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Phytoestrogens and Hepatocellular Carcinoma Chemoprevention

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ABSTRACT

Hepatocellular carcinoma (HCC) is the commonest primary malignant cancer of the liver and the third leading cause of cancer mortality worldwide. Statistically liver cancer is the fifth most common cancer in men and the 7th most common cancer in women. The major common risk factors for hepatocellular are hepatitis B (HBV) and hepatitis C viruses (HCV). Phytoestrogens are natural plant substances that are structurally or functionally similar to estradiol. The three main classes are isoflavones, coumestans, and lignans. Major source of phytoestrogen include, legume seeds (beans, peas), flax seed and especially soy products.Phytoestrogens have anticarcinogenic potential, but they have also significant estrogenic properties. Interest in phytoestrogens has been fueled by epidemiologic data that suggest a decreased risk of liver cancer in women from countries with high phytoestrogen consumption. In this review, the role of phytoestrogens and consumption of phytoestrogen-rich foods such as soy containing isoflavones, coumestans, and lignans for the prevention of hepatocellular carcinoma is reviewed.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality worldwide and the most common liver cancer and its incidence is increasing year by year [1, 2] .Statistically liver cancer is the fifth most common cancer in men and the 7th most common cancer in women worldwide [3, 4] and also accounting for 7.5% and 3.5% of all cancers among men and women, respectively. The geographical variability in HCC incidence rates is associated with etiological factors such as infections by hepatitis B (HBV) , hepatitis C viruses (HCV) and exposure to aflatoxin B1[5]. It is obvious that men are more affected by HCC than women because of higher rates of cirrhosis in men, greater alcohol consumption, exposure to toxins (tobacco and aflatoxins) and the influence of male sex hormones [3,6]* . The major common risk factors for hepatocellular are obesity, Cirrhosis, chronic hepatitis B virus infection and dietary exposure to the fungal hepatocarcinogen aflatoxin B_1, oral contraceptive steroids, aflatoxins, iron accumulation and tobacco smoking [7-14]. It has been reported that number of new cases of liver cancer have been increased year by year of which 82% are from developing countries. China alone accounts for 55% liver cancer death worldwide [15, 16]. The incidence of liver cancer is high in all low-resource regions of the world, with the exception of Western Asian and Northern African countries other than Egypt. The highest are recorded in Thailand, Japan, Korea, and certain parts of China. In most high-resource countries, age standardized rates are below 5/100,000 in men and 2.5/100,000 in women. Intermediate rates (5–10/100,000 in men) are observed in areas of Southern and Central Europe [17]. The 5-year survival rate was 8% in the United States [18], 9% in Europe [19], and 5% in developing countries [20]. Recently, phytoestrogens have attracted considerable attention for their potential anticancer activity. Because of side effects of all anticancer drugs, there is search for "natural" alternatives or complements to traditional therapy. Further, the increased enthusiasm in phytoestrogens as potential anticancer agents is evidenced by the published data. The population-based studies show that the mortality due to breast, ovarian, prostate, and colon cancer has a negative correlation with the phytoestrogens and cereal intake in the diet [21, 22]. There are more than 100 in vitro studies, which show that phytoestrogens can inhibit a wide range of both hormone-dependent and hormone-independent cancer cells [23]. Phytoestrogens are structurally similar to mammalian estrogens. Many epidemiological studies have reported that diets rich in phytoestrogens (PE), particularly soy and unrefined grain products, may be associated with low risk of some cancers. Major source of phytoestrogen include, legume seeds (beans, peas) , flax seed and especially soy products [24,25]. Several epidemiological studies have indicated that the Western diet is one of the main factors causing the high incidence of the some cancers such as colon cancer (Rose et al. 1986, Trowell and Burkitt 1981[26].

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CLASSIFICATION OF PHYTOESTROGENS

Phytoestrogens are a group of biologically active plant compounds with a chemical structure that is similar to estradiol, an endogenous estrogen [27, 28]. There contain three main classes of phytoestrogens isoflavones, coumestans, and lignans (fig.1) [29].

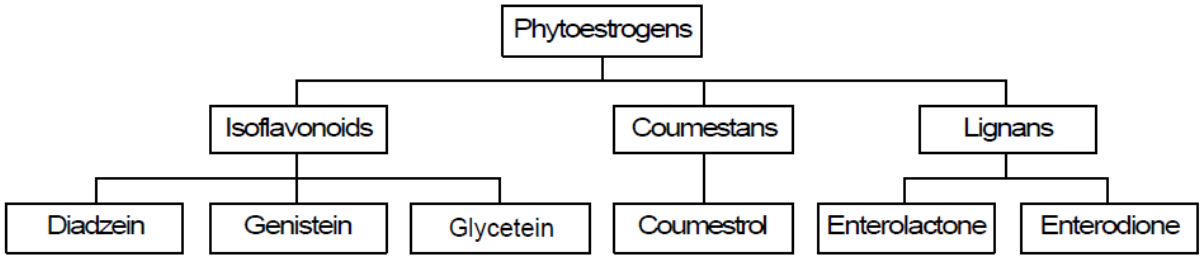

Fig1. Classification of phytoestrogens

Of these groups , isoflavones have dominated phytoestrogen research, because there is convincing in vitro evidence of their cancer inhibitory effects and soy foods are a major dietary component in Asia where hormone-related cancers are less prevalent [30 -33]. To date, 15 different chemical forms of isoflavones have been discovered [34].
It has been reported that the major isoflavone glycosides are genistin, daidzin and glycitin and their respective aglycones are genistein, daidzein and glycitein. Genistein and daidzein are found in high quantities in such food products as soybeans, tofu, kidney beans, chickpeas, lentils and peanuts. The richest source of isoflavonoids is the soybean, a large component of many Asian diets. Soybeans contain approximately 2 g of isoflavones per kilogram fresh weight [35]. Lignans are constituens of higher plants, such as whole grains and legumes with exceptionally high concentrations of lignans found in flaxseed.
Lignans are recognized as a class of natural products with a wide spectrum of important biological activities. Most of the known natural lignans are oxidized at C9 and C9´ and, based upon the way in which oxygen is incorporated into the skeleton and on the cyclization patterns; a wide range of lignans of very different structural types can be formed. Due to this fact, lignans are classified in eight subgroups (Chang et al., 2005; Suzuki & Umezawa, 2007. Lignans can be further classified in "lignans with C9 (9´)-oxygen" and "lignans without C9 (9´)-oxygen" (fig.2) [36].

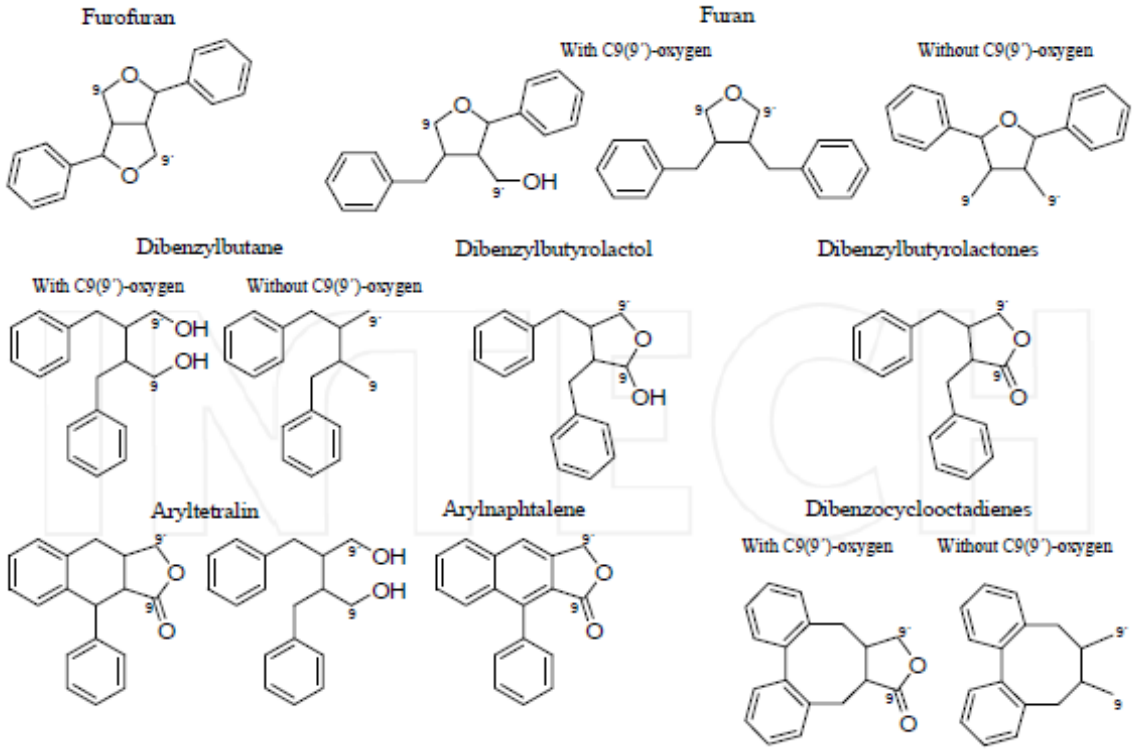

Fig. 2. Main subclasses of lignans and their subgroups [36]

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Mammalian lignans, mainly enterolactone and enterodiol, are produced from precursors such as secoisolariciresinol and diglucoside in plant foods by the action of bacterial flora in the colon [37]. Another phytoestrogen in the human diet with estrogen activity is coumestans, which are found in soybean sprouts [38]. Coumestans, relative to lignans and isoflavonoids have a generally a lesser oestrogenicity. Compared to isoflavones and lignans, estrogenic coumestans appear to have a relatively restricted distribution in plants and generally occur at much lower levels [39].

SOURCES OF PHYTOESTROGENS

Main source of phytoestrogens include; fruits (plum, pear, apple grape berries,), vegetables (beans, sprouts, cabbage, spinach, soybeans, grains, hops, garlic, onion,…), wine, tea, and they have been identified in a number of botanical dietary supplements. They include a wide variety of structurally different compounds such as isoflavones, mainly found in soy, lignans found in grains, stilbenes found in the skin of grapes [40]. The most important dietary sources include isoflavones (e.g. soy products) and lignans (e.g.flaxseed, grains, nuts, vegetables, fruits) [41, 42]. Lignan-containing foods include legumes, seeds, cereals/grains, berries, dried fruit, and vegetables [43]. The two main isoflavonoids (namely genistein and diadzein) are present in all soy bean foods either as aglycone (unconjugated form) or as beta-glycoside (conjugated form) [44]. Legumes are the main source of coumestrol, the coumestan showing the highest estrogenic activity and low level of coumestrol have been found also in brussel sprouts and spinaches, while the highest concentrations are reported in clover and in soybean sprouts [40].

METABOLISM OF PHYTOESTROGENS

Isoflavones undergo hydrolysis due to the action of the brush border and bacterial β-glucosidases to remove the sugar moiety; the aglycone form is then either absorbed or undergoes further metabolism by intestinal bacteria in the large bowel (Chen et al., 2003; Setchell et al., 2003). The isoflavone daidzein is usually metabolized to dihydrodaidzein or O-desmethylangolensin (Bowey et al., 2003; Setchell, 1998; Yuan et al., 1995; Zubik and Meydani, 2003). In a small number of persons daidzein may also be metabolized in the intestine to equol, a metabolite that has greater estrogenic activity than daidzein (Muthyala et al., 2004) [45]. Metabolism of phytoestrogens by the gastrointestinal microflora yield a number of metabolites including equol and O-desmethylangolensin.Parental compounds and their metabolites are absorbed into the bloodstream, becoming rapidly detectable in the plasma and urine [46-51]. Plasma isoflavone, the complete metabolic activation of soy isoflavones, is proposed to occur locally within target tissue. Most research reported a role for the CYP family of cytochrome P450 enzymes in the intratumour metabolism of phytoestrogen compounds [52-53]. Thus, intestinal flora seems to have an important influence on the metabolism and absorption of isoflavones. Studies have shown that only about 30–40% of subjects produce significant quantities of equol after isoflavone consumption [54-56].

PHYTOESTROGENS AND HEPATOCELLULAR CARCINOMA

Many studies indicated that consumption of soya foods is associated with reduced risk of HCC. This may reflect a counteracting effect of isoflavones on estrogen and testosterone levels that reduces HCC risk, perhaps by modifying the hormonal milieu and reducing the cell proliferation associated with increased cancer risk, and/or it may reflect an independent antitumor effect related to inhibition of angiogenesis or induction of apoptosis [57].
Several epidemiological findings for isoflavone and soy food intake and HCC are inconsistent. Many studies have reported an inverse association between phytoestrogen intake and HCC mortality. It has been reported that genistein consumption was lower at first diagnosis in patients with HCC than in those with cirrhosis. In several studies, in contrast, no association with HCC was seen for frequency of tofu and pulses intake [58-64].

PHYTOESTROGENS AND OTHER CANCERS

1. BREAST CANCER

Many epidemiological studies have indicated that diets rich in phytoestrogens, particularly soy and unrefined grain products, may be associated with low risk of some cancers, especially steroid hormone dependent, e.g. breast and prostate cancers [65-67]. Infact, the association between soy food intake and breast cancer risk is controversial. Although isoflavones, such as those found in soy, have been shown to inhibit breast cancer, correlations between the consumption of isoflavone-containing foods and breast cancer risk have been inconsistent in epidemiological studies. Several studies have indicated that countries with the highest epidemiological consumption have the lowest rates of breast cancer [66]. Many dietary intervention studies revealed a direct association between the consumption of soy products and a reduction in circulating steroid hormone levels. Daily consumption of 154 mg isoflavones for the duration of a single menstrual cycle correlated with substantially decreased plasma concentrations of 17β-oestradiol and progesterone in a cohort of premenopausal women .Serum concentrations of 17β-oestradiol are approximately 40% lower in Asian women than in their Caucasian counterparts [68-70].

2. OVARIAN CANCER

Few studies have investigated the association between ovarian cancer and intake of phytoestrogens. Isoflavonoids, a class of phytoestrogens, have estrogenic, antiestrogenic, and antiproliferative effects and inhibit the growth and proliferation of ovarian cancer [71-75]. Meta-analysis study has shown that high intake of isoflavonoids is associated with a decreased risk

of ovarian cancer [76]. Genistein is known as the major component of isoflavone, which is present in high-soy diets. Numerous studies have shown that genistein has antineoplastic effects against ovarian cancer. Several epidemiological studies have shown that women who have high consumption of isoflavones have a relatively low incidence of ovarian cancer. A decreased risk for ovarian cancer was found in women with the highest quartile intake of genistein than in women with the lowest quartile intake (Zhang et al., 2004). Myung et al have shown that the highest soy intake was associated with a lower ovarian cancer risk than the lowest soy intake (Myung et al., 2009) [45]. Few epidemiologic studies have indicated the association between Tofu, lignans and isoflavones consumption and reduced risk of ovarian cancer [77].

3. PROSTATE CANCER

Many epidemiological investigations have indicated that a relationship between reduced risk of prostate cancer with consumption of soy and isoflavones [78-82]. In addition to epidemiological studies, many in vitro and in vivo studies have concurred on the protective effects of phytoestrogen against prostate cancer [83-88]. Strom et al. have showed a protective trend of genistein and daidzein against prostate cancer [82]. The results of several analysis studies showed that consumption of soy foods was associated with a reduction in prostate cancer risk of ’26% in men. Many epidemiology studies has shown that consumption of tofu and soy milk is associated with a reduction in prostate cancer risk of ’30%. The extensive associations between soy consumption and prostate cancer risk from the epidemiologic studies are supported by animal studies showing that dietary soy protein [89-91] and soy phytochemical extracts inhibit experimentally induced prostate tumorigenesis [92].

4. COLORECTAL CARCINOMA

The incidence of colorectal cancer is much lower in Asian countries, such as China and Japan, than in Western societies. Several studies have reported lowered colorectal cancer risk associated with the consumption of soy foods [93-101]. Most studies reported that higher dietary lignan intake was associated with a considerable reduction in colorectal cancer risks. Several epidemiologic studies reported the association between soy foods consumption and reduced colorectal cancer risk in Asia [102,103]. Soy or isoflavones have also shown other anticarcinogenic activities in in vitro and animal studies [104], High consumption of soy-containing foods was found to be associated with a reduced risk of colon cancer in a case-control study of multiethnic populations in Hawaii [105], a reduced risk of rectal cancer in casecontrol studies conducted in China [106] and Japan [107], and a reduced risk of colorectal adenomas, precursors to colorectal cancer, in a case-control study of multiethnic populations in Southern California [108]. Furthermore, a prospective cohort study in Japan reported an inverse association between soy food intake and colon cancer risk [102].

MECHANISM OF ACTION OF PHYTOESTROGENS

Phytoestrogens acts by Multi-targeted mechanisms [109-111]. Their targets are summarized in the following section under four categories:

Receptor and molecular targets
Enzymes and metabolic pathways
Cytotoxic effects
Anti-metastatic effects

RECEPTOR AND MOLECULAR TARGETS

Isoflavones have affinity for the estrogen receptor beta with antagonistic and partial agonistic actions [112]. Genistein down-regulates androgen receptor by decreasing the chaperone activity of Hsp 90 (Heat shock protein) which is required for stabilization of the receptor [113]. In vitro studies reported that genistein is a tissue-specific androgen receptor modulator [114]. It should be noted that genistein had an anti-androgenic effect on testis, prostate and brain in intact male mice, whereas androgenic effect was observed on prostate and brain tissues of the castrated mice. Recent study reported a ligand-dependent difference in transcriptional regulation of prostate specific antigen (PSA) by genistein [115].

ENZYMES AND METHABOLIC PATHWAYS

Daidzein and genistein can inhibit and induce various enzymes involved in sex steroid metabolism [116-121]. These compounds inhibit steroid metabolizing enzymes such as 5-alpha reductase [111], aromatase [122] and 17- β hydroxysteroid dehydrogenase type 1 [116]. Isoflavones are stimulators and inhibitors of SULT (Sulfotransferases) in a dose dependent manner. Nishiyama et al. Several studies reported that daidzein and genistein are predominantly sulfated by SULT1A1 and SULT1E1, respectively in humans and inhibit the sulfation of the endogenous substrate, beta-estradiol [123] and demonstrated that equol, genistein and daidzein inhibited human SULT1E1 in that order of potency[120].

CYTOTOXIC EFFECTS

Cytotoxic effects reported by several studies include caspase mediated apoptosis, inhibition of VEGF (Vascular Endothelial Growth Factor), inhibition of TGF beta (Transforming Growth Factor) and inhibition of activation of transcription factors like NF-κB which play an important role in cell growth, differentiation, proliferation and apoptosis [111]. Many studies

reported suppression of angiogenesis by phytoestrogens (124). Other reported pathways include Inflammatory and steroid pathway modulation via inhibition of prostaglandin synthesis (125).

ANTI-METASTATIC EFFECTS

Genistein acts by inhibition of the focal adhesion kinase (FAK), p38 mitogen-activated protein kinase (MAPK) and heat shock protein 27 (HSP27) pathways. These pathways aid in cell detachment and cell invasion. Many studies reported that genistein caused a compensatory increase in promotility agents such as FAK, p38 MAPK, HSP27 due to its antimotility effect on prostate cancer cells [126]. Human studies performed by Xu et al. Other studies reported that genistein blocks MEK4 (Mitogen-activated protein kinase 4) in addition to p38 mitogen and decreases MMP-2 (Matrix Metalloproteinase-2) [127].

CONCLUSION

This review highlights the role of phytoestrogens in HCC chemoprevention. Phytoestrogens were originally proposed as cancer protective agents following epidemiological observations revealing a low liver cancer incidence in soy-consuming populations; hence, much attention has been focused on the chemopreventive effect of liver cancer. In addition, much work needs to be done on optimizing the bioavailability of the drug and determining its pharmacokinetic, pharmacodynamics, and safety profile clinically. Furthermore, most studies have used whole soy product while each of subgroup of phytoestrogens must be used alone and flow-up clinically.

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