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The potential toxic side effects of flavonoids

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Abstract: Flavonoids are a class of phytochemical molecules abundant in many plants, fruits, vegetables, and leaves. Flavonoids possess a series of significant biological activities, including anticancer, antioxidant, antiviral, and anti-inflammatory properties. They become an important source of dietary supplements and natural health products. Though many studies confirmed the safety of flavonoids, the potential toxicity of flavonoids is still a remarkable field of research to be explored. The enthusiasm for flavonoids expressed by the public has sometimes overlooked their toxicity and also consumed the flavonoids exceeding the body requirements. The current review focused on the potential toxicity of flavonoids to make the public consume flavonoids with caution. This review summarizes the current toxicity which has been reported *in vivo* and *in vitro* experiments. The toxicity involves carcinogenicity and mutation, liver and kidney toxicity, and the influence on the thyroid and reproductive function and intestinal flora disorders. The mechanism of toxicity is fully complicated, and current evidence indicates that natural flavonoid glycosides act on different targets with different doses *in vivo* and *in vitro* experiments. Though most kinds of flavonoids are considered safe, flavonoids proposed as food supplements need to be assessed their tolerable upper intake level as there have been reports of toxic flavonoids.

Introduction

Flavonoids are a large number of small molecules abundant in fruits, vegetables, and legumes. It has been widely known for centuries that derivatives of plant origin have a broad spectrum of biological activity (Jin, 2019; Martins *et al.*, 2019). Evidence provided suggestions that flavonoids play an important role in chronic disease prevention and viral diseases treatment through a multi-factorial action involving the antioxidant, anti-inflammatory, and other biological activities (Niedzwiecki *et al.*, 2016; Pal and Konkimalla, 2016; Pandey *et al.*, 2017; Volobuff *et al.*, 2019, Istifli *et al.*, 2020). They have a lot of beneficial effects associated with some chronic diseases such as cancer, Alzheimer's disease (AD), and atherosclerosis (Burke *et al.*, 2018; Liu *et al.*, 2017; Szczechowiak *et al.*, 2019; Zhang *et al.*, 2019). Flavonoids have attracted more enthusiasm from scientists and the public in the development and utilization of natural medicines for their broad spectrum of biological activity and low toxicity. Thus, some people widely consume flavonoids, particularly referred to as plant isoflavones, as dietary supplements and natural health products exceeding the usual dietary intake levels (Jucá *et al.*, 2020). In this condition, the concentration of flavonoids in humans is higher than the normal amount of that from the consumption provided by conventional intake. As we all know, compelling data have shown that the consumption of flavonoids can cause adverse health effects if the doses consumed exceed the threshold. Surprisingly, many studies also proved that low doses of these compounds have the potential for adverse effects. Although in this condition many biological effects published in a great number of scientific studies based on *in vitro* experiments, as well as animal and human studies declared the safety of the flavonoids, the potential toxicity found among the safety evaluation of flavonoids should be paid with caution. Our aim in this review was to present an overview of the reports in which the toxic side effects and the possible risk when exposed to flavonoids. Hence, we thoroughly analyzed many original articles in the process of our literature search and found the possible potential toxicity involves carcinogenicity, liver toxicity, and the influence on the thyroid function and reproductive system, the intestinal flora disorder, and neurological abnormalities.

Carcinogenicity

A great number of studies have shown that flavonoids negatively correlate with cancer (Chang *et al.*, 2018; Nimptsch *et al.*, 2016). Recent case-control research that

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analyzed 1522 breast cancer patients in Chinese women revealed that there was an inverse correlation between the risk of breast cancer and the intake of total flavonoids (Feng *et al.*, 2020). Phytoestrogens are particularly demonstrated in that they have the capacity of protecting against breast cancer and other hormone-related cancers. However, it is interesting to find that many flavonoids can still induce cell mutation and promote tumor cell proliferation in *in vitro* and animal experiments. Due to the large species of flavonoids, the mechanisms of their carcinogenesis are still not clear and need further exploration. It is also notable that some flavonoids such as phytoestrogen can exert biphasic effects in some tumor cell lines with different doses (Jodynis-Liebert and Kujawska, 2020).

Previous studies have shown that genistein can promote the proliferation of estrogen-dependent MCF-7 cells at low concentrations and is cytostatic at higher concentrations (Kabała-Dzik *et al.*, 2018; Limer *et al.*, 2006). These findings were consistent with another animal experiment in which MCF-7 cells were implanted in ovariectomized mice. The possible mechanism explored by the authors is probably that genistein is related to the estrogen receptor pathway in MCF-7 cells. There is also an animal experiment also showed daily intake of genistein (250 mg/kg diet) enhanced an aggressive progression of prostate cancer in transgenic adenocarcinoma mouse prostate mice, while consumption of a higher dose of 1000 mg/kg daily did not result in the inhibitory progression of cancer (El Touny and Banerjee, 2009). The mechanism suggested that it could enhance the proliferative and metastatic early-stage prostate cancer in an estrogen-and phosphatidylinositol 3 kinases (PI3K)-dependent pattern. It was also found that daidzein also influenced the proliferation of T-47D breast cancer cell lines in biphasic dose-dependent ways (Murata *et al.*, 2004). At low concentrations it could have the ability to promote cell growth and inhibit cell proliferation at a higher concentration of 157 mM; the underlying mechanism might be relevant to cell cycle regulatory protein, p53 (Ying *et al.*, 2002). Quercetin was also reported to promote the cells' proliferation in a dose-dependent manner. Low concentrations of quercetin increased the proliferation of the human breast cancer cell lines, MCF-7 SH and MCF-7 WT (Miodini *et al.*, 1999; Wu *et al.*, 2018). The possible mechanism in *in vitro* experiments involves the reactive metabolites of quercetin oxidation, which influences the formation of DNA and ER-dependent pathways (Andres *et al.*, 2018; Rietjens *et al.*, 2005; van der Woude *et al.*, 2005). Interestingly two previous studies *in vivo* revealed that quercetin could promote carcinogenesis in rodents (Singh *et al.*, 2010; Zhu and Liehr, 1994). The experiment showed that male hamsters with quercetin daily intake for around 6 months caused an increase in kidney tumor (>5 mm) and abdominal metastases compared to the control group (Zhu and Liehr, 1994). The other study reported enhanced cell proliferation and the tumor latency of mammary glands by quercetin at a low dose daily intake in female rats for 8 months compared to the control group (Singh *et al.*, 2010). Although some phytoestrogen is reported to have the ability to act on the biphasic dose-response ways, many pieces of evidence suggest flavonoids have the biological activity of anticancer. Though the experiments mentioned above revealed that some kind of flavonoids could induce tumor development with the application of different doses, there is still lacking the convincing evidence it could act in a biphasic pattern in the human condition.

Hepatotoxicity and nephrotoxicity

Though many data have also confirmed that flavonoids have exhibited significant liver-protection and renal-protection properties *in vitro* and *in vivo* (Kandemir *et al.*, 2020; Levin *et al.*, 2019; Levin *et al.*, 2016; Papackova *et al.*, 2018), few studies also showed the potential hepatotoxicity and nephrotoxicity with epigallocatechin gallate (EGCG) intake (James *et al.*, 2015; Lambert *et al.*, 2010; Levin *et al.*, 2019; Levin *et al.*, 2016). The underlying mechanism of flavonoids is not clear but could be proposed that the transitory intake results in oxidative stress leading to liver and kidney injury under high-dose conditions. The results indicated that plasma alanine aminotransferase (ALT) increased and the survival rate reduced by 85% after a single dose of EGCG (1500 mg/kg) in male CF-1 mice, moderate to severe hepatic necrosis was also found following treatment with EGCG (750 mg/kg) (Lambert *et al.*, 2010). A serial of experiments has indicated that the underlying mechanisms of hepatotoxic effects of EGCG are correlated with the increasing use of green tea dietary supplements, which may probably cause an inflammatory cascade that leads eventually to hepato-toxicity (Hu *et al.*, 2018; James *et al.*, 2018; Wang *et al.*, 2015). Similar results were also observed in Beagle dogs treated with Polyphenon E, a kind of tea polyphenol mixture that contained 60% EGCG (Swezey *et al.*, 2003). There are many case reports relevant to human hepatotoxicity for the consumption of green tea-containing products. A randomized, double-blind clinical trial in Germany demonstrated that two patients in the group treated with epigallocatechin gallate had to remove from the experiment because of hepatotoxicity. The doses of more than 1200 mg intake daily may be used with caution (Levin *et al.*, 2019). EGCG was overall well tolerated in the other 45 patients, these inconsistent results revealed that genetic and/or lifestyle factors may play an important role in susceptibility to EGCG-mediated hepatotoxicity.

It is previously reported that EGCG caused nephrotoxicity *in vivo* experiments, as exhibited by increases in serum creatinine, the most important biomarker of nephropathy (Fatima *et al.*, 2016; Fatima *et al.*, 2015; Rasheed *et al.*, 2017). The underlying mechanism was probably that high-dose EGCG impairs kidney functions through the suppression of antioxidant enzymes and heat-shock protein expressions, which might augment oxidative stress (Inoue *et al.*, 2011). The recent study indicated that EGCG (100 mg/kg/day) would result in a deteriorated oxidative stress condition in streptozotocin-induced diabetic mice. Histopathological examination also confirmed EGCG caused renal injury in diabetic mice (Rasheed *et al.*, 2017). However, whether EGCG-induced nephrotoxicity is dose-related remains to be determined, some authors suggested that the administration duration be one of the crucial factors in the course of EGCG-induced toxicity. Therefore, though many studies have demonstrated the EGCG has the biological activity of mitigating or preventing diabetes,

patients with diabetes are still advised to consume EGCG as dietary supplements with caution.

Quercetin is another kind of flavonoid that is relevant to nephrotoxicity. There was an important study conducted by the US National Toxicology Program (NTP) about the safety evaluation of quercetin (National Toxicology Program, 1992). In this study, groups of 50 male and female rats were treated with 0, 1000, 10000, or 40000 ppm quercetin (>95% pure) in feed for 104 weeks. The results showed chronic nephropathy and increased incidence of kidney adenomas were observed in high dose-related male rats. There was no obvious kidney injury in female rats with quercetin intake. Hard *et al.* (2007) re-evaluated the renal histopathology in Fischer 344 rats and confirmed that the similar increase in renal tumors in mid- and high-dose males rats (Hard *et al.*, 2007). They also found that nephropathy was already promoted by the high quercetin dose from the intervention of 6 months. Based on the above studies in rats, the question is proposed whether quercetin could aggravate the underlying renal deleterious processes with a high dose of quercetin consumption not only in animals but also in human beings. Though there are no valuable adverse effect of quercetin on kidney function found in human intervention studies, we should consider cautious interpretation when quercetin was consumed by people with renal failure (Andres *et al.*, 2018)

Thyroid toxicity

The effect of flavonoids on thyroid toxicity involves many factors, such as the duration of intake and the realistic exposure conditions. Though many studies *in vivo* and *in vitro* have demonstrated that many kinds of flavonoids can interfere with thyroid function and metabolism (Baldissarelli *et al.*, 2016; Bennetau-Pelissero, 2016; Giuliani, 2019; Habza-Kowalska *et al.*, 2019), the explicit mechanism is much complicated and needs to be further explored. Although many flavonoids can interfere with thyroid function, phytoestrogens are the most concerning substances influencing thyroid function and metabolism. Many studies have reported that phytoestrogens and quercetin could have possible thyroid-disruptive properties.

Soy and soy foods are the most common nutritional substances of phytoestrogens; they are rich in high protein content and often act as the production of meat analogs and milk substitutes for some vegetarians and some kids allergic to milk. Most researches about thyroid toxicity are isoflavones of soy components, which have estrogenic properties highly contained in soybeans (Rizzo and Baroni, 2018). Soy isoflavones are reported to be involved in the whole process of thyroid hormone metabolism. They can act as competitive substrates to affect the ionization process and further change the activity of TPO enzyme and TTR binding proteins (Hüser *et al.*, 2018; Renko *et al.*, 2015; Sathyapalan *et al.*, 2011; Šošić-Jurjević *et al.*, 2014). The iodinated isoflavones were detected in human urine after consumption with isoflavonoids. Some studies found that genistein and other related flavones could inhibit the binding of TTR to T_4 and T_3. Thus, they may alter the kinetics and distribution of thyroid hormones in the body. The most interesting finding is different targets are found in the different animal models concerning the influence on the thyroid system. A study in rats reported that the consumption of a standard soy-based rodent diet reduced TPO activity in rats by approximately 50% compared to a soy-free diet (Šošić-Jurjević *et al.*, 2017). Silverstein *et al.* (2014) found that ovarian function influenced thyroid function through the effects of isoflavones in adult female cynomolgus monkeys (Silverstein *et al.*, 2014). It has been assumed that altered sexual hormones also have an influence on the synthesis and stability of serum thyroid hormone distribution proteins through the regulation of the hypothalamic-pituitary-thyroid axis.

In human studies, it was found that flavonoids could intervene with many key processes to affect thyroid function (D'Adamo and Sahin, 2014; Hüser *et al.*, 2018; Nakamura *et al.*, 2017; Sathyapalan *et al.*, 2011). Under conditions of iodine deficiency, the published results supported an association between an increased risk of developing goiter. The incidence of autoimmune thyroid disease in children after early fed with powdered milk containing soybean was significantly higher than that of the control group, especially in the iodine deficiency (Andersson *et al.*, 2007). Importantly, human observational and interventional studies indicated if the iodine intake is adequate, the consumption of soy-based foods is unlikely to hurt the thyroid gland system in healthy humans (Andres and Lampen, 2013). The data also showed that there were no significant adverse effects observed in adult subjects after consumption of abundant soybean protein rich in isoflavone (Tonstad *et al.*, 2016; Xiao *et al.*, 2014). Another study also reported that the plasma concentration of free triiodothyronine (FT_3) decreased slightly and did not cause any discomfort to post-menopausal females after 30 g soy protein powder intake for 8 weeks (Persiani *et al.*, 2016).

Estrogen activity of phytoestrogens

Phytoestrogens have the potential hormone-like activities because of their diphenolic ring, which makes them have the ability to bind ER receptors (Smith *et al.*, 2020). Daidzein and genistein are two predominant types of soy isoflavones in daily intake. Though daidzein and genistein with weakly estrogenic activities have been reported to be approximately 10^{-2} to 10^{-3} fold less potent than endogenous estrogen (Mortensen *et al.*, 2009), excessive or improper intake may also lead to the disorder of hormone metabolism and endocrine function (Cederroth *et al.*, 2012; Hamilton-Reeves *et al.*, 2010). Concerning the safety of soy isoflavones of hormone-like activities, the later reproductive health outcomes in infants fed with soy isoflavones and the potential risk of cancer in adults are the main concepts that should be taken into consideration.

Soy protein-based infant formula (SBIF) is the only alternative for infants allergic to cow's milk-based formula, diarrhea due to lactose intolerance (Merritt and Jenks, 2004). Infant exposure to soy formula often lasts from birth to one year of life, an important stage of development that is particularly sensitive to dietary intake. Several countries have restricted the consumption of soy protein-based infant formula because of the concern with the safety of early

isoflavone exposure in infants and the following reproductive system development (McCarver *et al.*, 2011). Though many data showed that the number of isoflavones intake in infants was much less than that in normal infants, there is still concern regarding the infants fed with SBIF (Dinsdale and Ward, 2010). Though several animal experiments data showed only slight adverse effects in rats with early exposure to soy isoflavones (Badger *et al.*, 2002; Cederroth *et al.*, 2010; Kaludjerovic *et al.*, 2012; Klein *et al.*, 2002), only very few studies have traced the outcome on reproductive health at adulthood, it is not sure whether SBIF has some correlation with detrimental effects on reproductive health at adulthood (Strom *et al.*, 2001; Zhao *et al.*, 2019). Indisputably there are a lot of considerations that need to be taken into in the course of analysis of the findings from animal models to humans. Many animal experiments have demonstrated that isoflavones have different outcomes on the reproductive system and sexual development of male and female animals in adulthood after long-term exposure to soy isoflavone.

The research on female animals mainly focused on mammary gland development, sexual maturation, and endocrine function. Some studies have suggested that early exposure be likely to enhance the differentiation of the mammary gland and further reduce the potential cancer risk (Blei *et al.*, 2015; Kakehashi *et al.*, 2012; Santos *et al.*, 2016). Some data shows that female rats treatment with genistein resulted in fewer terminal end buds and advanced development and ductal elongation which was related to the lower mammary cancer risk (Blei *et al.*, 2015; Rimoldi *et al.*, 2007). The mechanism by which genistein influences mammary gland maturation and development needs to be further explored. The other reproductive organ worthy of attention is the uterus that is also sensitive to early isoflavone exposure. Neonatal mice treated with genistein had greater uterine gland number and increased uterine weight and epithelial cell height (Jefferson *et al.*, 2002; Jefferson *et al.*, 2009). Another experiment data also showed there is a higher incidence of absence in the uterine corpora lutea in female mice after intervention with genistein (Jefferson *et al.*, 2011). While some data showed that daidzein did not cause any abnormity in the uterus, suggesting that daidzein may not have a measurable estrogenic effect on the mouse uterus, implying that daidzein may not have a similar estrogenic effect on the mouse uterus (Jarić *et al.*, 2018; Zhang *et al.*, 2018). The most important factor in the animal study is serum levels of soy isoflavone exposure in the neonatal mouse model resemble those of human infants, which attracts people's attention to ovarian development in adults. The studies on the male animal model mainly have involved male sexual maturation of the reproductive system and fertility (Cederroth *et al.*, 2010; Robertson *et al.*, 2002; Ronis *et al.*, 2018; Yatkin *et al.*, 2007). An influential study was that twin marmoset monkeys which evoke many European countries' attention and reduce the daily dosage of SBIF (Sharpe *et al.*, 2002). In this study, one twin was fed with SBIF from the beginning of day four or five of life. The serum testosterone of marmoset treated with SBIF had consistently reduced compared with its twin-fed cow milk formula. What is notable was that the dose of monkey's daily intake was about 1.6–3.5 mg isoflavones/kg body weight, which is less than half the exposure level of a human infant SBIF intake. While the consequent study demonstrated normal fertility and progression of puberty in the same subject group and feeding protocol (Tan *et al.*, 2006). Some people still concern about whether there is a relation between the declining sperm count occurring among men and soy isoflavone exposure (Mumford *et al.*, 2015). Two meta-analyses confirmed that neither soy nor isoflavone intake affects total or bioavailable circulating testosterone concentrations in men (Hamilton-Reeves *et al.*, 2010; Reed *et al.*, 2020). Based on the data gathered from animal and human studies, there seem to draw such conclusions that no obvious effect on sexual maturity in males. The experiment data showed that exposure did not affect preputial separation, fertility, sperm count, and testosterone levels with high oral doses of soy isoflavone treatment (Cederroth *et al.*, 2010; West *et al.*, 2005).

Currently, there is still a debate regarding whether the physiological impact of soy isoflavone consumption influences infants (Reed *et al.*, 2020; Zou *et al.*, 2020). Though several published studies and case reports describing feminizing effects, including reduced testosterone levels in men, recently, a meta-analysis including 41 studies showed that either soy or isoflavone intake affects male reproductive hormones (Reed *et al.*, 2020). A longitudinal prospective study is needed to show that the timing of exposure may modulate effects of later health, and it will be of great importance to further take the influence on reproductive outcomes at later stages of development into consideration.

Affecting gut microbiota, and neurobehavioral disorders

Recent studies reported that consumption of some kinds of flavonoids, especially genistein and daidzein influenced the gut microbial flora (Matthies *et al.*, 2012; Vázquez *et al.*, 2017; Wyns *et al.*, 2010). There are still many differences in experiments between the animal model and human beings; the data showed that there were close correlations between diet-responsive intestinal metabolites and gut microbes in soy-fed neonatal pigs (Piccolo *et al.*, 2017). In this study, the author suggested that bacteria species diversity and a greater percentage of cyanobacteria within the duodenum of sow-fed pigs are related to dietary intake. Another study also showed that a soy formula diet affected the intestinal epithelial lining, microbial populations, and intestinal epithelial barrier as well as anti-inflammatory markers (Yeruva *et al.*, 2016). The studies in human beings also demonstrated that phytoestrogen consumption or exposure might also influence the gut microbe composition (Yoshikata *et al.*, 2018; Iino *et al.*, 2019; Smith-Brown *et al.*, 2016; Wu *et al.*, 2016). The study showed that soy intake dosage was associated with the number of equol-generating bacteria within the intestine among Asian populations (Yoshikata *et al.*, 2018). Another study found that the gut microbial flora was surprisingly quite similar between the vegans consuming a soy-rich diet and the omnivores groups (Wu *et al.*, 2016). Though daidzein and genistein of plasma metabolome were predictably elevated in vegans relative to omnivores, equal concentrations did not differ between the

two groups of individuals. These findings suggest that a vegan or soy-rich diet perhaps alters gut bacteria-derived metabolism but not necessarily the gut microbiota themselves.

It is also being recognized that the gut microbiome can affect the host's neurobehavioral state, which has been hypothesized to be related to the microbiome-gut-brain axis (Alò *et al.*, 2019; Marshall *et al.*, 2019; Kolatorova *et al.*, 2018; Rosenfeld, 2015). The first solid evidence relevant to gut microbiota disturbances with neurobehavioral disorders is related to germ-free (GF) mice that lack a resident gut microbiome (Sudo *et al.*, 2004). GF mice are more anxious, less exploratory, and show cognitive and social deficits. These findings suggest that there is, probably, a crosstalk between the gut microbiota and brain with bacteria. A study revealed that early exposure to GEN could also cause behavioral abnormalities such as increased defensive behaviors and decreased aggressive behaviors in male C57BL/6 mice (Wisniewski *et al.*, 2005). Another study demonstrated that the male offspring of the CD1 mice had significant changes in anxiety and aggressive behaviors in adults after the mice's daily exposure of dams to genistein (100 μg/g of body weight) during late pregnancy and early lactation (Rodriguez-Gomez *et al.*, 2014). Westmark reported that there may be a potential linkage between feeding infant soy formula and subsequent risk for autistic behaviors in autistic children (Westmark, 2013). Additional data from this cohort revealed that febrile seizures in autistic boys and girls might be related to soy-based formulas (Westmark, 2014). The current study emphasizes the correlation analysis between gut metabolite changes produced by the bioactive forms of the flavonoids and behavioral responses. The underlying mechanism of the microbiome-gut-brain axis is still unclear and needs to be further explored.

Conclusions and Recommendations

We reviewed the available evidence on the potential toxicity of flavonoids. In the study of the relationship between flavonoids and human health, there are still many contradictions among cell culture, animal models, human experiments, and epidemiological investigation. Flavonoids extracts are often used in cell culture or animal models, while foods with abundant flavonoids such as soybean are often used in human experiments. Due to the complexity of the food composition and its decomposition into other metabolites in the digestive system, the observed results are likely to have the effect of other ingredients. We know the results were also influenced by many factors, such as the design of the experiment, the selection of subjects, and the effect of observation cases. Especially inhuman experiments, many factors are difficult to control. Therefore, there are still great limitations in inferring the possible consequences of the human body from the results of human cell culture and animal experiments. Also, the dosage of flavonoids observed in cell culture is dose-dependent, and it is difficult to evaluate the proper concentration in the human body. Combined with the limitations of animal experiments and the limited epidemiological data, it is difficult to conclude the toxic effect of flavonoids on human health. Although many pieces of research have been done, the data in this field about the toxicity is still insufficient. A large number of long-term human studies are still needed to thoroughly demonstrate its clinical effects and to detect its effects on estrogen target tissues, such as the breast and endometrium. At present, the consumption of soybean food and isoflavone supplements is increasing, so it is necessary to study the potential toxicity of these substances. However, there has been little evidence that SBIF and other factors have effects on the reproductive function of infants and young children in adulthood. This delay may prevent researchers from exploring the potential toxicity of SBIF. Considering the above reasons and animal experimental data, it is necessary to study the effect of SBIF on the growth and development of infants and later. Besides, it is necessary to further study the effects of SBIF on animals of different genders, and the reasonable standard dose of soy isoflavone as food and drug intake to the human body in different ages and regions.

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