based evidence, the findings of some experiments of soy isoflavones, excluding (Tai et al. 2012) and (Alekel et al. 2010) were incomplete, uncertain, or relatively irrelevant in confirming some of the proposed health benefits of consuming soy protein or isoflavones. There are also real concerns that elevated levels of serum isoflavone can refer to hormone-associated disorders (Zaheer and Humayoun Akhtar 2017).

Generally, consuming moderate quantities of commonly prepared and minimally processed soy foods may provide major and fundamental health benefits (D'Adamo and Sahin 2014).The most recent studies published on the safety profile, toxicity and side effects of soy isoflavones revealed that some questions have been articulated for the potential impact of infant nutrition of soy protein formulas due to their isoflavone content (Campos 2020). In addition, the specialists of many pediatric communities in many countries have informed infant health caregivers that the use of soy protein recipes in infants must be approved for a limited number of cases due to the deficiency of evidence.

The publication released in 2006 for the recommendations of the Hepatology and Nutrition Committee of the European Society for Pediatric Gastroenterology (ESPGRAN), summarized the current information on the formulation and use of soy protein formulas of cow's milk as a substitution for breastfeeding. The main issues were the protection and adequacy for the normal growth and development of children. Testa et al. proposed in an argument that the use of soy-based infant formula (SFs) throughout infancy could minimize the risk of many diseases occurring in elder age, but they cannot find any supportive data or evidence to validate this assumption (Testa et al. 2018).

Miscellaneous effects

Effect of isoflavones on immune system

Genistein is fundamentally equivalent to 17 estradiol (E2) and it has been proposed that it serves as an E2 or E2 antagonist. Genistein have been shown to suppresses the in vivo antigen-specific immune reaction and in vitro lymphocyte proliferation reaction. Genistein, however, increases the natural killer (NK) and cytotoxic T cell-mediated cytotoxic response and the synthesis of T cell cytokines. Consequently, the immunity effect of genistein is immune-dependent on the cell (Table 5). In animal models, genistein has been used to treat many diseases because of its peculiar effect on immune function. Also, genistein has been found to suppress allergic inflammatory responses (Sakai et al. 2006).

Effect on Crohn's disease-irritable bowel disease

The most widespread immunity-associated intestinal problem is irritable bowel syndrome (IBS). This is including the changes in intestinal permeability, gut motility, and hypersensitivity which could result from any psychological stress (Tanaka et al. 2011).

Chronic visceral pain is among the significant characteristics of IBS that are in association with estrogen secretion in females. During every menstrual cycle, females with IBS show further recurrent functional bowel disorders (Heitkemper et al. 2003). In women with IBS, estrogen limitation can impair hypersensitivity and gastrointestinal permeability (Smith et al. 2006). Serious symptoms of IBS are correlated with higher intestinal permeability (Zhou, Zhang, and Nicholas Verne 2009). On the other hand, β-type estrogen receptors (ERβ) are mainly expressed in the colon and they can be triggered by bioactive compounds such as isoflavones (estrogen) and reduce intestinal hypersensitivity (Houghton et al. 2002). On the other hand, β-type estrogen receptors (ERβ) are primarily expressed in the colon and can be triggered by isoflavones compounds such as estrogen and decrease gut hypersensitivity (Braniste et al. 2009). Diadzein, glycetin, and genistein act as 17-β estradiol with a good affinity to ERβ with soy isoflavones (Morito et al. 2001).

In vitro studies by Jalili et al (Jalili et al. 2016) have shown that in smooth muscle cells, both soy phytoestrogens and vitamin D can reinforce each other to bind ERs and modulate ER protein expression (Somjen et al. 2004). In addition to the impact of such nutrients mostly on particular receptors in the colonic tissue, the psychological elements of IBS could be impaired and persistent visceral pain may be alleviated (Karaahmet et al. 2013). The potential effects of soy isoflavones and vitamin D on the IBS-Syndrome Severity Scoring System have been recorded significantly different. In patients taking soy isoflavones or vitamin D, IBS-SSS was substantially lower compared to patients who did not receive it.

The benefits of either soy isoflavone or vitamin D supplementation on the intensity of stomach pain, intestinal cramping length, abdominal distension, bowel satisfaction, the positive effects of bioactive compounds on the reduction of intestinal cramping, and flatulence have also been reported (Jalili et al. 2016). In addition, vitamin D plays an important function for optimum gastrointestinal tract barrier homeostasis. Furthermore, vitamin D deficiency is related to more extreme prognostic factors of IBS. Interestingly, vitamin D and soy isoflavone interaction results have markedly increased overall IBS score, which may have a subsequent synergistic impact on intestinal hypersensitivity (Kong et al. 2008).

Anti-microbial and anti-parasitic activity

As an anti-microbial, and healing ability, formononetin was reported to exhibit many pharmacological potentials. Zhu et al showed that formononetin possibly has powerful antifungal properties on *Candida alibicans* (Y0109) and *C. alibicans* (SC5314) with a 8 μg/mL Minimum inhibitory concentration (MIC) rating (Zhu 2014).

Aspergillus fumigatus, *Microsporum gypseum*, and *Trichophyton rubrum* showed that formononetin was inactive. In another patent, formononetin has been shown to have anti-*Cryptosporidium parvum* effects and was able to cause *Cryptosporidium parvum* to decline *C.parvum* oocysts by 89% (Hussain and Green 2017). Li et al isolated tobacco roots isoflavone and showed that it has powerful antibacterial effects on *Proteus vulgaris*, *Staphylococcus aureus* , *Escherichia coli*, and *Bacillus subtilis* (over 90% inhibition) (Li et al. 2012).

Anti-viral activity

The general formula library of isoflavones was compiled by Iadonato et al and showed that these compounds are likely to have antiviral potent properties for various viruses, such as Alfuy V, Banzi V, HIV, Dengue V, Chikungunya V, Kokobera V, Hepatitis B V, Japanese encephalitis V, bovine diarrhea V, human cytomegalovirus V, Murray Valley V, llheus V, tick-borne encephalitis V, and St. Louis encephalitis V (Hussain and Green 2017). The authors indicated that these compounds could contribute to the treatment of HCV (anti-hepatitis C virus activity) infections identified in isoflavone inhibitor studies.

Limitations and recommendations

Food and Agriculture Organization (FAO) of the United Nations estimated the annual needs of kudzu and soybeans between 50 and 217.6 million tons, respectively (Kwun, Kim, and Shin 2009; Masuda and Goldsmith 2009). Also, Japan has declared a recommended daily dietary dose of isoflavones allowance of 15–22 mg supplementation/day for a 60-kg man (Messina 2008; Tanaka et al. 2016). Other studies announced that doses below 2 mg/kg body weight per day were safe for most population (Barnes 2003). In addition, the daily consumption of 80 mg isoflavones derived from red clover was potentially considered safe botanical dietary supplement for postmenopausal women (Imhof et al. 2006). FDA claimed that the threshold daily intake of soy protein for cholesterol reduction is 25 g (Lante et al. 2018). Generally, cosumption of isolfavones or isoflavones-containg food is complex issue and the potential health outcomes are largely driven by the source, active ingredients, dose, and administration period of the bioactive compounds. The biological effect of isoflavones typically depends on age, health conditions, and existence of specific essential gut microflora. However, the long-term administration of botanicals' isoflavones still need further investigations. Also, introducing phytoestrogen-rich formulas to infants outlined many concerns especially for their future reproductive development. Based on the above consdertion, botaicals' isoflavones considers an optimum options to prevent or alleviate many health disorders and thus enhancing their future diatery lifestyle.

Conclusions

Isoflavones are stress-associated metabolites that have possible potential health benefits. Although the botanical source (soybean, red clover and kudzu) comprise different bioactive compounds, they possibly exhibit prospective antiaging, anticancer and microbiome modulating effects.

Undoubtedly, the molecular mechanisms for understanding the bioavailability of isoflavones are still obscure and require further analysis. Despite isoflavones revealed a high number of potentially relevant and influential therapeutic effects against various serious health concerns, pioneering researches for the association between isoflavones chemical structure and its multifunctional implication are recommended to be added to the research agenda. However, the isoflavones targeting the microbiome and their promising anti-aging compounds were ultimately novel and yet limitedly investigated. Likewise, the full pattern discussing the connection between isoflavones and gut microbiota is extremely complex and need further refinement and scrutiny. This could be because of the diversity of factors affecting the bioavailability of isoflavones and the role of microflora in its metabolism. Besides, the findings developed regarding the limitations of isoflavones on various target organs are still with a limited scope covering. Furthermore, the researches on plant-derived isoflavones over the past 3 decades were plenty but significantly growing unstandardized and non-protocoled. Moreover, the safety of isoflavone consumption and long-term intake of isoflavone-containing products are a challenge-led approach to the upcoming potential studies. Therefore, future researches are suggested to fill the gap in a hands-on manner with respect to the microbiome-associated metabolism, age-related diseases, long term intake and the molecular mechanisms involved.

Disclosure statement

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