Chapter

Modulation of Edible Plants on Hepatocellular Carcinoma Induced by Aflatoxin B_1

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Abstract

Aflatoxin B_1 (AFB_1) 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 AFB_1 exposure from agricultural product contamination is too difficult. This up-to-date review aims to collect insight on how edible plants attenuate AFB_1-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 AFB_1-toxicity though 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 AFB_1. Furthermore, a few edible plants could handle AFB_1 in pre-exposure phase including anti-AFB_1 biosynthesis and AFB_1 absorption. Although the detoxification mechanisms of AFB_1 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 AFB_1 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 B_1 (AFB_1) 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. AFB_1 is a Class 1 carcinogen classified by the International Agency for Research on Cancer (IARC), suggesting sufficient evidence of carcinogenicity caused by AFB_1 in both animals and human [4]. Consequently, it is considered as a serious contaminant in many foodstuffs.

Once the AFB_1 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, AFB_1-8,9-epoxide, is resulted from epoxidation [3, 4]. AFB_1-8,9-epoxide is the genotoxic form and can react efficiently with DNA at the N7 site of guanine to form AFB_1 adduct. This adduct can adversely affect DNA sequence and genetic materials. However, human defensive mechanisms are able to detoxify AFB_1 toxicity through phase II metabolism enzymes. AFB_1 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 drug proliferation, edema, and lethargy could also be observed after exposure to high dose of AFB_1 [8].

Regarding the current situation, there are many ways to avoid the risk of AFB_1-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 AFB_1: cultivation of AFB_1 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 AFB_1-induced toxicity. For example, oltipraz, a synthetic derivative of natural compound originated from cruciferous vegetables, is reported on its capacity to reduce AFB_1 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 AFB_1-induced hepatocarcinogenicity by decreasing the absorption of AFB_1, controlling metabolic pathway, and increasing AFB_1 excretion [6, 9]. To update the involvement of edible plants as chemoprevention for AFB_1, this review is aimed to emphasize the mechanistic alleviation of AFB_1-induced liver toxicity by polyphenol-containing plants.

2. Effects of edible plants on toxicity induced by AFB_1

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 AFB_1 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 AFB_1 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 AFB_1; 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 AFB_1 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 AFB_1 relating to timing of I3C exposure. Pre-exposure to I3C prior to AFB_1 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 AFB_1 would be excreted rapidly. In contrast, pre-exposure to AFB_1 triggered the adverse effects such as DNA abnormality and increase of liver cancer risk. The explanation was that pre-exposure to AFB_1 generates AFB_1-8,9-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 AFB_1-8,9-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 AFB_1.

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, AFB_1-DNA adduct in rat's liver was reduced due to an increase of GST activity, a phase II detoxification enzyme for AFB_1 [17]. Likewise, other previous studies reported that SF could competitively inhibit CYP1A2 in human liver cells [16], causing a decrease of AFB_1-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, AFB_1-DNA adducts were clearly determined. The results indicated that no significant difference was observed among tested groups on AFB_1-DNA adduct level ($p = 0.68$). On the contrary, an inverse linear correlation of dithiocarbamates, a metabolite of sulforaphane, and AFB_1-DNA adduct excretion was noted ($p = 0.002$, $R = 0.31$). It can be implied that exposure to glucosinolates might decrease AFB_1-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 heath, 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-κB) 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 AFB_1-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 AFB_1 [27]. Besides, hepatic nuclear AFB_1-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 AFB_1 [28]. Similarly, the levels of GST-P and γ-glutamyl transpeptidase positive hepatic foci induced by AFB_1 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 AFB_1-induced human liver cancer are still currently limited, and most reports have been retrieved from China. As some Chinese commonly consume food contaminated with AFB_1, 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, AFB_1-albumin adducts (AFB_1-AA) and AFB_1-mercapturic acid (AFB_1-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 AFB_1-AA level, an indicator of AFB_1 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, AFB_1-NAC, an indicator of AFB_1 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 AFB_1 biotransformation by inhibition of phase I metabolism enzymes as can be seen from the reduction of AFB_1-AA. GTP also has an induction effect to phase II metabolism enzymes which transform AFB_1–8,9-epoxide to AFB_1-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 AFB_1-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 AFB_1. Then, the expression of CYP450 including CYP1A2 and CYP3A was investigated; both of them have an identical role in transforming AFB_1 to AFB_1-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 AFB_1 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 AFB_1 treated alone, confirming the capability of purple rice bran extract on the prevention of AFB_1-induced genotoxicity [39].

Apart from purple rice bran extract, other anthocyanin-rich plants are also studied for their effects on AFB_1-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 AFB_1. Before exposure to AFB_1, 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 AFB_1-induced toxicity, and results showed that turmeric and curcumin decreased AFB_1-adduct formation, biomolecule damage, and hepatotoxicity [43–46], and it also inhibited acute toxicity through disturbing the lysis of erythrocytes [47]. During AFB_1 metabolism, free radicals generated by AFB_1 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 AFB_1 to excretable forms [43–46].

Turmeric is found to be capable of reducing both AFB_1-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 AFB_1-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 AFB_1 toxicity indicated that both compounds could reduce absorption of AFB_1 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 AFB_1 compared to untreated group [53]. These findings suggest that chla and CHL have a strong potential to decrease AFB_1 absorption. The effects of chla and CHL co-exposure with AFB_1 have also been studied in animal model by emphasizing on antioxidant activities. Both bioactive compounds are capable of reducing AFB_1 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 AFB_1-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 AFB_1-N7-guanine level in urine compared to placebo group [56].

Several studies were in agreement that chla and CHL reduce AFB_1-induced liver cancer through decreasing AFB_1 absorption in digestive tract contributing to the decrease of AFB_1 bioavailability. Besides, chla and CHL are the powerful antioxidants which effectively lower AFB_1-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 AFB_1-contaminated foods.

2.6 Ginger (*Zingiber officinale* Roscoe)

Ginger (*Zingiber officinale* Roscoe) contained high content of phenolic compounds in which 6-gingeerol 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 AFB_1-induced toxicity.

In in vitro model of AFB_1-treated HepG2 cells, ginger extract-pretreated cells exhibited higher percent cell viability and lower intracellular ROS production and DNA strand break when compared to AFB_1 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 AFB_1 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 AFB_1 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 AFB_1-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 AFB_1-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 AFB_1. Furthermore, treatment of velvet tamarind extract before AFB_1 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 AFB_1 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 AFB_1. 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 AFB_1. AFB_1 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 AFB_1 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 AFB_1-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 AFB_1-induced hepatotoxicity. The result showed the presence of lycopene followed by the addition of AFB_1 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 AFB_1-exposed cells, and decrease in AFB_1-N7-guanine adducts. These results clearly showed that both β-carotene and lycopene could prevent AFB_1-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 AFB_1-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 AFB_1 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 AFB_1 exposure were observed in HepG2 cells. Preincubation with VEAF followed by the addition of AFB_1 obviously enhanced cell viability. It inhibited oxidative stress through declining ROS level and TBAR content induced by AFB_1 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 VEAF treatment group up to 59.1% suppression compared to AFB_1-treated group. This evidence proved the alleviating potential of VEAF on AFB_1-induced oxidative stress resulting in cytoprotection against AFB_1 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 AFB_1 biosynthesis in *Aspergillus flavus*, quercetin notably decreased AFB_1 production (51%) in corn flour supplemented with quercetin at 48-hour incubation. Quercetin has an ability to inhibit the expression of necessary enzymes for AFB_1 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 AFB_1. 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 AFB_1 consumption, quercetin depicted the prevention of genotoxicity caused by AFB_1 in rat liver microsomes. Co-incubation with quercetin significantly decreased micronuclei formation compared to treated with AFB_1 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 AFB_1 ($p < 0.05$). 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 AFB_1 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 AFB_1-induced cell death, but it also suppressed the liver toxicity caused by AFB_1 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 AFB_1 toxicity by administration of quercetin AFB_1.

AFB_1 also caused increase of cytotoxicity in a bovine mammary epithelial cell line. The pre-incubation with quercetin affected to increase cell viability, AFM_1 biosynthesis (low toxic metabolite of AFB_1), GSH content, and mRNA level of glutathione S-transferase alpha 1 (GSTA1) which are important for AFB_1 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 μM AFB_1. 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 AFB_1 [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 AFB_1 [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]			/	/	/		/	
Dialium guineense	[62]			/	/			/	
Parkia biglobosa	[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 AFB_1-induced toxicity.

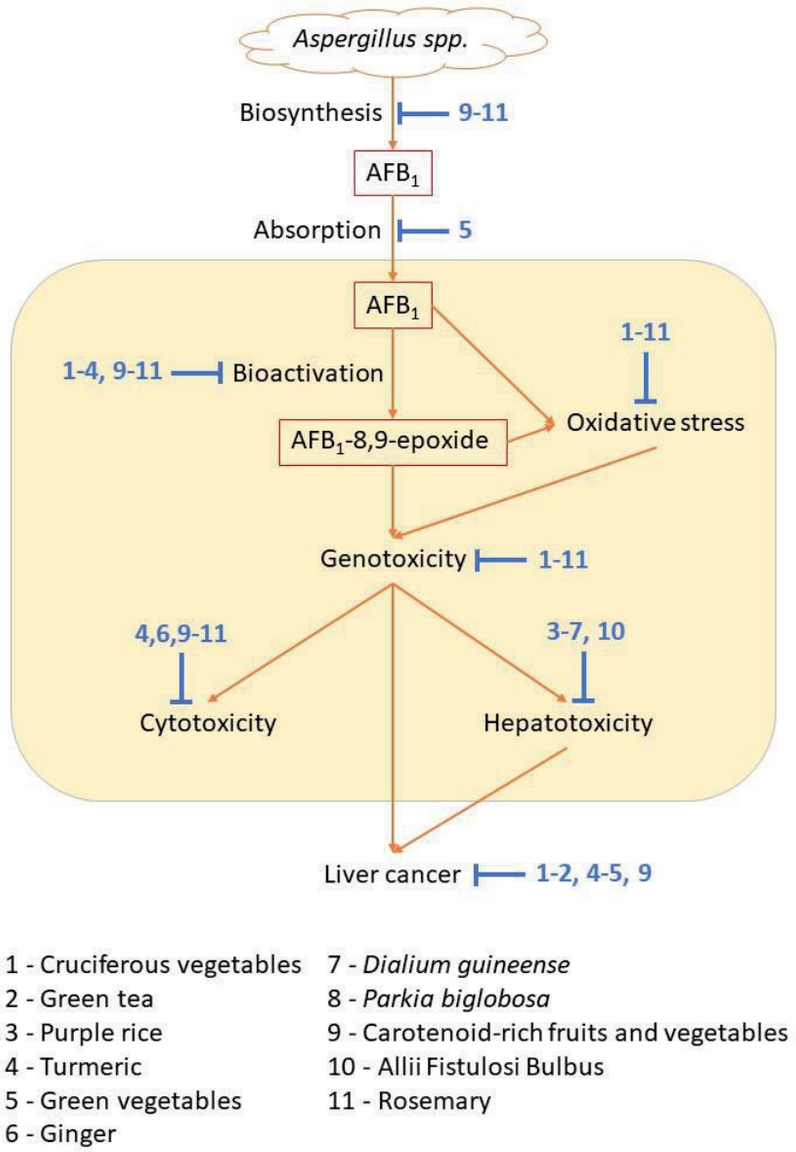

Figure 1.
Protective effects of edible plants against AFB_1-induced toxicity.

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Conflict of interest

Authors declare no conflict of interest.

Abbreviations

AFB_1	Aflatoxin B_1
AFB_1-AA	AFB1-albumin adducts
AFB_1-NAC	AFB1-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
chla	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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References

[1] International Agency for Research on Cancer. Cancer Today: Estimated Number of Deaths in 2018, Worldwide, Both Sexes, all Ages. 2018. Available from: http://gco.iarc.fr/today/online-analysis [Accessed: March 30, 2019]

[2] Balogh J, Iii D, Asham E, Burroughs S, Boktour M, Saharia A, et al. Hepatocellular carcinoma: A review. J Hepatocell Carcinoma. 2016;**3**:41-53. DOI: 10.2147/JHC.S61146

[3] Chitapanarux T, Phornphutkul K. Risk factors for the development of hepatocellular carcinoma in Thailand. Journal of Clinical and Translational Hepatology. 2015;**3**(3):182-188. DOI: 10.14218/JCTH.2015.00025

[4] International Agency for Research on Cancer. Chemical Agents and Related Occupations. Lyon: WHO; 2009. 599 p

[5] Moudgil V, Redhu D, Dhanda S, Singh J. A review of molecular mechanisms in the development of hepatocellular carcinoma by aflatoxin and hepatitis B and C viruses. Journal of Environmental Pathology, Toxicology and Oncology. 2013;**32**(2):165-175. DOI: 10.1615/JEnvironPatholToxicolOncol.2013007166

[6] Kensler TW, Roebuck BD, Wogan GN, Groopman JD. Aflatoxin: A 50-year odyssey of mechanistic and translational toxicology. The Journal of Toxicological Sciences. 2011;**120**(S1):S28-S48. DOI: 10.1093/toxsci/kfq283

[7] Bbosa GS, Kitya D, Odda J, Ogwal-Okeng J. Aflatoxins metabolism. Health (Irvine Calif). 2013;**05**(10):14-34

[8] Kumar P, Mahato DK, Kamle M, Mohanta TK, Kang SG. Aflatoxins: A global concern for food safety, human health and their management. Frontiers in Microbiology. 2017;**7**:2170. DOI: 10.3389/fmicb.2016.02170

[9] Lavkor I, Var I. The control of aflatoxin contamination at harvest, drying, pre-storage ad storage periods in peanut: The new approach. In: Abdulra'Uf L, editor. Aflatoxin Control, Analysis, Detection and Health Risks. Rijeka: IntechOpen; 2017. pp. 45-65. DOI: 10.5772/intechopen.68675

[10] Sanlier N, Guler SM. The benefits of Brassica vegetables on human health. Journal of Human Health Research. 2018;**1**(1):104

[11] Kensler TW, Egner PA, Wang JB, Zhu YR, Zhang BC, Lu PX, et al. Chemoprevention of hepatocellular carcinoma in aflatoxin endemic areas. Gastroenterology. 2004;**127**(5 Suppl):310-318. DOI: 10.1053/j.gastro.2004.09.046

[12] Herr I, Büchler MW. Dietary constituents of broccoli and other cruciferous vegetables: Implications for prevention and therapy of cancer. Cancer Treatment Reviews. 2010;**36**(5):377-383. DOI: 10.1016/j.ctrv.2010.01.002

[13] Wallig MA, Heinz-Taheny KM, Epps DL, Gossman T. Synergy among phytochemicals within crucifers: Does it translate into chemoprotection? The Journal of Nutrition. 2018;**135**(12):2972S-2977S. DOI: 10.1093/jn/135.12.2972S

[14] Dashwood RH, Arbogast DN, Fong AT, Pereira C, Hendricks JD, Bailey GS. Quantitative inter-relationships between aflatoxin B1 carcinogen dose, indole-3-carbinol anti-carcinogen dose, target organ DNA adduction and final tumor respose. Carcinogenesis. 1989;**19**(1):175-181. DOI: 10.1093/carcin.10.1.175

[15] Dashwood RH. Indole-3-carbinol: Anticarcinogen or tumor promoter in brassica vegetables? Chemico-Biological

Interactions. 1998;**110**(1-2):1-5. DOI: 10.1016/s0009-2797(97)00115-4

[16] Latté KP, Appel KE, Lampen A. Health benefits and possible risks of broccoli—An overview. Food and Chemical Toxicology. 2011;**49**(12):3287-3309. DOI: 10.1016/j.fct.2011.08.019

[17] Wiriyachan N, Fiala JLA, Croy RG, Egner PA, Wogan GN, Ruchirawat M, et al. Sulforaphane-mediated reduction of aflatoxin B1-N7-guanine in rat liver DNA: Impacts of strain and sex. Toxicological Sciences. 2011;**121**(1):57-62. DOI: 10.1093/toxsci/kfr026

[18] Techapiesancharoenkij N, Fiala JLA, Navasumrit P, Robert G, Wogan GN, Groopman JD, et al. Sulforaphane, a cancer chemopreventive agent, induces pathways associated with membrane biosynthesis in response to tissue damage by aflatoxin B1. Toxicology and Applied Pharmacology. 2015;**282**(1):52-60. DOI: 10.1016/j.taap.2014.11.004

[19] Higdon JV, Delage B, Williams DE, Dashwood RH. Cruciferous vegetables and human cancer risk: Epidemiologic evidence and mechanistic basis. Pharmacological Research. 2007;**55**(3):224-236. DOI: 10.1016/j.phrs.2007.01.009

[20] Kensler TW, Chen JG, Egner PA, Fahey JW, Jacobson LP, Stephenson KK, et al. Effects of glucosinolate-rich broccoli sprouts on urinary levels of aflatoxin-DNA adducts and phenanthrene tetraols in a randomized clinical trial in He Zuo township, Qidong, people's Republic of China. Cancer Epidemiology, Biomarkers and Prevention. 2005;**14**(11 I):2605-2613. DOI: 10.1158/1055-9965.EPI-05-0368

[21] Kensler TW, Ng D, Carmella SG, Chen M, Jacobson LP, Muñoz A, et al. Modulation of the metabolism of airborne pollutants by glucoraphanin-rich and sulforaphane-rich broccoli sprout beverages in Qidong, China. Carcinogenesis. 2012;**33**(1):101-107. DOI: 10.1093/carcin/bgr229

[22] Venkateswara B, Sirisha K, Chava V. Green tea extract for periodontal health. Journal of Indian Society of Periodontology. 2011;**15**(1):18-22. DOI: 10.4103/0972-124X.82258

[23] Khlangwiset P, Wu F. Costs and efficacy of public health interventions to reduce aflatoxin–induced human disease. Food Additives and Contaminants. Part A, Chemistry, Analysis, Control, Exposure and Risk Assessment. 2010;**27**(7):998-1014. DOI: 10.1080/19440041003677475

[24] Yuan JM, Sun C, Butler LM. Tea and cancer prevention: Epidemiological studies. Pharmacological Research. 2011;**64**(2):123-135. DOI: 10.1016/j.phrs.2011.03.002

[25] Yin X, Yang J, Li T, Song L, Han T, Yang M, et al. The effect of green tea intake on risk of liver disease: A meta analysis. International Journal of Clinical and Experimental Medicine. 2015;**8**(6):8339-8346

[26] Sonoda J, Narumi K, Akio K, Toshiro M. Green tea catechins-pharmacokinetic properties and health beneficial effects. Pharmaceutica Analytica Acta. 2015;**6**(2):1-6. DOI: 10.4172/2153-2435.1000333

[27] Ito Y, Ohnishi S, Fujie K. Chromosome aberrations induced by aflatoxin B1 in rat bone marrow cells in vivo and their suppression by green tea. Mutation Research. 1989;**222**:253-261. DOI: 10.1016/0165-1218(89)90141-9

[28] Qin G, Gopalan-Kriczky P, Su J, Ning Y, Lotlikar P. Inhibition of aflatoxin B1-induced initiation of hepatocarcinogenesis in the rat by green tea. Cancer Letters. 1997;**112**(2):149-154. DOI: 10.1016/S0304-3835(96)04568-5

[29] Qin G, Ning Y, Lotlikar P. Chemoprevention of aflatoxin B1-initiated and carbon tetrachloride-promoted hepatocarcinogenesis in the rat by green tea. Nutrition and Cancer. 2000;**38**(2):215-222. DOI: 10.1207/S15327914NC382_11

[30] Zhang Z-Q, Liang Y, Wang J-S, Yu J, Zhang L, Wang K, et al. Phase IIa chemoprevention trial of green tea polyphenols in high-risk individuals of liver cancer: Modulation of urinary excretion of green tea polyphenols and 8-hydroxydeoxyguanosine. Carcinogenesis. 2005;**27**(2):262-268. DOI: 10.1093/carcin/bgi147

[31] Tang L, Tang M, Xu L, Luo H, Huang T, Yu J, et al. Modulation of aflatoxin biomarkers in human blood and urine by green tea polyphenols intervention. Carcinogenesis. 2008;**29**(2):411-417. DOI: 10.1093/carcin/bgn008

[32] Kong JM, Chia LS, Goh NK, Chia TF, Brouillard R. Analysis and biological activities of anthocyanins. Phytochemistry. 2003;**64**(5):923-933. DOI: 10.1016/S0031-9422(03)00438-2

[33] Park JH, Wang Z, Choi MK, Lim SS, Lee J-Y, Huang B, et al. Anti-diabetic effect of purple corn extract on C57BL/KsJ db/db mice. Nutrition Research and Practice. 2015;**9**(1):22-29. DOI: 10.4162/nrp.2015.9.1.22

[34] Reyna GS, Torres AG, Valenzuela R, Rincón-Cervera MÁ, Villanueva-Espinoza ME. Adding a purple corn extract in rats supplemented with chia oil decreases gene expression of SREBP-1c and retains Δ5 and Δ6 hepatic desaturase activity, unmodified the hepatic lipid profile. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2018;**132**:1-7. DOI: 10.1016/j.plefa.2018.03.005

[35] Long N, Suzuki S, Sato S, Naiki-Ito A, Sakatani K, Shirai T, et al. Purple corn color inhibition of prostate carcinogenesis by targeting cell growth pathways. Cancer Science. 2013;**104**(3):298-303. DOI: 10.1111/cas.12078

[36] Nair V, Bang WY, Schreckinger E, Andarwulan N, Cisneros-Zevallos L. Protective role of ternatin anthocyanins and quercetin glycosides from butterfly pea (*Clitoria Ternatea* Leguminosae) blue flower petals against lipopolysaccharide (lps)-induced inflammation in macrophage cells. Journal of Agricultural and Food Chemistry. 2015;**63**(28):6355-6365. DOI: 10.1021/acs.jafc.5b00928

[37] Tsuda T. Dietary anthocyanin-rich plants: Biochemical basis and recent progress in health benefits studies. Molecular Nutrition and Food Research. 2012;**56**(1):159-170. DOI: 10.1002/mnfr.201100526

[38] Punvittayagul C, Sringarm K, Chaiyasut C, Wongpoomchai R. Mutagenicity and antimutagenicity of hydrophilic and lipophilic extracts of Thai northern purple rice. Asian Pacific Journal of Cancer Prevention. 2014;**15**(21):9517-9522. DOI: 10.7314/APJCP.2014.15.21.9517

[39] Suwannakul N, Punvittayagul C, Jarukamjorn K, Wongpoomchai R. Purple rice bran extract attenuates the aflatoxin B1-induced initiation stage of hepatocarcinogenesis by alteration of xenobiotic metabolizing enzymes. Asian Pacific Journal of Cancer Prevention. 2015;**16**(8):3371-3376. DOI: 10.7314/APJCP.2015.16.8.3371

[40] Ajiboye TO, Raji HO, Muritala HF, Ojewuyi OB, Yakubu MT. Anthocyanin extract of *Lannea microcarpa* fruits stall oxidative rout associated with aflatoxin B1 hepatocarcinogenesis. Food Bioscience. 2013;**4**:58-67. DOI: 10.1016/j.fbio.2013.09.002

[41] World Health Organization. WHO Monographs on Selected Medicinal Plants. Vol. 1. Malta: WHO; 1999. 295 p

[42] Sharma RA, Gescher AJ, Steward WP. Curcumin: The story so far. European Journal of Cancer. 2005;**41**(13):1955-1968. DOI: 10.1016/j.ejca.2005.05.009

[43] El-Agamy DS. Comparative effects of curcumin and resveratrol on aflatoxin B 1-induced liver injury in rats. Archives of Toxicology. 2010;**84**(5):389-396. DOI: 10.1007/s00204-010-0511-2

[44] Nayak S, Sashidhar RB. Metabolic intervention of aflatoxin B1 toxicity by curcumin. Journal of Ethnopharmacology. 2010;**127**(3): 641-644. DOI: 10.1016/j.jep.2009.12.010

[45] El-Bahr SM. Effect of curcumin on hepatic antioxidant enzymes activities and gene expressions in rats intoxicated with aflatoxin B1. Phytotherapy Research. 2015;**29**(1):134-140. DOI: 10.1002/ptr.5239

[46] Sharma V, Sharma C, Pracheta P, Sharma S. Protective potential of *Curcuma longa* and curcumin on aflatoxin B1 induced hepatoxicity in swiss albino mice. The Medical Journal of Cairo Univerisity. 2011;**1**(3):116-122

[47] Mathuria N, Verma RJ. Aflatoxin induced hemolysis and its amelioration by turmeric extracts and curcumin in vitro. Acta Poloniae Pharmaceutica. Drug Research. 2007;**64**(2):165-168

[48] Wang WH, Chiang IT, Ding K, Chung JG, Lin WJ, Lin SS, et al. Curcumin-induced apoptosis in human hepatocellular carcinoma j5 cells: Critical role of ca(+2) -dependent pathway. Evidence-based Complementary and Alternative Medicine. 2012;**2012**:512907. DOI: 10.1155/2012/512907

[49] Darvesh AS, Aggarwal BB, Bishayee A. Curcumin and liver cancer: A review. Current Pharmaceutical Biotechnology. 2011;**13**(1):218-228. DOI: 10.2174/138920112798868791

[50] Mishra VK, Bacheti RK, Husen A. Medicinal Uses of Chlorophyll: A critical overview. In: Hua L, Elisa S editor. Chlorophyll: Structure, function and medicinal uses. Nova Science Publishers; 2011. pp. 177-196

[51] Tumolo T, Lanfer-Marquez UM. Copper chlorophyllin: A food colorant with bioactive properties? Food Research International. 2012;**46**(2):451-459. DOI: 10.1016/j.foodres.2011.10.031

[52] Mata JE, Yu Z, Gray JE, Williams DE, Rodriguez-Proteau R. Effects of chlorophyllin on transport of dibenzo(a,l)pyrene, 2-amino-1-methyl-6-phenylimidazo-[4,5-b] pyridine, and aflatoxin B1 across Caco-2 cell monolayers. Toxicology. 2004;**196**(1-2):117-125. DOI: 10.1016/j.tox.2003.11.008

[53] Jubert C, Mata J, Bench G, Dashwood R, Pereira C, Tracewell W, et al. Effects of chlorophyll and chlorophyllin on low-dose aflatoxin B1 pharmacokinetics in human volunteers. Cancer Prevention Research. 2009;**2**(12):1015-1022. DOI: 10.1158/1940-6207.CAPR-09-0099

[54] Kumar M, Verma V, Nagpal R, Kumar A, Behare PV, Singh B, et al. Anticarcinogenic effect of probiotic fermented milk and chlorophyllin on aflatoxin-B1-induced liver carcinogenesis in rats. The British Journal of Nutrition. 2012;**107**(7):1006-1016. DOI: 10.1017/S0007114511003953

[55] Abdel-Latif MS, Elmeleigy KM, Aly TAA, Khattab MS, Mohamed SM. Pathological and biochemical evaluation of coumarin and chlorophyllin against aflatoxicosis in rat. Experimental and Toxicologic Pathology. 2017;**69**(5):285-291. DOI: 10.1016/j.etp.2017.01.014

[56] Egner P, Wang J, Zhu Y, Zhang B, Wu Y, Zhang Q, et al. Chlorophyllin intervention reduces aflatoxin—DNA

adducts in individuals at high risk for liver cancer. 2001;**98**(25):14601-14606. DOI: 10.1073/pnas.251536898

[57] Vipin A, Raksha R, Kurrey NK, Anu A, Venkateswaran G. Protective effects of phenolics rich extract of ginger against aflatoxin B1-induced oxidative stress and hepatotoxicity. Biomedicine and Pharmacotherapy. 2017;**91**:415-424. DOI: 10.1016/j.biopha.2017.04.107

[58] Bhandari U, Shamsher AA, Pillai KK, Khan MSY. Antihepatotoxic activity of ginger ethanol extract in rats. Pharmaceutical Biology. 2003;**41**(1):68-71. DOI: doi.org/10.1076/phbi.41.1.68.14697

[59] Abd-Allah GA, El-Bakry KA, Bahnasawy MH, El-Khodary ESR. Protective effects of curcumin and ginger on liver cirrhosis induced by carbon tetrachloride in rats. International Journal of Pharmacology. 2016;**12**(4):361-369. DOI: 10.3923/ijp.2016.361.369

[60] Ogu GI, Ezeadila J, Ehiobu JM. Antioxidant and antimicrobial activities of *Dialium guineense* (wild) leaf extract. Pharmacy and Pharmacology Research. 2013;**1**(1):1-7

[61] Okeke NC, Udeani TK, Onyebuchi UL. Wound-healing and antimicrobial properties of dichloromethane fraction of *Dialium guineense* (Wild) fruit coat. Research in Pharmaceutical Sciences. 2016;**11**(3):219-226

[62] Adeleye AO, Ajiboye TO, Iliasu GA, Abdussalam FA, Balogun A, Ojewuyi OB. Phenolic extract of *Dialium guineense* pulp enhances reactive oxygen species detoxification in aflatoxin B1 hepatocarcinogenesis. Journal of Medicinal Food. 2014;**17**(8):875-885. DOI: 10.1089/jmf.2013.0157

[63] Dedehou V, Olounladé P, Adenilé D, Alowanou G, Azando E, Hounzangbé-Adoté M. A review on medicinal plants of *Parkia biglobosa* (Mimosaceae -Fabaceae) and *Pterocarpus erinaceus* (Leguminosae - Papilionoidea). Journal of Medicinal Plants Studies. 2016;**4**(6):132-137

[64] Ajiboye TO, Adeleye AO, Salau AK, Ojewuyi OB, Adigun NS, Sabiu S, et al. Phenolic extract of *Parkia biglobosa* fruit pulp stalls aflatoxin B1-mediated oxidative rout in the liver of male rats. Revista Brasileira de Farmacognosia. 2014;**24**:668-676. DOI: 10.1016/j.bjp.2014.10.010

[65] Kotake-Nara E, Nagao A. Absorption and metabolism of xanthophylls. Marine Drugs. 2011;**9**:1024-1037. DOI: 10.3390/md9061024

[66] Saini RK, Nile SH, Park SW. Carotenoids from fruits and vegetables: Chemistry, analysis, occurrence, bioavailability and biological activities. Food Research International. 2015;**76**:735-750. DOI: 10.1016/j.foodres.2015.07.047

[67] Widomska J, Zareba M, Subczynski WK. Can xanthophyll-membrane interactions explain their selective presence in the retina and brain? Food. 2016;**5**(1):E7. DOI: 10.3390/foods5010007

[68] Haskell MJ. Provitamin A carotenoids as a dietary source of vitamin A. In: Tanumihardjo S, editor. Carotenoids and Human Health. New Jersey: Humana Press; 2013. pp. 249-260. DOI: 10.1007/978-1-62703-203-2_15

[69] Reddy L, Odhav B, Bhoola K. Aflatoxin B1-induced toxicity in HepG2 cells inhibited by carotenoids: Morphology, apoptosis and DNA damage. Biological Chemistry. 2006;**387**(1):87-93. DOI: 10.1515/BC.2006.012

[70] He Y, Campbell TC. Effects of carotenoids on aflatoxin B1-induced

mutagenesis in *S. typhimurium* TA 100 and TA 98. Nutrition and Cancer. 1990;**13**(4):243-253. DOI: 10.1080/01635589009514066

[71] Norton RA. Effect of carotenoids on aflatoxin B1 synthesis by *Aspergillus flavus*. Phytopathology. 1997;**87**(8):814-821. DOI: 10.1094/PHYTO.1997.87.8.814

[72] Yilmaz S, Kaya E, Kisacam M. The effect on oxidative stress of aflatoxin and protective effect of lycopene on aflatoxin damage. In: Abdulra'uf LB, editor. Aflatoxin-Control, Analysis, Detection and Health Risks. Rijeka: InTech; 2017. pp. 67-88. DOI: 10.5772/intechopen.69321

[73] Fukaya M, Nakamura S, Nakagawa R, Kinka M, Nakashima S, Matsuda H. Cyclic sulfur-containing compounds from *Allium fistulosum* 'Kujou'. Journal of Natural Medicines. 2019;**73**(2):397-403. DOI: 10.1007/s11418-018-1272-0

[74] Lee YH, Yang H, Lee SR, Kwon SW, Hong EJ, Lee HW. Welsh onion root (*Allium fistulosum*) restores ovarian functions from ltrozole induced-polycystic ovary syndrome. Nutrients. 2018;**10**(10):E1430. DOI: 10.3390/nu10101430

[75] Hwang JT, Shun EJ, Chung MY, Park JH, Chung S, Choi HK. Ethanol extract of *Allium fistulosum* inhibits development of non-alcoholic fatty liver disease. Nutrition Research and Practice. 2018;**12**(2):110-117. DOI: 10.4162/nrp.2018.12.2.110

[76] Lee JK, Choi EH, Lee KG, Chun HS. Alleviation of aflatoxin B1-induced oxidative stress in HepG2 cells by volatile extract from Allii fistulosi bulbus. Life Sciences. 2005;**77**(23):2896-2910. DOI: 10.1016/j.lfs.2005.03.028

[77] D'Andrea G. Quercetin: A flavonol with multifaceted therapeutic applications? Fitoterapia. 2015;**106**:256-271. DOI: 10.1016/j.fitote.2015.09.018

[78] Tiwari S, Shankar J. Integrated proteome and HPLC analysis revealed quercetin-mediated inhibition of aflatoxin B1 biosynthesis in *Aspergillus flavus*. 3 Biotech. 2018;**8**(1):47. DOI: 10.1007/s13205-017-1067-0

[79] Li XM, Li ZY, Wang YD, Wang JQ, Yang PL. Quercetin inhibits the proliferation and aflatoxins biosynthesis of *Aspergillus flavus*. Toxins (Basel). 2019;**11**(3):E154. DOI: 10.3390/toxins11030154

[80] Choi KC, Chung WT, Kwon JK, Yu JY, Jang YS, Park SM, et al. Inhibitory effects of quercetin on aflatoxin B1-induced hepatic damage in mice. Food and Chemical Toxicology. 2010;**48**(10):2747-2753. DOI: 10.1016/j.fct.2010.07.001

[81] Kohli E, Raj HG, Kumari R, Rohil V, Kaushik NK, Prasad AK, et al. Comparison of the prevention of aflatoxin B1-induced genotoxicity by quercetin and quercetin pentaacetate. Bioorganic and Medicinal Chemistry Letters. 2002;**12**(18):2579-2582. DOI: 10.1016/S0960-894X(02)00478-X

[82] Abdel-Wahhab MA, Aljawish A, El-Nekeety AA, Abdel-Aiezm SH, Abdel-Kader HAM, Rihn BH, et al. Chitosan nanoparticles and quercetin modulate gene expression and prevent the genotoxicity of aflatoxin B1 in rat liver. Toxicology Reports. 2015;**2**:737-747. DOI: 10.1016/j.toxrep.2015.05.007

[83] El-Nekeety AA, Abdel-Azeim SH, Hassan AM, Hassan NS, Aly SE, Abdel-Wahhab MA. Quercetin inhibits the cytotoxicity and oxidative stress in liver of rats fed aflatoxin-contaminated diet. Toxicology Reports. 2014;**1**:319-329. DOI: 10.1016/j.toxrep.2014.05.014

[84] Eftekhari A, Ahmadian E, Panahi-Azar V, Hosseini H, Tabibiazar M, Maleki Dizaj S. Hepatoprotective and free radical scavenging actions of quercetin nanoparticles on aflatoxin

B1-induced liver damage: In vitro/in vivo studies. Artificial Cells Nanomedicine and Biotechnology. 2018;**46**(2):411-420. DOI: 10.1080/21691401.2017.1315427

[85] Ghadiri S, Spalenza V, Dellafiora L, Badino P, Barbarossa A, Dall'Asta C, et al. Modulation of aflatoxin B1 cytotoxicity and aflatoxin M1 synthesis by natural antioxidants in a bovine mammary epithelial cell line. Toxicology In Vitro. 2019;**57**:174-183. DOI: 10.1016/j.tiv.2019.03.002

[86] Hernández MD, Sotomayor JA, Hernández Á, Jordán MJ. Rosemary (*Rosmarinus officinalis* L.) oils. In: Preedy VR, editor. Essential Oils in Food Preservation, Flavor and Safety. London: Elsevier; 2015. pp. 677-688. DOI: 10.1016/B978-0-12-416641-7.00077-8

[87] Mahmoud MA, El-Zaidy M, Al-Othman MR, ARM AE-A, Al-Gahtani MF. Efficacy of *Rosmarinus officinalis* essential oil on *Aspergillus flavus* and parasiticus. Journal of Pure and Applied Microbiology. 2014;**8**(8):185-190

[88] Costa S, Utan A, Speroni E, Cervellati R, Piva G, Prandini A, et al. Carnosic acid from rosemary extracts: A potential chemoprotective agent against aflatoxin B1. An in vitro study. Journal of Applied Toxicology. 2007;**27**(2):152-159. DOI: 10.1002/jat.1186

[89] Offord EA, Macé K, Avanti O, Pfeifer AM. Mechanisms involved in the chemoprotective effects of rosemary extract studied in human liver and bronchial cells. Cancer Letters. 1997;**114**(1-2):275-281. DOI: 10.1016/S0304-3835(97)04680-6