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Modulation of Edible Plants on Hepatocellular Carcinoma Induced by Aflatoxin B₁

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Abstract

Aflatoxin B₁ (AFB₁) is one of the major causes of liver cancer especially hepatocellular carcinoma that has high incidence and mortality rate in many countries. Owing to the climate that is suitable for fungal growth, the avoidance of AFB₁ exposure from agricultural product contamination is too difficult. This up-to-date review aims to collect insight on how edible plants attenuate AFB₁-toxicity. Cruciferous vegetables, green tea, purple rice, turmeric, green vegetables, ginger, *Dialium guineense*, *Parkia biglobosa*, carotenoid-rich fruits and vegetables, *Allii Fistulosi Bulbus*, and rosemary have reported their capabilities to alleviate AFB₁-toxicity through several mechanisms. All these plants showed anti-genotoxic activity while some of them are able to reduce hepatotoxicity, liver cancer, and oxidative stress and modulate metabolism enzymes induced by AFB₁. Furthermore, a few edible plants could handle AFB₁ in pre-exposure phase including anti-AFB₁ biosynthesis and AFB₁ absorption. Although the detoxification mechanisms of AFB₁ activated by various edible plants have been investigated in pre-clinical study for a decade, clinical trial is still rarely clarified. Further study associating with a protective effect on AFB₁ toxicity still needs to be carried out especially in the clinical study.

Keywords: mycotoxins, liver cancer, natural products, detoxification, chemoprevention

1. Introduction

Liver cancer is the third most common cause of cancer mortality worldwide especially in developing countries. Epidemiological studies among all continents found that Asia and Africa have higher incidence rate than western world [1]. Hepatocellular carcinoma (HCC), arise due to excessive growth of abnormal liver cells, is most commonly found among all liver cancer types [2]. Four main potential causes of HCC have been identified as viral infection (chronic hepatitis B and C), metabolic syndrome (diabetes and nonalcoholic fatty liver disease), immune-related disease (autoimmune hepatitis), and toxic substances (alcohol and aflatoxins) [3].

Aflatoxin B₁ (AFB₁) is a noxious carcinogen produced by certain fungi *Aspergillus flavus* and *A. parasiticus* which mostly contaminate in agricultural

products such as rice, chili, and peanuts. AFB₁ is a Class 1 carcinogen classified by the International Agency for Research on Cancer (IARC), suggesting sufficient evidence of carcinogenicity caused by AFB₁ in both animals and human [4]. Consequently, it is considered as a serious contaminant in many foodstuffs.

Once the AFB₁ is absorbed through human body, it is metabolized at the liver site by phase I metabolizing enzymes including hydroxylation, hydration, demethylation, and epoxidation. Nontoxic metabolites are resulted from hydroxylation, hydration, and demethylation while the reactive metabolite, AFB₁-8,9-epoxide, is resulted from epoxidation [3, 4]. AFB₁-8,9-epoxide is the genotoxic form and can react efficiently with DNA at the N7 site of guanine to form AFB₁ adduct. This adduct can adversely affect DNA sequence and genetic materials. However, human defensive mechanisms are able to detoxify AFB₁ toxicity through phase II metabolism enzymes. AFB₁ can be converted into excretable forms after binding with glutathione and glucuronic acid generated by specific enzyme, glutathione S-transferase (GST) and UDP-glucuronosyltransferase (UGT), respectively [5–7]. Besides acute toxicity such as hepatic necrosis, bile duct proliferation, edema, and lethargy could also be observed after exposure to high dose of AFB₁ [8].

Regarding the current situation, there are many ways to avoid the risk of AFB₁-induced liver cancer as determined by two main periods, pre- and post-harvest period and exposure period [6]. During harvest time, several techniques are used for controlling and reducing the chance of harmful effects resulted from AFB₁: cultivation of AFB₁ tolerance plants, biocontrol using competitive fungi, irrigation, and insecticide. For exposure period, most researches aim to determine the effects of several foods or supplementary foods that are capable of decreasing AFB₁-induced toxicity. For example, oltipraz, a synthetic derivative of natural compound originated from cruciferous vegetables, is reported on its capacity to reduce AFB₁ toxicity. In addition, green tea polyphenol and chlorophyllin (a derivative of chlorophyll found in green leafy vegetables) are also stated. These natural compounds have a potential against AFB₁-induced hepatocarcinogenicity by decreasing the absorption of AFB₁, controlling metabolic pathway, and increasing AFB₁ excretion [6, 9]. To update the involvement of edible plants as chemoprevention for AFB₁, this review is aimed to emphasize the mechanistic alleviation of AFB₁-induced liver toxicity by polyphenol-containing plants.

2. Effects of edible plants on toxicity induced by AFB₁

2.1 Cruciferous vegetables

Cruciferous vegetables belong to *Brassica* genus, Brassicaceae family which are usually known as broccoli, Brussels sprouts, cabbage, cauliflower, kale, and radishes and commonly used for food consumption. They are not only rich sources of fibers, vitamins, and carotenoids as their important components, but also contain higher glucosinolate content than other vegetables [10]. Glucosinolates are secondary metabolites in cruciferous veggies and can be divided into three classes based on their structure: aliphatic glucosinolates, indole glucosinolates, and aromatic glucosinolates.

Nearly 200 types of glucosinolates have been reported in scientific literature, especially glucobrassicin and glucoraphanin. These two compounds can be transformed into hydrolysis products such as isothiocyanates, sulforaphane (SF), and indole-3-carbinol (I3C) by β -thioglucosidase (myrosinase) enzyme when plant cells are damaged. This mechanism could also be processed by bacteria in the gastrointestinal tract [11, 12].

The studies of anticancer effects of glucosinolates and their hydrolysis products revealed that numerous existing compounds also had anticancer mechanism against various types of cancers. For instance, the presence of sulforaphane could suppress carcinogen and prevent DNA adduct (a biomarker of AFB₁ exposure) directly through an inhibition of phase I metabolism enzymes. At the same time, it induces phase II metabolism enzymes which play an important role in converting carcinogens to the inactive metabolites and excreting from the body. Their hydrolysis products exhibit an ability to scavenge the free radicals, inhibit inflammation and angiogenesis, and also induce an apoptosis of cancer cells [11].

Previous studies investigated the effects of bioactive compounds such as I3C and 1-cyano-2 hydroxy-3 butene (Crambene), derivatives of glucosinolate group found in cruciferous veggies, on HCC occurrence. Glucosinolates did not only respond for abnormal liver cells, but they also enhance AFB₁ detoxification in the rat model. Pre-exposure to the high-dose combination of I3C and Crambene (0.15 and 0.165%, respectively) protected the liver cells effectively more than low-dose combinations and single exposure [13]. Risk reduction of liver cancer could also be observed in rainbow trout when pre-exposed to I3C at the dose 2000 ppm prior to AFB₁; however, the adverse effects and increase of liver cancer incidence were reported when the exposure sequence was reversed [14]. In addition, further studies revealed a dose-dependent relationship between I3C dose after exposure to AFB₁ and the incidence of liver cancer and other cancer types [15]. Thus, it could be summarized that the incidence of liver cancer is induced by AFB₁ relating to timing of I3C exposure. Pre-exposure to I3C prior to AFB₁ reduced the liver cancer incidence, but post-exposure reversely raised the liver cancer incidence [15]. Accordingly, subsequent mechanistic studies indicated an induction of I3C on phase I and II metabolism enzyme activities [16]. Continuous exposure to I3C might enhance phase II enzyme activity, so the absorbed AFB₁ would be excreted rapidly. In contrast, pre-exposure to AFB₁ triggered the adverse effects such as DNA abnormality and increase of liver cancer risk. The explanation was that pre-exposure to AFB₁ generates AFB₁-8,9-epoxide and this reactive metabolite would be more activated when treated later with I3C. In addition, I3C could be able to induce both phase I and II metabolism enzyme activities, thus AFB₁-8,9-epoxide was more generated as a result of activation of phase I metabolism. Although phase II enzyme was also stimulated, it was not enough to eliminate AFB₁.

Not only I3C is frequently reported, but other glucosinolate derivatives like SF and H-1,2-dithiole-3-thione (D3T) are also stated. For example, while rats were pre-exposed to these derivatives, AFB₁-DNA adduct in rat's liver was reduced due to an increase of GST activity, a phase II detoxification enzyme for AFB₁ [17]. Likewise, other previous studies reported that SF could competitively inhibit CYP1A2 in human liver cells [16], causing a decrease of AFB₁-DNA adduct. Remarkably, upregulation of gene expression-related tissue repairing system and number of hepatocytes were observed after induction of SF [18].

The current epidemiological and clinical studies revealed that only lung, colorectal, breast, prostate, and pancreatic cancers were given the positive response to glucosinolates while animal model showed the effective inhibition of liver cancer and other cancer types through various mechanisms. Nevertheless, randomized clinical trial of glucosinolates on liver cancer showed different results [11, 19]; comparison between broccoli sprout extract treatments and control group was studied simultaneously. After treatment, AFB₁-DNA adducts were clearly determined. The results indicated that no significant difference was observed among tested groups on AFB₁-DNA adduct level ($p = 0.68$). On the contrary, an inverse linear correlation of dithiocarbamates, a metabolite of sulforaphane, and AFB₁-DNA adduct excretion was noted ($p = 0.002$, $R = 0.31$). It can be implied that exposure to glucosinolates might decrease AFB₁-induced toxicity [20]. Besides, various compounds of

glucosinolates have the potential to increase excretion of many carcinogens through glutathione S-transferase stimulation. Once the GST was stimulated, carcinogenicity and risk of diseases in human were also decreased [21].

2.2 Green tea

Green tea, *Camellia sinensis*, is a beverage that contains high contents of phenolic compounds at approximately 30% of dry weight. One of the major phenolic compounds in green tea is catechin, particularly epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin gallate (ECG), and epicatechin (EC) [22].

Recent studies have demonstrated the positive effects of green tea on many diseases and adverse human health conditions such as coronary artery disease, oral health, bone integrity, thermoregulation balance, and kidney stones. Furthermore, an association between green tea consumption and the incidence of many types of cancer has also been reported such as oral and pharynx, esophageal, gastric, colorectal, bladder, prostate, breast, lung, skin, leukemia, pancreatic, and liver cancers [23, 24]. Various research methods including preclinical studies (*in vitro* and *in vivo*), epidemiology, and clinical trial were used to investigate the effect of crude green tea extract or single compound like EGCG on many types of cancer [25]. Overall, an anti-cancer mechanism of green tea extracts against cancer cells was evidently elucidated. Green tea extracts were able to induce apoptosis of cancer cells through inhibiting nuclear factor kappa light chain enhancer of activated B cells (NF- κ B) activity and B-cell lymphoma extra-large (Bcl-xL) mRNA expression. Besides, the reduction of angiogenesis of cancer cells was also resulted by green tea extracts through inhibition of vascular endothelial growth factor (VEGF) expression [26].

Previous studies have been reported on several protective ways against AFB₁-induced liver cancer from the exposure to catechin compounds and green tea extracts. For example, the reduction of chromosome aberration in rat bone marrow cells was observed after pre-exposure with green tea or EGCG for 24 hours prior to AFB₁ [27]. Besides, hepatic nuclear AFB₁-DNA binding and glutathione S-transferase placental form (GST-P) positive single hepatocyte, specific markers of hepatocarcinogenic potential in the rat model, were also reduced after pre-exposure with green tea extracts for 2–4 weeks prior to AFB₁ [28]. Similarly, the levels of GST-P and γ -glutamyl transpeptidase positive hepatic foci induced by AFB₁ and carbon tetrachloride were reduced during pre- or co-treatment with green tea extracts. Furthermore, the inhibition of hepatocarcinogenesis was also observed [29].

The studies of green tea against AFB₁-induced human liver cancer are still currently limited, and most reports have been retrieved from China. As some Chinese commonly consume food contaminated with AFB₁, the risk of HCC is higher than other regions. A clinical study demonstrated a protective effect of 500 and 1000 mg/day green tea polyphenol (GTP) on hepatocarcinogenesis in 124 HCC patients who presented with HBsAg and aflatoxin-albumin adducts. Results showed that 8-hydroxydeoxyguanosine (8-OHdG) level, an oxidative DNA damage biomarker originating in urine specimens, significantly decreased ($p = 0.007$) during co-exposure with GTP for 3 months [30]. Besides, AFB₁-albumin adducts (AFB₁-AA) and AFB₁-mercapturic acid (AFB₁-NAC) level in blood and urine specimens of volunteers were compared among 500 and 1000 mg GTP treatment group and control group. This result revealed a reduction of AFB₁-AA level, an indicator of AFB₁ exposure, for both 500 and 1000 mg GTP treatment groups within 3 months. This reduction was strongly related to dose and duration of GTP exposure ($p = 0.049$). Furthermore, AFB₁-NAC, an indicator of AFB₁ elimination activated by phase II metabolism enzymes, significantly increased ($p < 0.001$) in both treatment groups related to dose and duration of GTP exposure as well

($p < 0.001$). Therefore, it could be summarized that GTP effectively modulated AFB₁ biotransformation by inhibition of phase I metabolism enzymes as can be seen from the reduction of AFB₁-AA. GTP also has an induction effect to phase II metabolism enzymes which transform AFB₁-8,9-epoxide to AFB₁-NAC [31].

Furthermore, results from a meta-analysis investigating the effect of green tea extracts on HCC and other liver diseases also showed that regular green tea drinkers had a lower incidence of HCC than nonregular drinkers approximately 26% ($R = 0.74$, 95% CI = 0.56–0.97, $p = 0.027$). Although there were some inconsistent results in this study ($I^2 = 80.1\%$, $p = 0.000$), no publication bias was detected and no data from one study significantly influenced the final conclusion [25].

2.3 Purple rice

Anthocyanins, members of flavonoid groups, are mostly found in blue, purple, orange, and red vegetables. Anthocyanins in plants play a vital role in attraction of bugs for pollination and insect resistance [32]. Pharmacologically, purple corn extracts have been known for its anti-diabetic and antiadipogenic effects, anti-prostate carcinogenesis, and others [33–35] while blue butterfly pea flower has a definite potential anti-inflammatory effect [36]. Furthermore, anthocyanin-rich plants were shown to protect neurodegenerative and also cardiovascular disease [37].

Purple rice bran (*Oryza sativa* L. var. *indica*) contained flavonoids and anthocyanins approximately 53 and 2 mg/g, respectively. Both compounds were reported to reduce AFB₁-induced toxicity, and they were capable of inhibiting mutagenicity in *Salmonella typhimurium* strains TA98 and TA100 [38]. In animal model, rats were pre-treated with purple rice bran extracts for a month before exposure to AFB₁. Then, the expression of CYP450 including CYP1A2 and CYP3A was investigated; both of them have an identical role in transforming AFB₁ to AFB₁-epoxide. The results showed that the extracts could not only inhibit the expression of CYP1A2 and CYP3A, but also increase the expression of GST and UGT which encouraged AFB₁ excretion. Further in *in vivo* studies, the genotoxicity was evaluated by micronucleus assay, and the result showed lower micronucleus formation in extract-pretreated group than AFB₁ treated alone, confirming the capability of purple rice bran extract on the prevention of AFB₁-induced genotoxicity [39].

Apart from purple rice bran extract, other anthocyanin-rich plants are also studied for their effects on AFB₁-induced cytotoxicity. For instance, *Lannea microcarpa*, a tropical African plant, has been studied for its activities against hepatotoxicity, DNA fragmentation, and oxidative stress induced by AFB₁. Before exposure to AFB₁, animals were pre-exposed with *Lannea microcarpa* extracts for 6 months. Results showed that hepatotoxicity, DNA fragmentation, and oxidative stress was lower in extract-pretreated group when compared to AFB₁-treated group [40].

2.4 Turmeric

Turmeric is a flowering plant widely used as a food ingredient in South Asia for a long period of time. It has been also applied in pharmacognosy field as a powerful anti-inflammatory resulting from rheumatoid arthritis, bruise, epilepsy, abdominal pain or discomfort, and asthma [41]. An *in vivo* study of turmeric clearly showed the anticancer properties of turmeric on liver, skin, and colorectal cancers. It has a strong potential to inhibit cancer cell growth through stimulating apoptosis and inhibiting phase I metabolism enzymes. It can also stimulate phase II metabolism enzyme activities which play an important role in converting reactive metabolites to excretable forms. Also, turmeric exhibits the antioxidant capacity which can effectively detoxify oxidative stress [42].

Curcumin is a major active component of turmeric. It belongs to curcuminoid group and commonly found in 2–8%. Previous *in vivo* studies investigated the effects of turmeric and curcumin on AFB₁-induced toxicity, and results showed that turmeric and curcumin decreased AFB₁-adduct formation, biomolecule damage, and hepatotoxicity [43–46], and it also inhibited acute toxicity through disturbing the lysis of erythrocytes [47]. During AFB₁ metabolism, free radicals generated by AFB₁ could be readily inhibited by turmeric and curcumin via decreasing lipid peroxidation and enhancing glutathione content. Likewise, they could activate several antioxidant enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), GST, and UGT which play a fundamental role in converting AFB₁ to excretable forms [43–46].

Turmeric is found to be capable of reducing both AFB₁-induced toxicity and HCC. Besides, it could also stimulate apoptosis of liver cancer cells through a mitochondria-dependent pathway and accumulation of calcium ions within the cells [48]. Turmeric showed the protective effect against AFB₁-induced liver cancer in animal model by inhibition of metastasis and growth factor expression related to the progression of angiogenesis [49].

2.5 Green vegetables

Chlorophyll (chla), a main component of green vegetables, consists of a porphyrin ring structure where magnesium is the central atom of the ring. Chla is important for plants' photosynthesis pathway and used as food additives. One of the characteristics of chla is almost insoluble in water while chlorophyllin (CHL), a derivative of chla, is completely soluble. CHL can be transformed into water-soluble form by saponification, a reaction that magnesium central atom is replaced with copper. *In vivo* and clinical studies in pharmacological researches of both chla and CHL revealed that they provided the therapeutic uses such as wound healing, anti-inflammation, anti-oxidation, anti-mutagenesis, and anti-carcinogenesis [50, 51].

Previous studies on the protective effects of chla and CHL on AFB₁ toxicity indicated that both compounds could reduce absorption of AFB₁ from apical to basolateral sides in Caco-2 cell line [52]. Accordingly, a crossover clinical trial demonstrated that chla and CHL exposure could reduce maximum concentration (C_{max}) and area under the curves (AUC) of AFB₁ compared to untreated group [53]. These findings suggest that chla and CHL have a strong potential to decrease AFB₁ absorption. The effects of chla and CHL co-exposure with AFB₁ have also been studied in animal model by emphasizing on antioxidant activities. Both bioactive compounds are capable of reducing AFB₁ toxicity through enhancing the expression of glutathione level and several antioxidant enzyme activities such as GPx, SOD, and CAT [54].

A recent study investigated the effects of CHL on AFB₁-induced hepatotoxicity and incidence of carcinogenesis in animal model. Exposure with CHL reduced hepatotoxicity and incidence of liver cancer [54, 55]. In a clinical study, a randomized controlled trial reported that daily exposure with CHL for 4 months decreased AFB₁-N⁷-guanine level in urine compared to placebo group [56].

Several studies were in agreement that chla and CHL reduce AFB₁-induced liver cancer through decreasing AFB₁ absorption in digestive tract contributing to the decrease of AFB₁ bioavailability. Besides, chla and CHL are the powerful antioxidants which effectively lower AFB₁-induced oxidative stress. These two compounds not only reduce hepatotoxicity, but also incidence of liver cancer. Thus, the consumption of green vegetables is one of the alternatives to reduce toxicity caused by consuming AFB₁-contaminated foods.

2.6 Ginger (*Zingiber officinale* Roscoe)

Ginger (*Zingiber officinale* Roscoe) contained high content of phenolic compounds in which 6-gingerol and 6-shogaol are main constitutions [57]. Ginger plays a critical role as hepatoprotective effects through antioxidant mechanism; for example, liver injury by administration of country-made liquor (CML) and iron-induced nonalcoholic fatty liver disease (NAFLD) [58] and liver cirrhosis induced by carbon tetrachloride [59]. It was also reported to show the protective effects against AFB₁-induced toxicity.

In *in vitro* model of AFB₁-treated HepG2 cells, ginger extract-pretreated cells exhibited higher percent cell viability and lower intracellular ROS production and DNA strand break when compared to AFB₁ treatment alone. In Wistar rats, pre-treatment with ginger extract also increased the activities of antioxidant enzymes: GPx, GST, CAT, and SOD, decreased malondialdehyde (MDA) level, and increased reduced glutathione (GSH) content. Co-incubation with ginger extract along with AFB₁ also showed a hepatoprotective effect as seen by the lower level of serum enzymes: alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH). Moreover, fat droplets and hepatocyte infiltration with macro-vesicles in liver induced by AFB₁ were normalized when pre-treated with ginger extract, clearly showing the effectiveness of ginger on AFB₁-induced hepatotoxicity [57].

Mechanism of ginger extract to reduce AFB₁-induced hepatotoxicity was demonstrated by *in vivo* study. The expression of nuclear factor-E2-related factor 2 (Nrf2), a redox-responsive transcription factor, was increased when pre-treated with ginger extract. Nrf2 was translocated into the nucleus to regulate the antioxidant response element (ARE) which is the promotor of detoxification and antioxidant genes. Moreover, administration of ginger extract induced the expression of heme oxygenase 1 (HO-1) which is associated with the normalization of redox status [57]. Therefore, ginger extract could reduce AFB₁-induced hepatotoxicity in both *in vitro* and *in vivo* through antioxidant activities controlled by the function of Nrf2 and HO-1.

2.7 Plants in family Fabaceae

2.7.1 *Dialium guineense*

Dialium guineense is a fruit-bearing tree known as the velvet tamarind. Their bark, leaves, seeds, and fruit showed biological properties such as antimicrobial activities, anti-infectious diseases, and wound-healing [60, 61]. Extract from *Dialium guineense* showed ROS scavenging activities and could normalize the levels of enzyme biomarkers of hepatotoxicity: ALP, AST, and AST induced by AFB₁. Furthermore, treatment of velvet tamarind extract before AFB₁ exposure increased the antioxidant activities of various enzymes including SOD, GPx, GR, CAT, GSH, and oxidized glutathione (GSSH), decreased lipid peroxidation, protein carbonyl and DNA fragmentation. *In vitro* and *in vivo* experiments have also confirmed the protective effects of velvet tamarind extract against hepatotoxicity induced by AFB₁ via antioxidant properties [62].

2.7.2 *Parkia biglobosa*

Parkia biglobosa, known as the African locust bean tree (ALBT), is a perennial tree legume growing in West Africa. Several parts of ALBT (bark, leaves, pods,

stem, and fruit pulp) showed medicinal properties such as antimicrobial activities, antihypertensive effects, antidiabetic activity, antidiarrheal activity, and others [63]. Pulp extract of ALBT exhibited abilities against antioxidant imbalance induced by AFB₁. When pretreated in animal model, pulp extract of ALBT were capable of inducing SOD, CAT, GPx, GR, and glucose-6-phosphate dehydrogenase (G6PD) activities and increasing GSH and GSSG content. In addition, pretreatment with pulp extract of ALBT reduced lipid peroxidation products, protein carbonyl, and DNA fragmentation induced by AFB₁. AFB₁ treatment also resulted in decrease of hepatocellular enzyme activities: ALP, ALT, and AST compared to control while the pretreatment with pulp extract of ALBT increased these enzyme activities in a dose-dependent manner. Accordingly, antioxidant imbalance and hepatotoxicity induced by AFB₁ were able to be alleviated by pretreatment with pulp extract of ALBT [64].

2.8 Carotenoid-rich fruits and vegetables

Carotenoids, natural plant pigments giving the color of fruits and vegetables, are responsible for the red, orange, and yellow colors in mangoes, corns, carrots, pumpkins, tomatoes, etc. More than 700 different carotenoids have long been characterized and classified as two main groups regarding their basic functional group [65]. Xanthophylls, yellow or orange-yellow pigments, are found widely in nature and the majority of their structure consists of oxygen as the core element such as lutein and zeaxanthin. Carotenes, one of another division of carotenoids, are hydrocarbon compounds without other functional groups including α -carotene, β -carotene, and lycopene [66]. Both xanthophylls and carotenes are almost known as fat-soluble compounds dissolved well in petroleum, ether, chloroform, and hexane but carotenes seem to be more soluble in these nonpolar aliphatic solvents compared to xanthophylls; some are water-soluble [67]. Carotenoids have a potential role as a provitamin A compound which can be converted within the body to vitamin A, and they are broadly accepted as free radical antioxidants inhibiting several types of cancers [68, 69].

Several carotenoids like β -carotene, canthaxanthin, lycopene, and cryptoxanthin were studied on the mitigation of AFB₁-induced mutagenesis in bacterial mutation assay. Mutagenesis was inhibited by the addition of all carotenoids, except lycopene, and cryptoxanthin was shown to be the most potent inhibitor among all tested carotenoids [70]. The comparison of both ionone rings, α and β type of carotenoids, was observed through suspended disc culture. The α -ionone ring carotenoids, α -carotene, lutein, or α -ionone, showed more inhibition of AF biosynthesis than β -ionone ring, and the existence of hydroxyl groups on the rings seemed to lessen the inhibition capacity [71].

Previous study demonstrated the effects of antioxidants β -carotene and lycopene on AFB₁-induced hepatotoxicity. The result showed the presence of lycopene followed by the addition of AFB₁ increased cell viability at approximately 14%, while pretreatment with β -carotene had the highest increase in cell survival up to 54%. Both carotenoids recovered mitochondrial dehydrogenase (MD) activity up to 85%, upregulated *p53* gene expression in AFB₁-exposed cells, and decrease in AFB₁-N7-guanine adducts. These results clearly showed that both β -carotene and lycopene could prevent AFB₁-induced toxicity in HepG2 cells [69].

Lycopene, a strong free radical scavenger having the greatest ability to cope with the singlet oxygen compared to the other carotenoids, can alleviate AFB₁-induced oxidative stress through the conjugation of the p-electron system with several

reactive oxygen species. It can protect DNA, proteins, and lipid damages against the carcinogenesis onset contributed to its numerous conjugated double bonds, high lipophilicity, and acyclic structure [72]. Regarding several scientific publications, lycopene has been confirmed as the carotenoid that exhibited robust positive effects on AFB₁ toxicities via several pathways.

2.9 Allii Fistulosi Bulbus

Allium plants like garlic and onion are well-known in Asian countries as food ingredients and remedial foods. They have been documented as medicinal foods worldwide due to their pharmacological properties. *Allium fistulosum* (*A. fistulosum*), a perennial herb in *Allium* genus, has been commonly utilized as appetite inducer and medication against cold symptoms [73]. Also, it has ability to activate the immune response and antihypertensive effect as well as antioxidant defense system. The consumption of *A. fistulosum* extract increased estrogen level, mediated the conversion of testosterone to estrogen, and conducted hormone balance in female rats resulting in the enhancement of ovarian function [74]. The extract is able to downregulate the accumulation of lipid in HepG2 cells without cytotoxic effect and fatty acid gene synthesis. Similarly, mice fed high-fat, high-sucrose diet displayed an increase in body weight, hepatic weight, and fat accumulation in hepatocytes, but these adverse effects were attenuated by extract supplementation [75].

The effects of Allii Fistulosi Bulbus (VEAF) extract on cytotoxicity and oxidative stress caused by AFB₁ exposure were observed in HepG2 cells. Preincubation with VEOF followed by the addition of AFB₁ obviously enhanced cell viability. It inhibited oxidative stress through declining ROS level and TBAR content induced by AFB₁ and promoting GSH level. The determination of 8-OHdG, an indicator of oxidative damage on DNA, was then investigated. The result showed the inhibitory effect in VEOF treatment group up to 59.1% suppression compared to AFB₁-treated group. This evidence proved the alleviating potential of VEOF on AFB₁-induced oxidative stress resulting in cytoprotection against AFB₁ toxicity [76].

Quercetin, flavonol, is one of the major bioactive compounds in *Allium* plants. It shows the potential to scavenge free radical and improve health effects, that is, aging, allergy, angioprotective properties, anti-inflammatory, anti-cancer, anti-obesity, arthritis, asthma, diabetes, etc. [77]. For AFB₁ biosynthesis in *Aspergillus flavus*, quercetin notably decreased AFB₁ production (51%) in corn flour supplemented with quercetin at 48-hour incubation. Quercetin has an ability to inhibit the expression of necessary enzymes for AFB₁ biosynthesis such as acetyl CoA synthetase, esterase, and O-methyl transferase A and involves in the MAPK pathway which is the major pathway to form AFB₁. Quercetin, therefore, has the ability to be an anti-aflatoxigenic agent [78]. Quercetin also inhibited proliferation of *Aspergillus flavus* and its AFB₁-biosynthesis through regulating the expression of development-related genes and aflatoxin production-related genes [79].

In HepG2 cells, quercetin decreased AFB₁-induced cytotoxicity and ROS production and increased GSH content while *in vivo* study showed enhanced antioxidant activities and reduced lipid peroxidation [80]. After AFB₁ consumption, quercetin depicted the prevention of genotoxicity caused by AFB₁ in rat liver microsomes. Co-incubation with quercetin significantly decreased micronuclei formation compared to treated with AFB₁ alone ($p < 0.05$) [81]. Corresponding to another study, serum cytokines, procollagen III, and nitric oxide were significantly reduced during co-administration with quercetin and AFB₁ ($p < 0.05$). Quercetin also upregulated the antioxidant enzymes that may affect the decrease of DNA fragmentation and apoptosis [82]. Likewise, the administration between

AFB₁-contaminated diet in rat resulted in a decrease of total proteins and RNA content and fatty acid synthase (Fas) and tumor necrosis factor (TNF) gene expression in the liver tissue caused by AFB₁ while co-administration with quercetin normalized these parameters [83].

Even though numerous studies revealed the hepatoprotective effects of quercetin against xenobiotic-induced cellular toxicity, low bioavailability of quercetin absorbed into circulation is the remarkable barrier [84]. One of the supreme strategies widely used is nanoformulation. Quercetin nanoparticles not only demonstrated a noteworthy reduction of AFB₁-induced cell death, but it also suppressed the liver toxicity caused by AFB₁ including ROS formation, lipid peroxidation, mitochondrial membrane potential collapse, and GSH depletion. In addition, both quercetin and quercetin nanoparticles significantly enhanced the function of hepatic enzymes (AST, ALT, and ALP) and hepatic antioxidant enzymes (SOD, CAT, and GPx) ($p < 0.05$). Interestingly, quercetin nanoparticles showed higher effects than quercetin [84]. These result reflexes an inhibiting ability of AFB₁ toxicity by administration of quercetin AFB₁.

AFB₁ also caused increase of cytotoxicity in a bovine mammary epithelial cell line. The pre-incubation with quercetin affected to increase cell viability, AFM₁ biosynthesis (low toxic metabolite of AFB₁), GSH content, and mRNA level of glutathione S-transferase alpha 1 (GSTA1) which are important for AFB₁ detoxification [85].

2.10 Rosemary plant (*Rosmarinus officinalis* L.)

Rosemary plant (*Rosmarinus officinalis* L.), naturally found in the western Mediterranean region, has been widely used as a food additive. As it contains high polyphenolic contents, it shows many pharmacological properties such as antioxidant activity and antimicrobial and antimycotic properties, etc. [86]. Previous study proved that the growth of *Aspergillus flavus* and *A. parasiticus* were significantly inhibited by 4% commercial rosemary essential oil from 28.2 to 59.5% and 41.5 to 52.4%, respectively [87]. Apart from antimycotic properties, dose-dependent exposure of carnosic acid—major polyphenolic compound in rosemary plants—clearly decreased cell death caused by 10 μ M AFB₁. Pre-treatment to carnosic acid also reduced the production of ROS and the concentration of 8-OH-deoxyguanine, clearly confirming an involvement of carnosic acid in the protection of cytotoxicity induced by AFB₁ [88]. Furthermore, both rosemary extract and its active components (carnosol and carnosic acid) exhibited a potent inhibition of DNA adduct formation. They not only inhibit phase I metabolizing enzymes but also induce phase II metabolizing enzymes such as GST that promote the cellular defensive mechanism against AFB₁ [89].

3. Conclusion

Consumption of AFB₁-contaminated food is the current major cause of HCC in many countries. Many studies aim to lower AFB₁-induced toxicity particularly the utilization of edible plants as protective foods. This review proposed the edible plants which could alleviate AFB₁-induced toxicity and concluded the possible mitigation of AFB₁ toxicities through several related pathways (**Table 1** and **Figure 1**). Although the detoxification mechanism of AFB₁ activated by various plants has been investigated in a pre-clinical study for a decade, clinical trial is still rarely clarified. Further investigation on a risk reduction of AFB₁ still needs to be carried out especially in the clinical study.

Plants	Reference	Protective effects							
		Inhibit AFB ₁ biosynthesis	Inhibit AFB ₁ absorption	Anti-oxidant	Anti-genotoxicity	Reduce cytotoxicity	Modulate metabolism enzymes	Inhibit hepatotoxicity	Decrease liver cancer
Cruciferous vegetables	[10]			/			/		/
	[14]				/				/
	[15]								/
	[16]			/			/		
	[17]				/		/		
	[20]				/				
	[21]						/		
Green tea	[25]								/
	[27]				/				
	[28]								/
	[29]								/
	[30]			/					
	[31]*						/		
Purple rice	[38]				/				
	[39]				/		/		
	[40]			/	/			/	
Turmeric	[43]			/				/	
	[44]			/	/		/	/	
	[45]			/				/	
	[46]			/				/	
	[47]					/			
	[48]					/			/
	[49]			/			/		/

Plants	Reference	Protective effects							
		Inhibit AFB ₁ biosynthesis	Inhibit AFB ₁ absorption	Anti-oxidant	Anti-genotoxicity	Reduce cytotoxicity	Modulate metabolism enzymes	Inhibit hepatotoxicity	Decrease liver cancer
Green vegetables	[52]		/						
	[53]		/						
	[54]			/				/	/
	[55]			/				/	/
	[56]				/				
Ginger	[57]			/	/	/		/	
<i>Dialium guineense</i>	[62]			/	/			/	
<i>Parkia biglobosa</i>	[64]			/	/				
Carotenoid-rich fruits and vegetables	[69]				/	/			/
	[70]				/				
	[71]	/							
	[72]			/			/		
Allii Fistulosi Bulbus	[76]			/		/	/		
	[78]	/							
	[79]	/							
	[80]			/		/			
	[81]				/		/		
	[82]*			/	/				
	[83]**			/	/			/	
	[84]			/		/		/	
	[85]			/		/	/		

Plants	Reference	Protective effects							
		Inhibit AFB ₁ biosynthesis	Inhibit AFB ₁ absorption	Anti-oxidant	Anti-genotoxicity	Reduce cytotoxicity	Modulate metabolism enzymes	Inhibit hepatotoxicity	Decrease liver cancer
Rosemary	[87]	/							
	[88]			/		/			
	[89]				/		/		
*Alleviate serum cytokine and procollagen III, NO.									
**Alleviate content of nucleic acid of liver tissue.									

Table 1.
The protective effects of edible plants against AFB₁-induced toxicity.

Figure 1.
Protective effects of edible plants against AFB₁-induced toxicity.

Acknowledgements

This work was funded and supported by Faculty of Pharmaceutical Sciences, Khon Kaen University, Khon Kaen, Thailand.

Conflict of interest

Authors declare no conflict of interest.

Abbreviations

AFB ₁	Aflatoxin B ₁
AFB ₁ -AA	AFB ₁ -albumin adducts
AFB ₁ -NAC	AFB ₁ -mercapturic acid
ALBT	African locust bean tree
ALP	Alkaline phosphatase

ALT	Alanine aminotransferase
ARE	Antioxidant response element
AST	Aspartate transaminase
AUC	Area under the curves
Bcl-xL	B-cell lymphoma-extra large
C _{max}	Maximum concentration
CAT	Catalase
CHL	Chlorophyllin
chl _a	Chlorophyll
CML	Country-made liquor
D3T	H-1,2-dithiole-3-thione
EC	Epicatechin
ECG	Epicatechin gallate
EGC	Epigallocatechin
EGCG	Epigallocatechin gallate
Fas	Fatty acid synthase
G6PD	Glucose-6-phosphate dehydrogenase
GPx	Glutathione peroxidase
GSH	Reduced glutathione
GSSH	Oxidized glutathione
GST	Glutathione S-transferase
GSTA1	Glutathione S-transferase alpha 1
GST-P	Glutathione S-transferase placental form
GTP	Green tea polyphenol
HCC	Hepatocellular carcinoma
HO-1	Heme oxygenase 1
I3C	Indole-3-carbinol
IARC	International Agency for Research on Cancer
LDH	Lactate dehydrogenase
MD	Mitochondrial dehydrogenase
MDA	Malondialdehyde
NAFLD	Nonalcoholic fatty liver disease
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
Nrf2	Nuclear factor-E2-related factor 2
8-OHdG	8-hydroxydeoxyguanosine
ROS	Reactive oxygen species
SF	Sulforaphane
SOD	Superoxide dismutase
TNF	Tumor necrosis factor
UGT	UDP-glucuronosyltransferase
VEAF	Allii Fistulosi Bulbus
VEGF	Vascular endothelial growth factor

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