

Evidence Based Phytopharmacological Potential of Herbal Extracts in Post-Ingestion Management of Mycotoxins in Animal Models

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Received date: Jun 24, 2015; Accepted date: Jul 10, 2015; Published date: Jul 15, 2015

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Abstract

Aflatoxins and ochratoxins are common mycotoxic food poisons and acute doses are responsible for causing liver and kidney damage and hepatocarcinoma. The strategy for managing mycotoxins has mainly been pre-ingestive. However, few solutions have been proposed for post-ingestion management and likewise there is no antidote for managing the condition. Studies have demonstrated that *Saccharomyces cerevisiae* and herbal extracts have potential of limiting the damage caused by reactive oxygen species and toxic effects associated with mycotoxins. Further evidence also shows that herbal extracts provides protection to a variety of cancer cell lines associated with mycotoxins. This study therefore examines the probable potential and options of using medicinal herbal extracts, on their own or in combinations with *Saccharomyces cerevisiae*, in the management of mycotoxicosis. A combination of the two has potential to offer a multifunctional approach in the management of post ingested mycotoxins such as aflatoxins and ochratoxins.

Keywords: Aflatoxins; Ochratoxins; Mycotoxicity; Herbal extracts; *Saccharomyces cerevisiae*; Hepatoprotection; Nephroprotection

Introduction

Aflatoxins are naturally occurring mycotoxins produced by the fungi *Aspergillus flavus* and *Aspergillus parasitus*. They were first isolated from peanut meal [1]. These mycotoxins are one of the greatest health hazards and they are major contaminants of food consumed by humans and animals. There are over twenty types of aflatoxins with aflatoxins B1 being the most dangerous. In animals, it has been associated with anorexia, reduced feed intake and, poor digestion [2]. It also has an impact on the immune system leading to immunosuppression and low weight gain [3]. Some cases of aflatoxin poisoning have been associated with reduced reproductive potencies [4]. Aflatoxin B1 has also been shown to be teratogenic, mutagenic and tremorgenic [4]. It is also associated with destructive effects of the vital organs of the body such as the kidneys, central nervous system and more importantly the liver.

An assessment of the effect of exposure of laboratory animals to different doses of aflatoxin B1 demonstrates that short exposure to large doses of aflatoxin B1 leads to acute toxicity characterized by fever, abdominal pains, lethargy, vomiting, edema, fatal loss of function of the liver and rough hair coat. Histological examination of the tissues in acute poisoning leads to the leucocytic infiltrations and vascular congestion of tissues. The liver fibroblast and mononuclear cells are also affected by the reactions of aflatoxin B1 in the liver [5]. In males aflatoxicosis is known to affect spermatogenesis and androgen biosynthesis in the testis. Epididymis, seminiferous tubules and vas deferens have also been cited to be targeted by aflatoxin B1 [5-9]. Deleterious effects on sexual maturation, hormone levels, gestation and growth of fetus are also reported [10,11]. Aflatoxins can cause death in 72 hours when administered in chronic doses [4-8].

The most toxic and prevalent ochratoxin is ochratoxin type A. The relevance of ochratoxins type B and C have not been determined yet and are considered less important. Ochratoxin A is common in cereals, coffee, fruits and red wine and is a potent human carcinogen. It bio accumulates in the bodies of animals. Meat and meat products contamination has been well demonstrated in cases of ochratoxins [12]. When ingested in diet, it is known to induce acute nephrotoxicity in mammals [12].

Types and structures of mycotoxins

Aflatoxins: There are four major type of aflatoxins designated as B1, B2, G1 and G2. They are designated so because of their RI values on thin layer chromatography plates. The structure of the aflatoxins is referred to as difurocoumarolactones which are also referred to as difurocoumarin derivatives. The structures consist of a bifuran ring that is fused to a coumarone nucleus with a pentanone ring in aflatoxin B and M while aflatoxin G is a six membered ring [12].

Ochratoxins: Like the aflatoxins ochratoxins are produced mainly by the fungus *Aspergillus ochraceus*. However, they are also produced by *Aspergillus niger* which has significant industrial applications. Some penicillium species have also been documented to be associated with production of ochratoxins (*P. verrucosum* and *P. carbonarius*) [12].

Ochratoxins, like aflatoxins, are secondary metabolites. Biosynthetically, their structures are those of a pentaketide derived from dihydrocoumarins family of compounds and are linked to a β -phenylalanine [13]. Metabolites of ochratoxin A include ochratoxin B which is a dechloro analog and ochratoxin C which is an ethyl ester. Others forms of ochratoxins that have been identified are ochratoxins α which is a chlorinated molecule and its analogue ochratoxin β . Recent findings have demonstrated variants of ochratoxins A. One is a

dechlorinated ochratoxin A [14] and another quinone/hydroquinone derived metabolites [15] with serious toxic properties. The composition of the various ochratoxin A derived metabolites has been well demonstrated by Khoury and Atoui, [16].

Pharmacodynamics and Biotransformation of Mycotoxins

The absorption of aflatoxins occurs through the gastrointestinal tracts with ingestion of small doses. The toxin is then transported to the body tissues and organs including the lipophilic tissues. Aflatoxin B1 accumulates in the liver with a very high concentration [17]. Aflatoxin B1 is metabolized through microsomal enzymes by hydroxylation, hydration, demethylation, and epoxidation reactions in liver cells. The biotransformation pathway for aflatoxin B1 has been demonstrated by Patterson and Allcroft [18]. Hydroxylation of aflatoxin B1 at carbon 4 or 22 yield's the production of aflatoxin M1 and aflatoxin Q1. Hydration reactions at carbon 2-3 double bonds lead to the formation of aflatoxin B2a. Aflatoxin B1-epoxide is formed by epoxidation at carbon 2, 3 double bonds. On the other hand, O-demethylation leads to the formation of aflatoxin P1 [18].

Aflatoxin B1 causes damage to the liver and adversely affects the key metabolic pathways of carbohydrates, proteins and lipids [19]. The impairment in the metabolism of proteins has been associated with the reduction in resistance of poultry to infections from *Salmonella* spp, coccidian and *Candida albicans* [20]. This has also led to the anticoagulation of blood as a result of the impairment of factor II and VII used for the biosynthesis of prothrombin and in the activation of the clotting process [21]. Aflatoxin is a cytotoxin and it interferes with the RNA and ultimately proteins synthesis. Aflatoxin B1 is excreted in urine, feces and in milk of the lactating mothers. It occurs as unchanged or other metabolites [22]. The Milk aflatoxin M1 is a metabolite of aflatoxin B1 [23].

Mycotoxins and Health

Aflatoxin B1 has been classified as a class one carcinogen and its concentration in the body of animals and humans have been correlated to the health effects of liver cancer and cirrhosis [24]. Moreover, it has also been associated with immune suppression, reproductive disorders, hepatic damage, hepatocarcinoma and nutritional disorders such as stunted growth. The nature of the response of the body to the toxin correlates to the levels of exposure to aflatoxins [25]. The activity of aflatoxins is associated with the pro-oxidant potential associated with aflatoxin B1. The reactions of aflatoxin B1 releases reactive oxygen species (ROS) such as the superoxide anion (O⁻), hydrogen peroxide (H₂O₂) and hydroxyl radical (-OH) promoted by liver enzymes [26]. The generation of ROS induces oxidative stress to the liver leading to damage of the liver cell membrane and cellular components. In contrast, ochratoxins are known to cause damage to the kidney [12]. There is a possibility that ochratoxins promote hepatotoxicity following evidence of hepatomegaly when used alone on laboratory animals [27,28].

Effects on body and organ weights

Ingestion of aflatoxins and ochratoxin individually or in combination has been demonstrated to affect the gross body weight and performance in animal study models [28-33]. Ingestion of aflatoxin contaminated food alters the percentage organ weight. In most of the cases, hepatomegaly has been reported while there was

hypertrophy of the spleen; thymus and bursa of fabricius in cases of aflatoxicosis [34,35]. Similar findings have also been demonstrated in ochratoxicosis [28,36,37]. Moreover, in mycotoxicosis involving a combination of aflatoxin and ochratoxin, a similar effect was observed in broiler chicken [29,32].

Effects on biochemical liver profiles

Damage to liver cells is indicated by the elevation of liver enzymes levels of aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH) and gamma glutamyl transferase (γ-GT) among other key liver enzymes [38,39]. This follows the distortion of the integrity of the permeable membrane leading to the leakage of intracellular enzymes out of the cells detectable in blood. Aflatoxins have been shown to significantly increase the levels of ALT, AST, uric acid, and creatine levels in the blood serum in mice fed on aflatoxin [40].

Aflatoxicosis and ochratoxicosis reduces serum total protein and albumin in animal models [33]. In addition, when aflatoxin is used alone, it has a similar effect [41]. Similarly, ochratoxins reduce the serum proteins in broilers [28,36,42,43]. The synergistic effect of combining aflatoxins and ochratoxins in chicks also lower the serum proteins and albumins [36,44]. It has been suggested that the reduction of the serum proteins and albumin could be as a result of the pathological damage induced on the tissues of the animal models by mycotoxins and ochratoxins [33].

Alkaline phosphatases have been reported to increase in dietary aflatoxicosis and ochratoxicosis alone and in combinations. This has been suggested to be as a result of impaired liver metabolism [33]. Similarly, serum creatine and uric acid levels were significantly elevated in broilers [33]. This has also been established in other study findings [35,36,42-44]. This elevation in creatinine and uric acid levels has been associated with the effect of aflatoxin and ochratoxin to the renal dysfunction.

Effects on hematological profiles

Both aflatoxins and ochratoxins significantly reduce the levels of hemoglobin in laboratory experimental animals [33,43-46]. However, this may not have a significant effect on other hematological parameters [33]. Many other studies have been able to identify a reduction in the total erythrocyte count and plasma cell volume following aflatoxin poisoning [47,48]. Similar findings have also been recorded in ochratoxin poisoning [44,46,49]. But, a decrease in total leucocyte count may occur as a result of aflatoxicosis [49] and ochratoxicosis [46]. Leucocytosis may also occur in cases of ochratoxin A as reported by Stove et al. [28]. The role of mycotoxins and ochratoxins in the induction of bone marrow toxicity is yet to be determined [33]. It has also been suggested that the reduction in hemoglobin levels may be as a result of the reduced capability of protein synthesis in both cases of aflatoxin and ochratoxin toxicosis [33]. Probably, similar effects take place in humans, and have a significant impact on the health of humans. A search for alternative intervention for mycotoxicosis is therefore significant.

Effects on lipid profile

Aflatoxin poisoning also affects the lipid profiles of the liver. The total cholesterol, triglycerides and LDL cholesterol are significantly elevated while HDL cholesterol values are significantly reduced [38,50,51]. However, in separate studies, it was shown that the

aflatoxins [45,52] cause a significant reduction in the levels of serum cholesterol and triglyceride. This has also been suggested to be the same case in ochratoxin [28,36,42,43] and in cases of combinations of mycotoxins [35] Studies have proposed the impairment of lipid metabolism as the main cause to the changes in the serum cholesterol and triglycerides. A similar effect in humans would have a serious health effect and requires the search for post ingestion intervention strategies.

Effects on antioxidant activity

The effect of aflatoxins on the antioxidant activity through the observation of the oxidative stress markers has also been demonstrated. It lowers the total antioxidant capacity, sodium/potassium (Na/K) – ATPase Activity), glutathione (GSH) levels are also depleted. On the contrary, malonyl dialdehyde levels are significantly increased in cases of aflatoxicosis [38,53-55]. The use of the antioxidants has been proposed to be one of the major mechanisms through which the effect of the ROS can be reduced and hence reducing the damage to the liver cells. Liver damage has been demonstrated to be associated with DNA damage in aflatoxin poisoning during increased protein oxidation [56]. These are the same effects reported on the health of humans following mycotoxicosis and hence there is need for an alternative interventions besides the regimens used currently.

Effects on immune system

Aflatoxin alone and in combinations causes a reduction in the humoral and cell mediated immune responses [43,57,58]. The immune response is also reduced when ochratoxin is used alone [27,28,48,59,60]. In cases of combined aflatoxin and ochratoxin, Campbell et al. [61] have indicated a reduced immune response in chicks. The reduction of the immune response is associated with the reduction in the proteins and globulins. It is also caused by impairment of the antigen processes during phagocytosis [37,41]. Moreover, it induces lymphotoxic activities in cases of ochratoxin A as an effect on lymphocytes [62].

Effects on histological findings

Hepatocytes swell and become vacuolated suggesting the toxic effects of aflatoxins. Regions of necrosis also become diffusely spread out in the liver parenchyma and are infiltrated with heterophils and lymphocytic aggregates [33]. Tissue damage occurs in the spleen, kidney and other tissues of the body in cases of aflatoxicosis [41,47]. Similar findings have also been suggested in ochratoxicosis [27,33,36,63].

Current Management Strategies of Mycotoxicosis in Humans and Animals

So far, no antidotes have been developed for the management of mycotoxin poisoning and more specifically for aflatoxin B1 which is the most dangerous [64]. L-methionine administered at 200 mg/kg body weight has been the most preferred remedy for management of aflatoxin B1. They are administered intraperitoneally (IP) after every 8 hours until the clinical symptoms diminish. Methionine is also a regimen used in management of hepatotoxicity caused by acetaminophen poisoning [65,66]. Similarly, sodium thiosulfate is administered IP at 50 mg/kg to manage aflatoxicosis. They are administered IP at 8 hours interval and are proven to offer therapeutic

potential in aflatoxin management [64]. The main strategies proposed for managing contamination before ingestions includes processes such as thermal inactivation, irradiation, drying, solvent extraction, adsorption from a solution, inactivation of the microbes and fermentation. The action levels for aflatoxins have also been documented [67]. Limited post ingestion solutions are available for management of aflatoxicosis and ochratoxicosis (Figure 1).

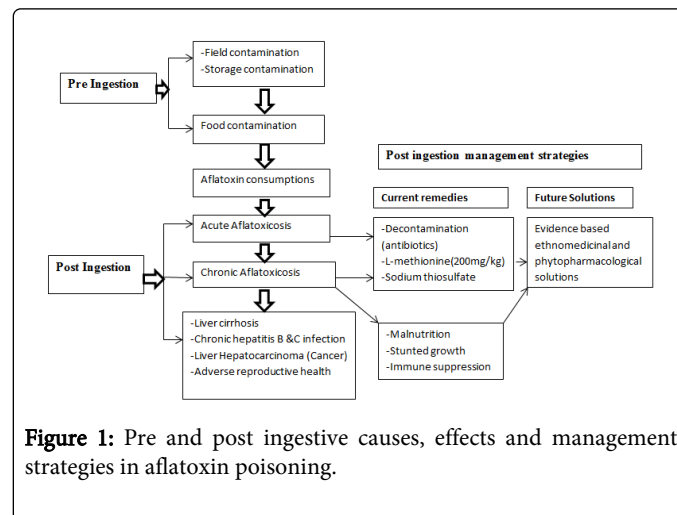


Figure 1: Pre and post ingestive causes, effects and management strategies in aflatoxin poisoning.

Chemoprotection and enterosorption techniques have also been applied in management of aflatoxin poisoning [64]. Esterified glucomanos and extracts from yeast have been very useful in management of aflatoxins. It has been suggested that they promote detoxification and also reduce the formation of aflatoxin epoxide; a potent toxin which cause damage to DNA and RNA. This reduces the effect of aflatoxin in causing hepatocellular damage and carcinoma. Chlorophyll has also been suggested to lower the biologically effective dose of aflatoxins [64].

Enterosorptive agents are suggested to bind to aflatoxins and make them biologically unavailable to humans and animals [68]. Adsorbents such as hydrated sodium calcium aluminosilicate have been indicated to protect against aflatoxicosis. Zeolites have also been suggested to be effective reactive oxygen species scavengers [69]. However, the use of enterosorptive and adsorbents is not effective since they bind to aflatoxins along with other nutrients essential to the body [68]. This may not be useful especially among pregnant women.

Alternative and Complimentary Management of Mycotoxicosis

Herbal extracts

Urtica dioica is the main plant with anti-oxidative properties that has been tested on animal models. In these studies, treatment of animals with *Urtica dioica* significantly reduced superoxide dismutase levels, and elevated the reduced levels of malonyldialdehyde and lowered glutathione levels. *Urtica dioica* (2 ml/kg) has demonstrated that it has potential in regeneration of the liver following partial hepatectomy in rat model when administered orally for seven days [70]. It was able to reduce the highly elevated levels of malonyl dialdehyde after partial hepatectomy. Similarly, the levels of superoxide dismutase and glutathione were elevated significantly following the administration of the *Urtica dioica* in the tissues of the

rat models. Hence, *Urtica dioica* has potential in the regeneration of the liver after liver damage caused by oxidative stress, proliferation and apoptosis after partial hepatectomy [70]. An oral dose of *Urtica dioica* (450 mg/kg) has also proven to be hepatoprotective and immunoprotective in mice exposed to 250 and 500 mg/kg acetaminophen poisoning administered IP [39].

Nigella sativa L. (2 ml/kg) and *Urtica dioica* (0.2 ml/kg) has been shown to reverse the toxic effect of carbon tetrachloride on lipid peroxidation, antioxidant and liver enzymes in hepatotoxicity in rats as animal models administered IP for 60 days. *Urtica dioica* and *Nigella sativa* when used alone and in a combination has been shown to decrease lipid peroxidation, liver enzymes and increase the antioxidant defense system activity in rats with induced damage [71]. It has been suggested that the high antioxidants; vitamin C, polyphenols and flavonoids present in *Urtica dioica* (2ml/kg) significantly inhibit aflatoxins B1 (25 µg/kg) induced oxidative damage through the scavenging of the reactive oxygen species (ROS) by stimulating the antioxidants defense systems in the body administered orally for 90 days [72].

Several studies on management of aflatoxicosis have been performed using various herbal extracts. In vitro hepatoprotective effect of both the ethanolic and aqueous extract of papaya fruits on rats administered at a dose of 250 mg/kg for 4 days have been demonstrated in aflatoxicosis by Hassan et al. [38]. It was shown that aqueous extracts had higher phenols and DPPH scavenging abilities compared to the ethanolic extracts. Oral aflatoxin (2 mg/kg body weight) alone causes significant increase in the biochemical parameters: ALT, AST and ALP. There was better improvement in lipid profiles for both aqueous extracts compared to ethanolic extracts administered orally on female Sprague-Dawley rats administered at a dose of 250 mg/kg body weight. Similarly, the oxidative stress markers; total antioxidant capacity, MDA and Na/K ATPase activity. Malonyl dialdehyde activity was significantly decreased in aqueous treated groups compared to the ethanolic extract treated groups. Hence, oral administrations of 250 mg/kg of papaya fruit extracts have significant hepatoprotective abilities [38]. Besides the hepatoprotective abilities, papaya has significant medicinal properties for many other medical conditions. Papaya contains alpha-tocopherol, lycopene, benzylisothiocyanate, proteolytic enzymes such as papain and chymopapain [73-76]. The phytochemical constituent of papaya contains various forms of alkaloids; carpain and carpasemine [77], triterpenes, organic acids [78,79]. Moreover, they also have cystatin, ascorbic acid, cyanogenic glucosides and glucosinolates [80] phenols [38] and flavonoids [80]. It is suggested that this group of chemicals provide protection to cells against cellular damage caused by exposure to high levels of free radicals [81-83], while it also aids in digestion [83-85]. Moreover, Osaka et al. [86] have reported that papaya is a good source of vitamins A, C, E, K and folate. It is also rich in fiber; in addition it is fat-free, cholesterol-free and is low in sodium, which further suggests its potential beneficial effects.

Encouraging findings have been established for *Ixora coccinea* Linn. (Rubiaceae), *Rhinacanthus nasuta*. Linn (Acanthaceae) and *Spilanthes ciliate* (Asteraceae) at a dose of 100, 200, 300 and 400 mg/kg administered orally for two days before a dose of 1.5 mg/kg of aflatoxins was administered IP and sacrificed by decapitation 72 hours later [87-90]. *Camelia sinensis* (green tea leaves) has shown cancer chemo protective activities as a result of the inhibitory effects on diverse cellular activities related to the development of cancer in aflatoxin treated laboratory models [91]. In addition, sage leaves

(*Salvia officinalis*) have also been indicated to have suppressive effects in tumor growth promotion on a variety of cell lines: Amelanotic melanoma cell line C32, renal cell adenocarcinoma ACHN, hormone-dependent prostate carcinoma LNCaP and finally the human breast cancer cell line MCF-7 in rats using a dose range of 5-400 µg/ml for a period of 48 hours [92]. This suggests strong anticancer properties. A similar effect can be replicated in the hepatocarcinoma caused by mycotoxins. Fenugreek seeds (*Trigonella foenum gracum*) from the family of Legomenaca have been demonstrated to have anticancer properties and antioxidant effects on MCF-7 breast cancer cell lines through the induction of apoptosis [93]. *Carum carvi* also referred to as caraway seeds belonging to Umbellifera have also demonstrated the antioxidant profile [94]. Galangal rhizomes (*Alpinia officinarum*) from the botanical family of Zingiberaceae have chemoprevention effect on tumor [95]. The same has been reported for ginger (*Zingiber officinale*) [96], Frankincense resins (*Gum olibanum*) [97], Myrrh (*Commiphora myrrha*) [98], Cinnamon barks (*Cimnomum zeylanicum*) [99]. Herbal extracts from these plants demonstrate possible significant hepatoprotection potential in cancer induced by aflatoxin B1 [100]. Similarly, combination of these herbs may also improve the biochemical profiles following post ingestion of mycotoxins.

Combined herbal extracts prepared as supplements have shown to be effective in the improvement of body weight in experimental models [33]. Performances of the animal models in studies have also demonstrated improvement [101]. Polyherbal supplementation in aflatoxin poisoning confers partial protection against significant change in organ weight [33]. The use of herbal extracts also confers partial protection in cases of either aflatoxin [58] or ochratoxins [28].

The effects of polyherbal extracts on tissues following aflatoxin poisoning showed pre-protection against significant change in hematological parameters [33]. The protection against significant elevation in liver enzymes: AST, ALT, ALP, Albumin and serum proteins have also been demonstrated in various studies in mycotoxicosis [33]. Herbal extracts have therefore been suggested to possess restorative role in protein synthesis. The use of curcumin and *Curcuma longa* has also demonstrated improvement in the normal serum proteins following cases of aflatoxicosis in animal laboratory models [58,102]. Polyherbal extracts are also protective against significant damage to the kidney. They have been shown to reduce the significant elevation in the values of creatinine and uric acid [33]. This therefore suggests the protective effects of the two herbs in mycotoxicosis. This is also the case with the protection against the significant changes in lipid profiles; cholesterol and triglycerides suggesting their protective role in the mycotoxin poisoning [33]. Protection against immunotoxicity by herbal supplementations has also been suggested by various studies. It is suggested that it protects the immune organs from histotoxic effects caused by the mycotoxins [33]. Using *Curcuma longa* and 5% extract of artichoke has demonstrated improvement in the immune response in aflatoxicosis and ochratoxin poisoning [58]. No mechanism of action responsible for immunoprotection has been suggested. Histological improvements in liver tissues and other organs have also been improved by curcumin and *Curcuma longa*, 5% aqueous extract of artichoke [58,102]. It has been suggested that herbal extracts cause toxin neutralization [33,103]. No precise protective mechanism of action has been determined for the protective action of the herbal extracts. Other studies using carbon tetrachloride and acetaminophen have shown that protective effects of polyphenols and flavonoids target the antioxidation processes in the

body. The mechanism of action of most herbal extracts has been reviewed by Sabeena and Ajay, [104].

Saccharomyces cerevisiae

Studies have evaluated the potential of a dose of 4×10^{16} CFU of *Saccharomyces cerevisiae* administered for 7 days and tested for its ability to reduce aflatoxins induced toxicity in animal models has been demonstrated. It was shown that aflatoxin at 0.7 mg/kg can reduce the weight of experimental animals [40]. However, animal models fed on *Saccharomyces cerevisiae* for 7 days showed improvement in the gross weight gain following aflatoxin poisoning [40]. The levels of superoxide dismutase, glutathione, total antioxidant capacity, and Na^+/K^+ ATPase are also significantly reduced in both the liver and kidney in aflatoxin treated groups [38,40]. There was also a significant increase in the non-enzymatic antioxidants superoxide dismutase and glutathione levels in *Saccharomyces cerevisiae* treated models and a decrease in the levels of malonyldialdehyde compared to the controls. Histopathological studies also showed a significant damage to the liver tissues in aflatoxin B1 treated mouse models. It can be concluded that *Saccharomyces cerevisiae* is a safe and successful agent in counteracting the aflatoxin toxicity and is also hepatoprotective against aflatoxin induced damage. It is therefore a beneficial agent in the modulation of the activity of aflatoxins [40]. In another study of *Saccharomyces cerevisiae* and lactic acid bacteria (*Lactobacillus rhamnosus*) the combination was able to significantly reduce serum ALT, AST, gamma glutamyl transferase, creatinine and blood urea nitrogen in comparison to the control groups. Glutathione was significantly increased in the studies more than the control. In addition, they were diminished products of aflatoxin in both the in vitro and in vivo studies [105]. The beneficial effects of *Saccharomyces cerevisiae* in management of aflatoxin B1 toxicity has also been evaluated in broilers [106] and Quails [107]. Bueno et al. [108] has also demonstrated that *Saccharomyces cerevisiae* is an important and efficient micro-organism in aflatoxin B1 quenching. Moreover, it is suggested that *Saccharomyces cerevisiae* cell wall have glucan, they reduce the frequency of micro nuclei induced by cyclophosphamide. Fermented yeast products from yeast have also been suggested to offer protection against damage of body tissues, elevation of liver and kidney enzymes [40]. *Saccharomyces cerevisiae* are known to produce glutathione. Glutathione has many beneficial effects such as in the protection against UV [109], heavy metals [110]. Glutathione has a significant role in reactive oxygen species damage to cells in organisms and protects against tissue damage [70]. Yeasts have now been adopted for the massive commercial production of glutathione [111].

Potential of combination of herbal extracts and *Saccharomyces cerevisiae*

Herbs have been demonstrated to work through the anti-oxidative mechanisms serving as free radical scavengers promoted by polyphenols, flavonoids, ascorbic acid, terpenoids for the superoxide's generated by the ROS pathways that cause damage to vital organs in the body [112,113]. The polyphenols also inhibit the actions of Cytochrome P-450 preventing the metabolism of aflatoxins at post ingestion [113,114]. Mineral elements also boost the protective abilities against damage by toxins [114]. They also inhibit the growth of cancer therefore offering potential for protection against development of hepatocarcinoma caused by aflatoxin poisoning [92-99]. *Saccharomyces cerevisiae* quenches the toxins in the GIT, while it elevates the levels of glutathione in the body conferring

hepatoprotection [40]. A combination of the two mechanisms will therefore be able to complement each other and offer multifunctional approach to management of mycotoxicosis in humans.

Animal Models in the Assessment of Mycotoxicosis

A comparative study on aflatoxin B1 metabolism in mice and rats has been done by Steyn et al. [115]. This study was able to show that albino mice have almost the same levels of susceptibility to the acute oral effects of aflatoxin B1 [116]. However, mice have been found to be resistant to the carcinogenic actions of aflatoxin B1 compared to rat models. In terms of metabolism, it has been shown that the mouse has a higher rate of metabolism of the aflatoxin B1 compared to the rats. This has been associated to the high activity of the cytochrome P450 in mice than in the rats hence inducing the resistance to the carcinogenic effects of aflatoxin B1 in the mouse model [115]. The mechanism in rat models has been associated with the conversion of the aflatoxin B1 to aflatoxin M1 in vivo [117]. The same mechanism has been proved to work in vitro [118]. Hence, acute effect of aflatoxins can be best demonstrated in mice while chronic effects are better when using rat as animal models. No comparative inter and intra specie studies of the suitability of birds and primates to rodents have been demonstrated in assessing the effects of aflatoxins and ochratoxins.

Relevance of Alternative Interventions of Mycotoxicosis to Humans

It is estimated that 55 billion people all over the globe suffer from uncontrolled aflatoxin poisoning worldwide [119]. The number of people with hepatocarcinoma is also growing. Furthermore, there have been no attempts to establish the number of liver cancer associated with mycotoxins exposure. There are also no drugs for management of mycotoxicosis in both humans and animals [64]. Four findings have been suggested by the Aflatoxin Workgroup, convened by the Centers for Disease Control and Prevention and World Health Organization. First, it was suggested that the burden of the diseases and impact on human health need to be quantified. Secondly; an inventory of the ongoing intervention strategies was to be created. Moreover, an evaluation on efficacy of the interventions was to be determined. Finally, results should be disseminated [120]. This review addresses the impact of mycotoxins on animal and human health and alternative post ingestion management strategies conducted in animal models. It has been shown that the alternative intervention have potential for management of mycotoxins and specifically aflatoxins and ochratoxins. Further clinical trials are needed using higher animals such as apes for evaluation of their effectiveness in management of aflatoxicosis before they can be adopted for use by humans and animals. No comparative studies have been done on the efficacy of either oral or other route of administration of herbal extracts to be considered for human application. However, oral administration of *Saccharomyces cerevisiae* is considered beneficial due to its ability to adsorb aflatoxins while at the same time exerting its effect in protecting the body organs against tissue damage through the anti-oxidative mechanisms.

Conclusion

The review has addressed aspects of mycotoxins on health and why there is need to conduct these studies in order to determine mechanisms that will help reduce the impact of mycotoxins on health.

This report also cites relevant studies that show independent efficacy of use of herbal extracts and *Saccharomyces cerevisiae* in post ingestion management of mycotoxins in animal models. A study investigating the efficacy of the combined therapy of the two regimens is therefore justified. It is therefore expected that the overall effect of the herbal extracts and *Saccharomyces cerevisiae* alone and when combined will significantly reduce the effect of mycotoxins in humans as demonstrated in animal models. Moreover, it is anticipated that combinations of herbal extract and *Saccharomyces cerevisiae* will target different pathways for management of mycotoxins allowing for multi-functional management of mycotoxins. However, clinical trials are needed to ascertain the adoption of the regimens for use in humans.

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