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Molecular mechanisms of aflatoxin neurotoxicity and potential neuroprotective agents

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ABSTRACT

Aflatoxins (AFTs) represent one of the most notorious classes of deadly mycotoxins produced by certain fungi that are found on agricultural crops. Aflatoxins are highly toxic to mammals and are known to cause a series of detrimental effects, including neuro-, hepato-, nephron-, and immuno-toxicity. In this original review we summarize the mechanisms of aflatoxin-induced neurotoxicity and the clinical potential of novel neuroprotective agents. Aflatoxin B1 (AFB1) is the most toxic congener among the 21 identified AFTs. Recent studies have shown that food borne exposure to AFB1 and/or its metabolites often leads to fatal neurotoxicity in animals and humans. Animal studies indicated that AFB1 exposure could induce abnormal behavioral changes, including anxiety, lethargy disorders, depression-like behavior, cognitive, learning and memory defects, and decreased feeding behavior. Mechanistically, AFB1 exposure has been associated with lipid peroxidation, ablation of non-enzymatic and enzymatic antioxidant defense systems and decreased neurotransmitter levels. AFB1 exposure has also been shown to induce DNA damage, apoptosis, pyroptosis, and mitochondrial dysfunction in the brain tissue. Several signaling pathways, including gasdermin D, toll like receptor 2 (TLR2), TLR4, Akt, NF-κB, ERK/MAPK, protein kinase C (PKC), and mitochondrial apoptotic pathways have been shown to participate in AFB1-induced neuronal or astrocyte cell death. Targeting these pathways by small molecules (e.g., quercetin, curcumin, and gallic acid, and dimethyl fumarate), Chinese herbal extracts (e.g., *Artichoke* leaf extract, *Chelidonium majus* ethanolic extract, pumpkin extract, and *Crocus sativus* L. tea), and probiotic supplements could effectively improve AFB1-induced neurobehavioral abnormalities and neurotoxicity. To date, the precise molecular mechanisms of AFB1-induced neurotoxicity and potential neuroprotective agents remain unclear. In the present review, the clinical manifestations, molecular mechanisms, and potential neuroprotective agents of AFB1-induced neurotoxicity are summarized in the broadest overview. It is most hopeful that this broad reaching review provides valuable insights and stimulates broader discussion to develop the effective neuroprotective agents against aflatoxins.

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1. Introduction

Mycotoxins are naturally occurring compounds which are secondary metabolites synthesized by toxin producing fungi that infest agricultural crops[1]. In recent decades, mycotoxin contamination in food and feed has posed serious threats to the global

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food safety and raised a public health concern worldwide[2]. Currently, such wide-spread contamination has been shown to be a serious threat to the economy and environment[2]. To date, over 500 known mycotoxins, including aflatoxins (AFTs, such as aflatoxin B1 (AFB1), aflatoxin B2, aflatoxin G1, aflatoxin G2, aflatoxin M1, and aflatoxin M2), ochratoxins (such as ochratoxin A, ochratoxin B, and ochratoxin C), trichothecenes (such as deoxynivalenol, T-2 toxn, HT-2 toxin, and nivalenol), fumonisins (such as fumonisin B1, fumonisin B2, and fumonisin B3), zearalenone (ZEN), fusarins (such as fusarin A, fusarin C, and fusarin D), ergot alkaloids (such as ergotamine), and tremorgenic toxins (such as paxilline and paspaline), have been found and recognized in foods or natural environments (Fig. 1)[3]. AFTs is considered as one of the most significantly notorious classes of mycotoxins. It has been reported that AFT contamination could occur in storage, preparation, and production of various grains and foods, and their processed products, such as cereals (e.g., corn, wheat, and rice), as well as Chinese herbal medicine, tea, nuts, drinking water, and edible oils[1,4-6]. AFT exposure can induce a variety of detrimental cellular effects in humans and animals, such as cancer, neuro-, hepato-, nephron-, and immuno-toxicity, and reproductive toxicity[1]. Chen et al.[7] reported that increased AFT intake via the consumption of peanuts, peanut oil, corn, and corn products in the Chinese population is coincident with an increase in the incidence of liver cancer. With the existing evidence of the harm that AFTs pose, understanding the molecular mechanisms behind the toxic effects caused by AFTs is pivotal and very important for optimum risk assessment and chemical prevention.

There are a total of 21 members in the family of AFTs identified thus far, these notably include AFB1, AFB2, aflatoxin G1 (AFG1), AFG2, and aflatoxicol M1 (AFM1)[1]. The AFB1 congener is the most toxic member of the AFT family. AFB1 differs from other members of the family by its special structure (such as two dihydrofuran rings, the details have been reviewed in Martínez et al.[8]). Recent studies have shown AFB1 exposure results in long-term neurological effects and acute/chronic neurotoxicity, which raised food safety concerns worldwide[9-10]. Worryingly, AFB1 has been detected in the brain tissue of children who had died from Kwashiorkor disease, indicating AFTs can transverse the blood brain barrier[11]. To this end, animal models have demonstrated that AFB1 has the ability to disrupt the blood-brain barrier and in addition accumulate in the brain tissues in rats, mice, or silver catfish, which culminates in neurotoxicity and abnormal neurobehavior changes (depression, anorexia, and learning/memory deficits)[10,12-15]. Consistently, an *in vitro* study[13] which employed a blood-brain barrier cell-based model showed AFB1 could cause direct damage the human brain microvascular endothelial cells, resulting in the disturbance of the blood-brain barrier and promoting the accumulation of AFB1 in the brain tissues. Moreover, AFB1 exposure has been

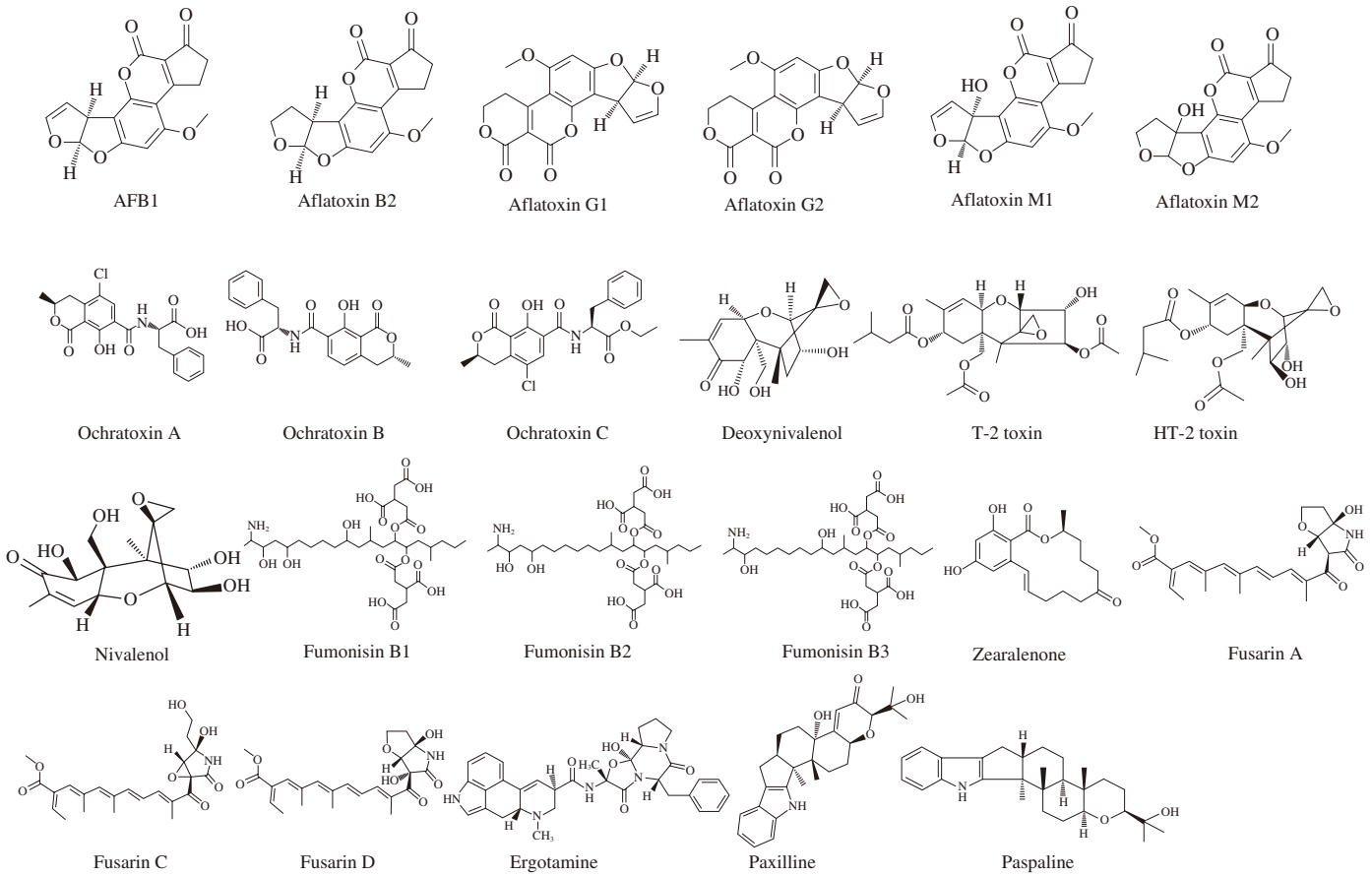

Fig. 1 The structure of different mycotoxins. The chemical compounds, including aflatoxins (such as AFB1, aflatoxin B2, aflatoxin G1, aflatoxin G2, aflatoxin M1, and aflatoxin M2), ochratoxins (such as ochratoxin A, ochratoxin B, and ochratoxin C), trichothecenes (such as deoxynivalenol, T-2 toxn, HT-2 toxin, and nivalenol), fumonisins (such as fumonisin B1, fumonisin B2, and fumonisin B3), zearalenone (ZEN), fusarins (such as fusarin A, fusarin C, and fusarin D), ergot alkaloids (such as ergotamine), and tremorgenic toxins (such as paxilline and paspaline) were shown.

shown to inhibit the neural development of zebrafish embryos and larvae, which is in line with its reported reproductive effects[16]. Madiha et al.[17] found that the oral administration of AFB1 to rats at the dose of 250 μg/kg body weight per day for 4 weeks induced significant peripheral neurotoxicity seen as damage to the sciatic nerves. Collectively, these mechanistic *in vitro* and animal model studies indicate that AFB1 neurotoxicity most likely involves physiological perturbations that lead to the induction of abnormal neurobehavior, the inhibition of neurotransmitters, regulation of neuropeptide secretion, and neuro-immunosuppression[9-10,18]. On the cellular level, AFB1-induced toxicity directly causes damage to neuronal cells, astrocytes, and glial cells by inducing reactive oxygen species (ROS) production, inflammatory responses, DNA damage, cell cycle arrest, pyroptosis, mitochondrial damage and cell apoptosis[10,12,18-19]. Several signaling pathways, including gasdermin D, protein kinase B (PKB, also named Akt)/p-p70 ribosomal protein S6 kinase (p70s6k), extracellular signal-regulated kinase (ERK)/ mitogen activated protein kinase (MAPK) pathway, nuclear factor kappa B (NF-κB), toll like receptor 2 (TLR2), TLR4, protein kinase C (PKC), and mitochondrial apoptotic pathways, have been shown to mediate AFB1-induced neurotoxicity[12,18-22]. It has been reported that anti-oxidant foods and probiotic supplements (e.g., quercetin, curcumin, gallic acid, and dimethyl fumarate), Chinese herbal extracts (e.g., *Artichoke* leaf extract, *Chelidonium majus* ethanolic extract, pumpkin extract, and *Crocus sativus* L. tea) could effectively inhibit ROS production, oxidative stress, mitochondrial dysfunction, inflammation, and cell apoptosis, helping counter some of the AFB1-induced neurobehavioral abnormalities and neurotoxicity[15,22-31].

In this review, we have summarized the available compendium of literature covering the abnormal neurobehavioral changes and molecular mechanisms of AFB1-induced neurotoxicity. Throughout the narrative we discuss the chemoprotective effects and neuro-protective mechanisms of the aforementioned anti-oxidant foods and probiotic supplements against AFB1-induced neurotoxicity. The overarching goal of this review is to provide insightful views and boost more investigation into molecular mechanism(s) of AFB1-induced neurotoxicity and more importantly the development of neuroprotective agents against this widespread food borne toxin.

2. AFB1 exposure induces neurobehavioral abnormalities

AFB1 exposure has been correlated with neurobehavioral disorders in mammals and aquatic animals[12,16]. Neurobehavioral disorders are usually associated with brain injury and neuro-impairment. The study from Subramaniam et al.[9] found that oral administration of AFB1 at the final concentrations of 5 and 25 μg/mL for 4 weeks (5 days/week) to rats induced significant depression, anhedonia and prolonged immobility. In another study[16], zebrafish embryos treated with 15−75 ng/mL AFB1 6 h post-fertilization displayed significant perturbations in their swimming patterns and neurodevelopmental toxicity. In addition, AFB1 exposure has been shown to decrease the feeding behavior of rats by directly downregulating the expression of anorexigenic peptides in the brain[32]. Linardaki et al.[15] found that intraperitoneal (i.p.) administration of AFB1 at the dose of 0.6 mg/kg body weight weight day for 4 days (the cumulative dose is 2.4 mg/kg) to mice manifested as serious memory and learning deficits. In conclusion, systemic AFB1 exposure is responsible for acute and chronic neurotoxicity, clinically these effects manifest as neurobehavioral abnormalities, including depression, anorexia, learning and memory defects.

3. AFB1 exposure-induced neuro-pathology

AFB1 can directly cross the blood-brain barrier and enter the brain tissue[11]. AFB1 exposure has been shown to directly perturb the structure of blood-brain barrier and thereby promote its accumulation in the brain tissue. *In vitro*, AFB1 exposure could induce marked cytotoxicity in various nerve cells, including IMR-32 cells, SH-SY5Y cells, ventricular zone-derived neural precursor cells, primary mouse astrocytes, BV2 cells (i.e., a mouse microglial cell line)[12,21,33]. Even at concentrations as low as 3.2 nmol/L, AFB1 exhibited the potent cytotoxicity against primary human brain microvascular endothelial cells, which constitute the main cellular matrix of the blood-brain barrier[13]. In line with these *in vitro* findings, it has been shown that an AFB1-contaminated diet results in a disrupted the blood-brain barrier in silver catfish[34]. Moreover, animal experiments showed that chronic exposure of AFB1 could result in various pathological changes in the brain tissues, such as cortical cell deterioration, dilation of the blood vessels, vascular congestion, gliosis, neuronal degeneration, and vacuolization[10]. AFB1 exposure reduced the thickness of hippocampus and dentate gyrus in the brain tissues of rats[27]. In addition, AFB1 exposure often manifests as peripheral neurotoxicity seen as myelin sheath degeneration and inflammatory cell infiltration in the sciatic nerves of rats[17]. Huang et al.[12] showed that when orally administrated to mice at 300 μg/kg body weight per day for 30 days, AFB1 accumulated in the brain at levels of 60 μg/kg. This corresponded with the appearance of pathological changes like fewer large cells in the red nucleus and red-cell infiltration. AFB1-8,9-exo-epoxide (AFBO) is a major metabolite of AFB1 generated via hepatic metabolism through the cytochrome P450 system. Several studies[35-37] have shown that CYP1A1, CYP1A5, CYP1A2, CYP2A13, CYP2A6, CYP3A4, and CYP3A37 are responsible for the metabolic transformation of AFB1 into AFBO in the liver tissues. AFBO is particularly toxic as it avidly binds to DNA and proteins, resulting in cytotoxicity[1]. However, AFBO has not detected in the brain tissues of mice treated with AFB1[12].

4. AFB1-induced neurotoxicity disrupts neurotransmitter functions

Neurotransmitters are endogenous chemicals that cross synapses to transmit impulses from one neuron to another “target” neuron, glandular, or muscle cells, and they play critical functions for behavior in humans and animals[38]. Overall, in the human central nervous system, there are over 40 known neurotransmitters, such as acetylcholine (Ach), nitric oxide (NO), serotonin (also called 5-HT), dopamine, norepinephrine, monoamines, and gamma-aminobutyric acid (GABA)[38]. Acetylcholinesterase (AchE) is the primary enzyme that is responsible for the hydrolytic metabolism of the Ach into choline and acetate. MAO is an enzyme that degrades or breaks down three neurotransmitters i.e., 5-HT, norepinephrine, and monoamines, which are associated with mood and anxiety. Therefore, the decreases of AchE activities or increases of monoamine oxidase (MAO) may lead to increases in anxiety and depression[39]. Inhibition of AchE

is also considered as the main mechanism of neurotoxicity caused by several neurotic toxins or drugs, such as cadmium, colistin and lincomycin hydrochloride[40-42]. Significantly decreased levels of AchE activity in the brains of silver catfish were detected after AFB1-dietry exposure[34]. Consistently, Linardaki et al.[15] reported that AFB1 administration at a dose of 0.6 mg/(kg·day) (i.p.) for 4 days significantly decreased the levels of AchE activity, and increased the levels of MAO activity in the brain tissue of mice that also manifested into a depression-like behavior state, memory and learning deficits. Molecular docking studies indicated that AFB1 and its major metabolites AFB2a, AFP1, AFM1, and AFQ1 could avidly dock at the peripheral anionic site of human AchE, suggesting AChE is maybe a key target for AFB1-induced neurotoxicity[43-44]. In addition, oral exposure of AFB1 at the doses of 32.8 or 327.9 μg/kg (twice per week) for 3 weeks significantly decreased the levels of dopamine and 5-HT; a corresponding decline was also observed in the dopamine metabolites (i.e., homovanillic acid and dihydroxyphenylacetic acid)[34]. So it follows, the inhibition of dopamine metabolites may contribute to AFB1-induced neurotoxicity. Elevated 5-HT levels were also suggested to be relative with AFB1-induced anorectic responses in animals. The 5-HT3 receptor antagonist granisetron and neurokinin-1 receptor antagonist aprepitant could effectively attenuate T-2 mycotoxin toxin induced anorectic responses in a dose-dependent manner[45]. The inhibition of both orexigenic (e.g., neuropeptide Y[NPY], orexin, and agouti gene-related peptide[AgRP]) and anorexigenic (e.g., α-melanocyte-stimulating hormone[α-MSH], cocaine and amphetamine-regulated transcript[CART], and thyrotropin releasing hormone[TRH]) peptides in the brain tissues also contributed to AFB1 exposure-induced decreases in feeding behavior[32].

In short, these perturbations in neural neurotransmitter levels, including Ach, 5-HT, dopamine, norepinephrine, and monoamines, is a key facet of AFB1-induced neurotoxicity. Therefore, drugs targeting the corresponding neurotransmitter metabolic enzymes (i.e., AchE and MAO) or receptors (i.e., 5-HT receptors) might effectively improve AFB1-induced neurotoxicity.

5. Molecular mechanisms of AFB1-induced neurotoxicity

Multiple *in vitro* cell model and animal studies have demonstrated that the molecular mechanisms of AFB1-induced neurotoxicity involved unequivocally oxidative stress, DNA damage, inflammatory response, GSDMD- mediated pyroptosis, cycle arrest, toll like receptor 2 (TLR2), Akt, TLR4, protein kinase C (PKC), and mitochondrial apoptotic pathways. The current knowledge-base on the role of each of these pathways in AFB1-induced neurotoxicity is addressed in detail below.

5.1 Oxidative stress

Oxidative stress is considered as one of the critical molecular mechanisms underlying the cytotoxicity pathways induced various chemical hazards or drugs (i.e., cadmium, T-2 mycotoxin, cisplatin, and colistin)-induced neurotoxicity[40,46-51]. The vernacular 'ROS' pertains to a class of reactive chemical species which contain oxygen radicals in the form of superoxide anion ($O_2^{-}\cdot$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (·OH), and singlet oxygen ($^1O_2$)[52]. Under nominal physiological conditions, intracellular antioxidant systems maintain the capacity to rapidly act to neutralize ROS. However, excess ROS production can overwhelm and exceed the intracellular antioxidant systems ability to scavenge free radicals, leading to oxidative damage ultimately resulting in cell death[46,53-54].

AFB1 treatment of IMR-32 cells (neuroblastoma cell line) at the dose range of 1−20 μg/mL for 24 h induced marked cytotoxicity with the excessive production of ROS. Furthermore, AFB1 treatment significantly upregulated the expression of nicotinamide adenine dinucleotide phosphate oxidase 2 (NOX2), a member of NOX family of proteins that are the major sources of ROS in the nervous system[55]. Significantly increased expression of NOX2 was also detected in AFB1-treated liver of mice[56]. Kallenborn-Gerhardt et al.[57] showed that nerve injury activated the expression of NOX2 protein, inducing oxidative damage in the dorsal root ganglia and manifested neuropathic pain, which was reversed by NOX2 knockout in mice. These key pieces of evidence indicate that the upregulation of NOX2 may play a pivotal role in AFB1-induced neuronal oxidative stress.

Superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPX) are the three most critical components of the cellular antioxidant system[52]. In general, SOD catalyzes the conversion of $O_2^{-}\cdot$ into H_2O_2, which is in turn converted into the harmless components H_2O and O_2 by CAT or GPX[52]. In a rat model, orally administered AFB1 at the dose of 0.025 mg/kg body weight per day for 30 successive days markedly increased the levels of malondialdehyde (MDA), and markedly decreased brain SOD activity and antioxidant glutathione (GSH) levels[10]. Consistently, oral administration of AFB1 at the dose of 25 μg/kg body weight per week for 8 weeks significantly elevated the levels of MDA, and inhibited the activities of GPX, SOD and the depleted the levels of GSH in the brains of rats[27]. Additionally, AFB1 exposure significantly promoted the production of ROS, with the downregulated SOD activities in human astrocytes, and neuronal cells (e.g., SH-SY5Y and IMR-32 neuroblastoma cells)[12,18-19]. AFB1 exposure also significantly downregulates the activities of GST in the cerebrum and cerebellum of rats. The conjugation between activated AFB1 (i.e., AFBO) with GSH, catalyzed by GST leads to the disruption of one of the most important detoxification reactions in the liver tissues[58].

Multiple studies showed that nuclear factor erythroid 2-related factor 2 (Nrf2)/ heme oxygenase 1 (HO-1), a critical endogenous antioxidant pathway, play a protective role against AFB1-induced liver and kidney toxicity[59]. Therefore, Nrf2 mediated recovery may also offer a protection against AFB1-induced neurotoxicity. At the genetic level, AFB1 treatment also inhibited the mRNA expression of the oxidation resistance 1 (*OXR1*) gene, which is known to play an essential role against oxidative stress[12].

Aside from ROS, reactive nitrogen species (RNS) also contribute to cellular oxidative stress. RNS species include a variety of nitric oxide (NO)-derived active substances, including *S*-nitrosothiols, nitrosonium cation, higher oxides of nitrogen, nitroxyl anion and dinitrosyl iron complexes[60]. In addition, $O_2^{-}\cdot$ may react with nitric oxide (NO·) to produce peroxynitrite ($ONOO^-$), which can cause DNA damage[53-54]. Adedara et al.[26] found that oral AFB1 administration at the dose of 75 μg/(kg·day) for 28 days to rats significantly increased the levels of ROS, RNS, and NO in the cerebrum and cerebellum. *In vitro*, a low dose AFB1 treatment (i.e.,

20 ng/mL) for 1−6 h in cultured mouse microglial and astrocytes significantly upregulated the mRNA levels of inducible nitric oxide synthase (iNOS), iNOS, NF-κB, and the inhibitor of NF-κB (IκB)[21]. Consistently, AFB1 and AFM1 exposure at the concentration range of 10−100 μmol/L for 24 h significantly elevated the expression of iNOS and NO levels in primary mouse microglia[19]. It is known that the activation of NF-κB induces the expression of iNOS, which in turn mediates the production of NO[61]. It has been shown that targeting inhibition of NF-κB by dimethyl fumarate could significantly inhibit AFB1-induced the expression of iNOS and NO production, thus improving AFB1 and AFM1-induced cytotoxicity in primary mouse neuronal cells and mouse astrocytes cells[19]. These data indicate that the NF-κB/iNOS/NO signal cascade is intimately involved in the process of AFB1-caused oxidative stress and neurotoxicity.

In summary, these studies indicate that AFB1 exposure-causes extensive oxidative stress in brain tissue via the induction of ROS and RNS production, the upregulation of NOX2, and NF-κB/iNOS/NO pathways, and the downregulation of antioxidant pathways (e.g., SOD, CAT, GPX, and GSH) (Fig. 2). Inhibition of OXR1 also contributes to AFB1-induced oxidative damage in nerve cells. So it follows, antioxidant supplementation or the inhibition of NOX2 and NF-κB/iNOS/NO pathways might provide effective neuroprotective effects against AFB1-induced oxidative stress and neurotoxicity.

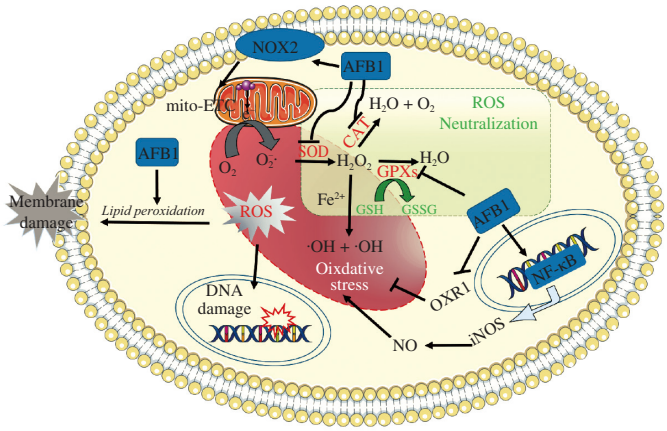

Fig. 2 An overview of AFB1-induced ROS production and oxidative stress pathways in nerve cells.

5.2 *Inflammatory responses and cell pyroptosis*

AFB1 is known to trigger the inflammatory responses in the central nervous system[21]. Inflammatory cells (i.e., neutrophils) and macrophages were increased in the nerve tissues in response to AFB1 exposure indicating that the immune response had been activated[17]. Astrocytes and microglia both belong to glial cell lineage and they play critical roles in various neurodegenerative diseases[62-64]. Astrocytes and microglia play important roles in maintaining brain homeostasis and regulating neuroinflammation and neuronal cell survival[62-64]. It has been illustrated that the activation of glial cells contributes to neurodegenerative diseases caused by cadmium, T-2 toxin, polybrominated diphenyl ethers quinone, and methylmercury[65-67]. Glial fibrillary acidic protein (GFAP) was expressed in the cell body of astrocytes, and it has been recognized as the biomarker for the abnormal activation and proliferation of astrocytes[68]. Early studies have shown that increased GFAP expression, along with the astrocyte activation was detected in neurodegenerative injury. Similarly, significantly increased expressions of GFAP in the rat cerebral cortex and hippocampus of rats were detected after chronic oral AFB1 exposure (at the dose of 0.025 mg/kg for 60 and 90 days)[10]. Consistently, AFB1 treatment at a low dose (i.e., 20 ng/mL) significantly increased the mRNA expression of inflammatory mediators including NF-κB (p50), IL-1β, and TNF-α, and significantly promoted the secretion of IL-1β, IL-6, TNF-α, and IL-10 in mouse microglial and astrocytes[21]. In another notable study[19], significantly increased AFB1-induced cytotoxicity was detected against primary mouse neuronal cells when they were co-cultured with microglial cells, compared to that in neuronal cell culture *per se*. Collectively, these findings indicate that the activation of microglia and astrocytes play a vital role in AFB1-induced neuroinflammation and it could also exacerbate AFB1 neurotoxicity.

Intragastrical administration with AFB1 at the doses of 0.75 or 1.5 mg/kg body weight for 30 successive days markedly upregulated the expression of phosphorylated (p)-NF-κB protein in the spinal cord of mice[69]. NF-κB is a critical transcription factor that regulates the expression of various pro-inflammatory genes, including those encoding cytokines and chemokines that participate in inflammasome regulation, such as IL-1β, IL-10, IL-6, and TNF-α[70-72]. These NF-κB-mediated inflammatory genes, were detected in the AFB1-treated microglial and astrocytes and rat brain tissues[19,21,26]. In addition, NF-κB can not only promote oxidative stress via the transcriptional upregulation of iNOS/NO pathway, but can also be activated by excess ROS production[1]. Indeed, inhibition of ROS by *N*-acetylcysteine (NAC) significantly attenuated AFB1-elevated expression of p-NF-κB protein[69]. Therefore, AFB1-induced NF-κB-mediated inflammatory response may be partly attributed to the production of excess ROS in nerve cells.

NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) is an intracellular inflammation sensor. NLRP3 inflammasome is a cytosolic multiprotein complex composed of a sensor (i.e., NLRP3), an adaptor (i.e., ASC) and an effector (i.e., caspase 1)[19,73]. The formation of NLRP3 inflammasome could lead to caspase 1-dependent release of the pro-inflammatory cytokines IL-1β and IL-18, and promote gasdermin D-mediated pyroptotic cell death. In the process of cell pyroptosis, GSDMD usually is cleaved by caspase-11 or caspase-1 to produce 31 kDa N-terminal fragment (i.e., GSDMD-N)[73]. Zhang et al.[19] found that AFB1 and AFM1 exposure significantly increased the expression of NLRP3, caspase-1 and GSDMD-N, and ASC proteins in primary mouse microglia. Inhibition of GSDMD by dimethyl fumarate markedly reduced the AFB1 and AFM1-induced inflammatory response and cell pyroptosis in microglial cells[19]. These studies highlight that the NLRP3 inflammasome mediated response and cell pyroptosis contribute to AFB1-induced neurotoxicity. In addition, the GSDMD inhibitor dimethyl fumarate could also decrease the levels of NO in primary mouse microglia, which then attenuated AFB1-induced neuronal cell death[19]. However, the precise molecular mechanisms for the cross-talk between GSDMD pathway and oxidative stress during AFB1 neurotoxicity remain unclear, and can provide an exciting avenue for further study.

Low-level AFT exposure has been shown to trigger the expression of some key TLRs (e.g., TLR2 and TLR4) and induce pro-inflammatory responses in various immune cells, such as human

dendritic cells, peripheral blood mononuclear cells, bovine blood neutrophils and mononuclear cells[74-76]. MyD88 protein is essential for the TLR activation-mediated NF-κB transcriptional activation[77]. Mehrzad et al. showed that AFB1 treatment at the low level (i.e., 20 ng/mL) significantly upregulated the mRNA expression of *TLR2*, *TLR4*, and *MyD88* genes in mouse astrocytes and microglial cells[21].

In summary, AFB1 and its metabolites could induce inflammatory response and cell pyroptosis, which may partly involve various signal pathways, including NLRP3, TLR2/4, NF-κB, and GSDMD signaling pathways (Fig. 3).

5.3 *Mitochondrial dysfunction and apoptotic pathways*

Mitochondria are fundamentally the cellular 'powerplant' and the main source of ATP[78]. Mitochondria are both sources and targets of ROS and RNS[78]. Excessive ROS or RNS production disrupt mitochondrial function, culminating in energy starvation that decreases cell viability. In neuronal cells, mitochondria are the most important organelle for calcium buffering and ATP production. Therefore, neuronal cells are highly susceptible to mitochondrial dysfunction. It has been reported that repeated exposure of rats to AFB1 significantly upregulated the activities of Na^+/K^+-ATPase and downregulated the activities of Mg^{2+}-ATPase in the nerve tissues; indicating mitochondrial energy metabolism is a key factor in AFB1-induced neurotoxicity[79].

AFB1-induced loss of mitochondrial membrane potential, may also contribute to the mitochondrial dysfunction in nerve cells[18]. Dietary exposure of chickens was found to perturb the function of mitochondrial respiratory complexes I, II, III, and V, causing a loss of mitochondrial membrane potential, leading to a decrease in ATP levels in the liver[80]. In line with these findings, the treatment of ECV 304 cells (a human umbilical endothelium cell line used model the blood brain barrier) with AFTs at the final concentration of 100 nmol/L, produced a marked decrease in the activity of mitochondrial respiratory complexes I, IV, V[81]. Collectively, these studies indicate that AFB1 may directly cause the loss of mitochondrial membrane potential and induce mitochondrial dysfunction by directly impairing mitochondrial respiratory chain activity. Park et al.[18] found that AFB1 exposure at the doses of 10−50 μmol/L for 24 h significantly upregulated mitochondrial calcium levels 2−6-fold in NHA-SV40LT cells. Inhibition of mitochondrial calcium overload could significantly inhibit AFB1-induced cytotoxicity in NHA-SV40LT cells, indicating that calcium overload-mediated mitochondrial dysfunction contributes to AFB1-induced neurotoxicity[18]. Similarly, Huang et al.[12] found that AFB1 treatment at the doses of 6 μg/mL for 24 h significantly increased the Bax/Bcl-2 ratio in IMR-32 cells. Consistently, a significant increase in the ratio of Bax/Bcl-2 in primary microglia and mouse BV2 cells treated with AFB1 and AFM1 was detected[19]. In another study, abnormal ultrastructure changes of mitochondria were detected in the sciatic nerve in rats after AFB1 exposure[17]. Furthermore, inhibition of oxidative stress by antioxidant *N*-acetylcysteine (NAC) significantly attenuated AFB1-induced ROS production and the increase of Bax/Bcl-2, finally inhibiting AFB1-induced cell death in BV2 cells[69]. These studies hint that mitochondrial dysfunction plays a vital role in AFB1-induced neurotoxicity.

Worryingly, evidence exists that AFB1 exposure could cause DNA damage by directly interacting with the DNA helix[1]. Huang et al.[12] reported that AFB1 treatment of IMR-32 neuronal cells at the final concentration of 2 μg/mL significantly induced DNA damage, which was evidenced by utility of the comet assay and the increased expression of γH2AX. Similarly, AFB1 exposure has been reported to induce DNA damage in primary microglia[19]. Notably, AFB1 exposure also downregulates the transcriptional expression of poly (ADP-ribose) polymerase 1 (*PARP1*), breast cancer susceptibility gene 2 (*BRCA2*), and RAD51 recombinase (*RAD51*) genes that play critical roles in the process of DNA repair; which likely exacerbates AFB1-induced DNA damage[12]. Moreover, AFB1 exposure could induce cell cycle arrest, and upregulate the expression of CDKN1A, CDKN2A, and CDKN2D genes in neuronal cells, which serve a cyto-protective role by repairing DNA damage[12]. Zhou et al.[69] found that inhibition of ROS production could reduce AFB1-induced G2-M phase arrest in BV2 microglia cells. In IMR-32 neuronal cells, AFB1 treatment induced apoptotic cell death in a dose and time dependent manner with the upregulation of caspases-9 and -3 expression[12]. Apoptotic cell death was induced by AFB1 exposure of mouse primary microglia and BV2 cells[19,69]. In a mouse model, AFB1 exposure over a ramped dosing schedule

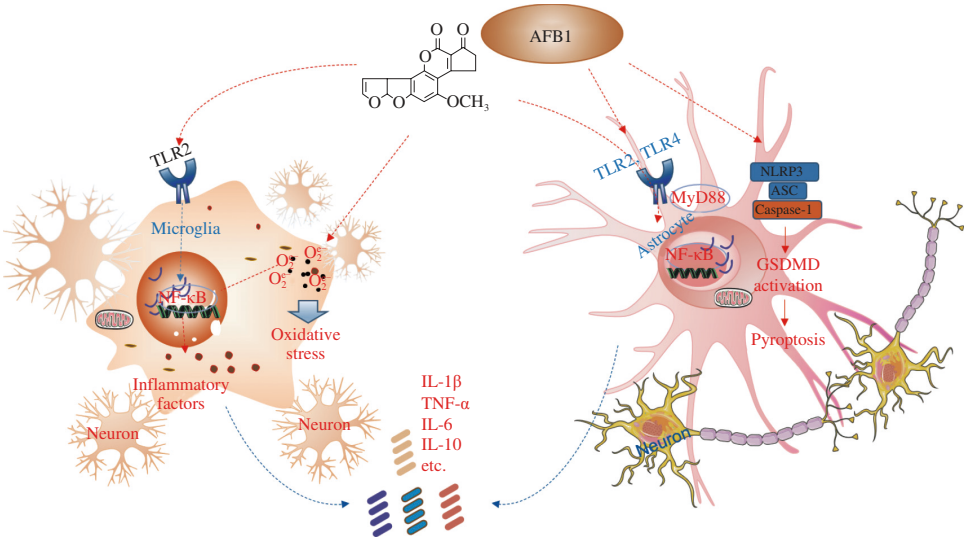

Fig. 3 AFB1 induces inflammatory responses, cell pyroptosis, and the critical signaling pathways in glial cells.

(i.e., 0.375, 0.75, and 1.5 mg/(kg·day), respectively, for 30 days) dose-dependently induce neuronal cell apoptosis in the spinal cord[69]. Oxidative stress is an important inducer of cell apoptosis, not surprisingly the inhibition of oxidative stress by antioxidant co-treatment significantly inhibited AFB1-induced apoptosis in nerve cells[69]. Similar results were obtained with HepG2 cells and in the liver or kidney tissues of mice[82-84]. In the liver or kidney tissues, AFB1 exposure could activate multiple apoptosis-related signaling pathways, including MAPKs, p53, and Akt pathways[85-86]. Park et al.[18] showed that AFB1 treatment could significantly inhibit the expression of phosphor (p)-Akt, and its downstream proteins p-p70s6k and p-ribosomal S6 kinase (s6k). The inhibition of the Akt pathway promoted AFB1-induced cytotoxicity in human NHA-SV40LT cells (a normal human astrocyte immortalized with SV40LT). In addition, inhibition of ERK/MAPK pathway by U0126, a small molecule inhibitor, could markedly inhibit AFB1-induced expression of p-ERK/MAPK protein and partly reversed AFB1-induced cell death[18]. These findings suggest that the inhibition of Akt pathway or the activation of p-ERK/MAPK pathway contributes to AFB1-induced neurotoxicity. However, there were no significant changes in the expression of p53 mRNA in AFB1-treated IMR-32 neuronal cells, indicating that the p53 pathway may not participate in AFB1-induced apoptosis in neuronal cells. Another studies investigated the effects of a lower dose of AFB1 (i.e., at 20 ng/mL) in mouse or human astrocytes and microglial (i.e., mouse BV2 cells and human NHA-SV40LT cells). The authors reported significantly upregulated mRNA expression of *p53*, *caspase-3*, and *caspase-8* genes[18,21]. Collectively, these studies indicate that AFB1-induced apoptosis may involves different signaling pathways in the different sub-types of nerve cells.

In overview, AFB1-induced neurotoxicity involves mitochondrial dysfunction, DNA damage and apoptosis, which may be partly dependent on the production of ROS, mitochondrial calcium overload, the downregulation of mitochondrial ATPase activities and activation of ERK/MAPK pathway (Fig. 3).

5.4 Protein kinases

The protein kinase C (PKC) pathway appears to be involved in AFB1 neurotoxicity. Souto et al.[20] found that acute exposure to AFB1 (oral administration at a signal dose of 250 μg/kg) significantly upregulated PKC activity in the cerebral cortex of rats after 48 h. It is well known that PKC is commonly involved in receptor desensitization, regulating membrane structure, regulating transcription, mediating the immune response, regulating cell growth, learning and memory[87].

6. Neuroprotective agents against AFB1-induced neurotoxicity

Many studies have reported that small molecular antioxidant compounds (e.g., quercetin, curcumin, and gallic acid, and dimethyl fumarate), Chinese herbal extracts (e.g., *Artichoke* leaf extract, *C. majus* ethanolic extract, pumpkin extract, and *C. sativus* L. tea) and probiotic supplements (e.g., *Bifidobacterium* sp. and *Lactobacillus* sp.) could effectively ameliorate AFB1-induced neurobehavioral abnormalities and neurotoxicity via ablation of the oxidative stress, inflammatory response, apoptotic or pyroptotic cell death. In the informative discussions below provide a summary of the current literature on these clinically promising neuroprotective agents (Table 1).

6.1 Small molecular antioxidant compounds

As discussed above a key mechanism of AFB1-induced neurotoxicity involves apoptotic or pyroptotic cell death via excessive ROS production, mitochondrial dysfunction, activation of NLRP3 inflammasome and upregulation of GSDMD (Fig. 4). So it follows, antioxidants such as NAC or the GSDMD inhibitor dimethyl fumarate can effectively inhibit AFB1-induced neurotoxicity[10,12,16,18-19,21]. Gugliandolo et al.[23] showed that oral administration of quercetin at 30 mg/kg per 3 days for 45 days (i.e., the cumulative dose is equal to 450 mg/kg) significantly improved AFB1-induced (i.e., oral administration at 0.75 mg/kg body weight per 3 days for 45 days) anxiety-like behavior in mice. Moreover, this quercetin supplementation regimen significantly downregulated the levels of MDA, upregulated the SOD and CAT activities and levels of GSH; and beneficially downregulated the levels of TNF-α and IL-1β in the brain tissue[23]. These data suggested that quercetin supplementation may offer a viable neuroprotection against AFB1-induced neurotoxicity by blocking oxidative stress and inflammatory responses. In another study, it was also reported that gallic acid supplementation at the final dose of 20 and 40 mg/kg could effectively ablated AFB1-induced neurobehavioral abnormalities, oxidative stress, inflammatory response, and apoptosis in the brain tissues[26]. Mazaheri et al.[24] found that low dose of AFM1 (i.e., 1 ppb, which is equal to 1 ng/mL) combined with *β*-lactoglobulin, a low-molecular-weight whey protein in milk, exhibited synergistic toxicity in PC12 neuronal cells. Curcumin pre-treatment could effectively block the synergistic neurotoxicity. Multiple studies have demonstrated that the beneficial effects of curcumin against AFB1-induced hepato-, nephron-, and immuno-toxicity is largely mediated via the activation of Nrf2 pathway and the inhibition of NF-κB pathways; which in turn culminates in the inhibition of oxidative stress, inflammatory responses, and apoptosis[82-84,88-96]. These valuable studies highlight the how small molecular antioxidants can be honed as food additives to prevent AFTs-induced neurotoxicity.

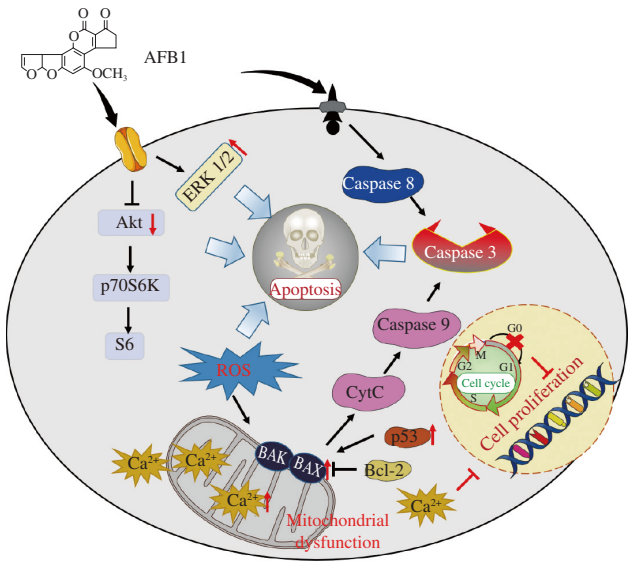

Fig. 4 AFB1-induced apoptotic cell death pathways in nerve cells.

Table 1
A tabulated summary of reported neuro-protective agents targeting AFB1-induced neurotoxicity.

Natural products/ bioactive substances	Models	Treatments	The protective effects	Reference
Gallic acid	Rats	Rats were orally administrated with AFB1 at 75 μg/kg body weight per day with or without with gallic acid at 20 or 40 mg/kg body weight per day for 28 days	Gallic acid supplementation significantly improved AFB1 exposure-induced anxiogenic-like behavior and the loss of motor activity. Corresponding, gallic acid supplementation significantly upregulated the activities of AchE, GST, CAT, SOD, GPX, and levels of GSH and IL-10, and downregulated the levels of NO and MPO, IL-1β, and TNF-α, and the activities of caspase-3 in the cerebrum and cerebellum of AFB1-treated rats	Adedara et al.[26]
Quercetin	Mice	Mice were orally administrated with AFB1 at 0.75 mg/kg body weight per 3 days with or without quercetin at 30 mg/kg body weight per 3 days for 45 days	Quercetin supplementation significantly improved AFB1 exposure-induced memory deficit and anxiety-like behavior. Meanwhile, quercetin supplementation significantly improved AFB1 exposure-induced inflammatory response and oxidative stress in the brain tissues	Gugliandolo et al.[23]
C. majus ethanolic extract	Rats	Rats were orally administrated with AFB1 at 80 μg/kg body weight per days with or without *C. majus* ethanolic extract at 300 mg/kg body weight per days for 28 days	*C. majus* ethanolic extract supplementation significantly downregulated the elevated levels of inflammatory and apoptotic markers and restoring the levels of AchE, dopamine and 5-HT in the cortex and hippocampus tissues of rats	Ra Kasem et al.[31]
Artichoke leaf extract	Rats	Rats were orally administrated with AFB1 at 72 μg/kg body weight per day with or without *Artichoke* leaf extract at 100 mg/kg body weight per day for 42 days	*Artichoke* leaf extract supplementation significantly inhibited AFB1-induced neuropathology changes, oxidative stress, and inflammatory response in the brain tissues of rats. It also upregulated the levels of AchE and MAO in the AFB1-treated brain tissues and improved the dysfunctional lipid profile, and dysregulation of lipid profile, glucose level, and insulin concentration	Ibrahim et al.[29]
Saffron (*C. sativus* L.) tea	Mice	Mice had ad libitum access to saffron infusion (90 mg styles/200 mL) for 2 weeks and were co-treated intraperitoneally with AFB1 at 0.6 mg/(kg·day) for 4 days	Saffron tea supplementation significantly improved AFB1 exposure-caused learning/memory impairment. Meanwhile, it also markedly reduced the levels of MDA, AchE, and MAO activities in the brain tissues of mice	Linardaki et al.[15]
Probiotic extracts	Rats	Rats were orally administrated with probiotic containing *Bifidobacterium* and *Lactobacillus* species at 2.5×10^{10} CFU/day, and co-treated with or without AFB1 at 25 μg/(kg·week) for 8 weeks	Probiotic supplementation significantly improved AFB1 exposure-induced the impairment of memory, locomotor activity, and anxiety, and depression-like behavior. Meanwhile, probiotic supplementation significantly inhibited the activation of glial cells, oxidative stress, and inflammatory response in the AFB1-treated brain tissues of rats	Aytekin Sahin et al.[27]

6.2 Chinese herbal extracts

In recent years, studies have found that several extracts of traditional Chinese medicine (including *Artichoke* leaf extract, *C. majus* ethanolic extract (CMEE), pumpkin extract, and *C. sativus* L. tea) could provide neuroprotective effects against AFB1-induced neurotoxicity in mice or rats[15,28-29,31,81]. Ibrahim et al.[29] found oral supplementation of artichoke leaf extract at 100 mg/kg for 42 days could inhibit AFB1-induced neurotoxicity in rats by increasing the levels of antioxidant enzyme activities, as well as reversing lipidemia, augmented plasmatic glucose, and concentrations of insulin. Notably, dietary supplementation with artichoke leaf extract has been demonstrated to serve a protective role against AFB1-induced liver toxicity in rats via the inhibition of oxidative stress[97]. Kasem et al.[31] found oral supplementation with CMEE at a dose of 300 mg/(kg·day) for 28 days could significantly inhibit AFB1-induced oxidative stress, inflammatory responses, apoptosis and reverse neurotransmitter depletion (e.g., AchE, dopamine, and 5-HT). Alonso-Garrido et al.[81] showed pumpkin extract (500 nmol/L) beneficially regulated the expression genes encoding mitochondrial complexes I, II and V to improve AFT-induced mitochondrial dysfunction in human ECV 304 cells. In another study, it has been found that Saffron (*C. sativus* L.) tea supplementation effectively ameliorated AFB1-induced learning and memory deficits by reducing oxidative stress and inhibiting MAO activity in the brain tissue of mice[15].

In summary, it is increasingly apparent that traditional Chinese medicine is a viable treatment against AFB1-induced neurotoxicity. Potential molecular mechanisms underlying these beneficial effects involve multiple molecular targets, including the genes involved oxidative stress, mitochondrial respiratory chain complexes and neurotransmitters.

6.3 Probiotic supplementation

Neurobehavioral abnormalities associated with gut dysbiosis, (i.e., significantly increased numbers of *Bifidobacterium* sp., and decreased numbers of *Lactobacillus* sp.) were observed in rats following oral administration of AFB1[9,27,98]. Aytekin Sahin et al.[27] study showed that of *Lactobacillus* and *Bifidobacterium* supplementation could effectively ameliorate AFB1-induced depressant-like behavior in a rat model. In addition, the neuroprotection provided by these probiotics could also relieve the deleterious effects on intestinal integrity, the regulation of microflora, or direct toxic effects of AFB1 to the intestine[27,99-100]. It also indicated the intestine-brain axis plays an important role in AFTs neurotoxicity. However, the precise molecular mechanisms remain poorly understood and necessitate further clinical trials.

7. Conclusions

Neurotoxicity is one of the most harmful effects of AFT exposure. Chronic exposure to AFB1 could lead to permeation across the blood brain barrier and accumulation in brain tissue. AFT neurotoxicity manifests into neuropathological changes such as various abnormal neurobehaviors, including depression, anorexia, learning and memory defects, and the impairment of locomotor activity. On the cellular and molecular levels, AFB1-induced neurotoxicity involves multiple actional mechanisms, including the induction of oxidative stress, the activation of glial cells, inflammatory response,

intestinal flora perturbations, abnormal changes of neurotransmitters, mitochondrial dysfunction, apoptosis, and pyroptosis. The critical signaling pathways involve the GSDMD, TLR2, TLR4, Akt, NF-κB, ERK/MAPK, PKC, cell cycle arrest, and mitochondrial apoptotic pathways. In view of the above, it is paramount that we pursue the development of novel neuroprotective agents for the treatment of AFB1-induced neurotoxicity. To date, several small molecular compounds (e.g., quercetin, curcumin, and gallic acid, and dimethyl fumarate), Chinese herbal extracts (e.g., *Artichoke* leaf extract, *C. majus* ethanolic extract, pumpkin extract, and *C. sativus* L. tea) or probiotics (e.g., *Bifidobacterium* sp. and *Lactobacillus* sp.) have shown promise as clinical agents for the amelioration of AFB1-induced neurobehavioral abnormalities and neurotoxicity by targeting the above-mentioned signaling pathways. These exciting findings highlight several future directions for prospective studies: 1) Human clinical trials and animal trials are required to fortify the neuroprotective effects of above-mentioned neuroprotective compounds or probiotics; 2) Probing the correlation between the environmental priority level of AFTs exposure and the induction of neurotoxicity-whether it could aggravate the occurrence of neurodegenerative diseases, such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, etc; 3) Deciphering the precise molecular mechanisms of gut dysbiosis contributing to AFB1-induced neurotoxicity; 4) Taking a deep dive into the neurochemistry and signaling basis of AFB1 exposure-induced depression. In conclusion, we are hopeful that this review provides valuable insights, and stimulates broader discussions towards the development effective neuroprotective agents targeting AFTs.

Conflicts of interest

All authors declare there are no conflict of interest.

Acknowledgments

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