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Fumonisin B1 neurotoxicity: Preclinical evidence, biochemical mechanisms and therapeutic strategies

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ABSTRACT

The neurotoxic effects of fungal toxins in both humans and animals have been well documented. Fumonisin B1 (FB1), a mycotoxin produced by fungi of the *Fusarium* species, is the most toxic fumonisin variant whose neurotoxic effect is still being elucidated. This review highlights the biochemical aspects of FB1 neurotoxicity, such as its mechanisms of action as well as therapeutic strategies. Both *in vitro* and *in vivo* studies have demonstrated that alteration in sphingolipid metabolism is a major event in FB-induced neurotoxicity. Studies have also shown that neurotoxicity due to FB1 involves dysregulation of several biochemical events in the brain, such as induction of oxidative stress and inflammation, mitochondrial dysfunction and associated programmed cell death, inhibition of acetylcholinesterase and alteration of neurotransmitter levels, decreased activity of Na^+K^+ ATPase, as well as disruption of blood-brain barrier. This review highlights the potential public health effects of FB1-induced neurotoxicity and the need to limit human and animal exposure to FB1in order to prevent its neurotoxic effect. Moreover, it is hoped that this review would stimulate studies aimed at filling the current research gaps such as delineating the effect of FB1 on the blood-brain barrier and appropriate therapies for neurotoxicity caused by FB1.

1. Introduction

Fumonisins are mycotoxins that are generated from the *Fusarium* species, principally *Fusarium verticillioides* and *Fusarium proliferatum*. Fumonisin was discovered in 1970 (Fig. 1) but finally named in 1988 after isolation of *F. verticillioides* strain MRC 826 from moldy corn [1–3]. Fumonisins contaminate foods of plant and animal origin, mainly maize based products, constituting a menace to the wellbeing of animals and humans [4–6]. Chemical analyses have indicated that there are about twenty-eight isomers of fumonisin, and that fumonisin B1 (FB1) is the most common and noxious [7,8]. However, hydrolyzed FB1 was reported to be less toxic than FB1 and could be a feasible means of limiting exposure to FB1 as well as toxicity caused by FB1 [9–11].

FB1 has been reported to cause toxicity in various mammalian organs, including neurotoxicity [12–14], hepatotoxicity [15], nephrotoxicity [16] and immunotoxicity [17]. Nonetheless, the incidence and severity of toxicity is dependent on strain and species [18]. In addition, the mycotoxin has been indicated as a potential mutagen by the International Agency for Research on Cancer [19]. Previous studies have also pointed out that FB1 elicits deleterious effects on cell development, differentiation, programmed cell death, gut structure and permeability. The neurotoxicity of FB1 has been ascribed to its inhibition of ceramide synthase (otherwise known as sphinganine/sphingosine N-acyltransferase), which is an important enzyme in sphingolipid metabolism [20].

Several *in vivo* and *in vitro* studies have reported various presentations of neurotoxicity arising from FB1 including neural tube defects (NTD), inhibition of neurodevelopment, neuronal degeneration, necrosis and disruption of the functions of astrocytes, all of which impair brain functions [21,22]. However, research on amelioration of neurotoxicity caused by FB1 is not yet as extensive as it can be. Despite the dearth of studies on the neurotoxicity of FB1 in humans, outcomes of

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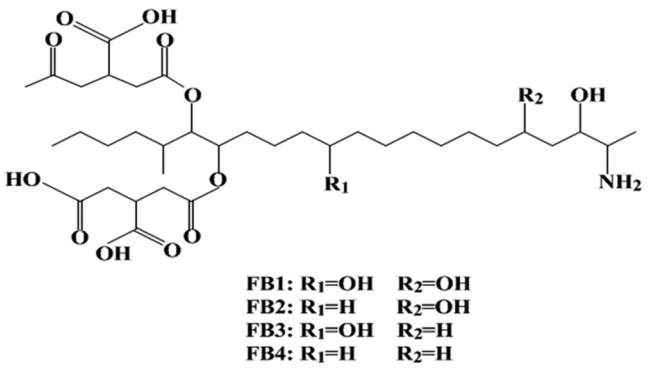

Fig. 1. Structure of Fumonisin B1(Bartok et al., 2010).

both *in vitro* and *in vivo* studies on FB1-induced neurotoxicity, such as incidence of NTD and alterations of sphingosine/sphinganine ratio, align with presentations of FB1 neurotoxicity in humans. For example, NTD was linked to consumption of FB1 in some parts of Texas, Transkei in South Africa and northern provinces of China [13]. In addition, alterations in sphingosine/sphinganine ratio, which is a common feature of FB1 exposure in experimental animals, is also utilized as an indicator of FB1 exposure in humans [23].

It was earlier reported that a lower volume of studies related to FB1 neurotoxicity, compared with its other forms of toxicity, was being conducted [13]. This review aimed to highlight various aspects of neurotoxicity caused by FB1 such as its pharmacokinetics, mechanisms of neurotoxic effects and potential means of ameliorating its neurotoxicity. In addition, it is hoped that the review would stimulate further research into FB1 neurotoxicity, especially the molecular details of its neurotoxic effect and if/how it enters the brain through the blood-brain barrier. This can generate better strategies for counteracting its deleterious effects.

2. Fumonisin B1 disrupts sphingolipid metabolism

Inhibition of ceramide synthase by FB1 has been suggested to underpin its toxicity. This is due to the structural similarity between FB1 and the sphingoid bases (sphingosine and sphinganine), which are substrates of ceramide synthase. This inhibitory effect of FB1 on ceramide synthase however varies with species-dependent pharmacokinetics [24]. The competition of FB1 with sphingosine and sphinganine for binding to ceramide synthase suppresses ceramide synthesis, thereby inhibiting the synthesis of more complex sphingolipids which are found in abundance in the brain, as illustrated in Fig. 2. [20,25]. Moreover, inhibition of ceramide synthase by FB1 leads to accumulation of the sphingoid bases, accumulation of both sphingosine-1-phosphate and sphinganine-1-phosphate, as well as alteration of the sphingosine/-sphinganine ratio. All of these have been reported to be veritable indicators of FB1 exposure [26–28]. Sphingosine-1-phosphate has been identified as a pleiotropic signaling molecule for which previous studies have provided evidence of significant contribution towards maintenance of integrity and permeability of the blood-brain barrier [29,30]. Sphingosine1-phosphate binds to five G-protein-coupled receptors on membranes (S1PR1–5), with studies identifying expression of S1PR1, S1PR2 and S1PR3 on the blood-brain barrier [31]. Binding of sphingosine-1-phosphate to SIPR3, which is expressed on the brain epithelium, was reported to elicit signaling cascades that are pro-inflammatory in nature [32].

It was earlier reported that mycotoxins can cross the blood-brain barrier by direct diffusion across the BBB due to their lipophilic nature or by disruption and damage of the BBB, thereby leading to the typical exchange of materials across the BBB [33]. However, reports of the ability of FB1 to cross the blood-brain barrier have been rather inconsistent. A study with carp fed 100 mg/kg of FB1 showed that FB1 crosses the blood-brain barrier and acts directly in the brain, causing neuronal degeneration and death [22]. This contrasts with another study which indicated that the imbalances in brain sphingolipid levels upon FB1 exposure could arise from blood sphingolipids, and not from direct activity of FB1 in the brain [34]. The outcome of this study was reinforced by another study on chickens fed 20.8 mg/kg of FB1 for 9 days showed

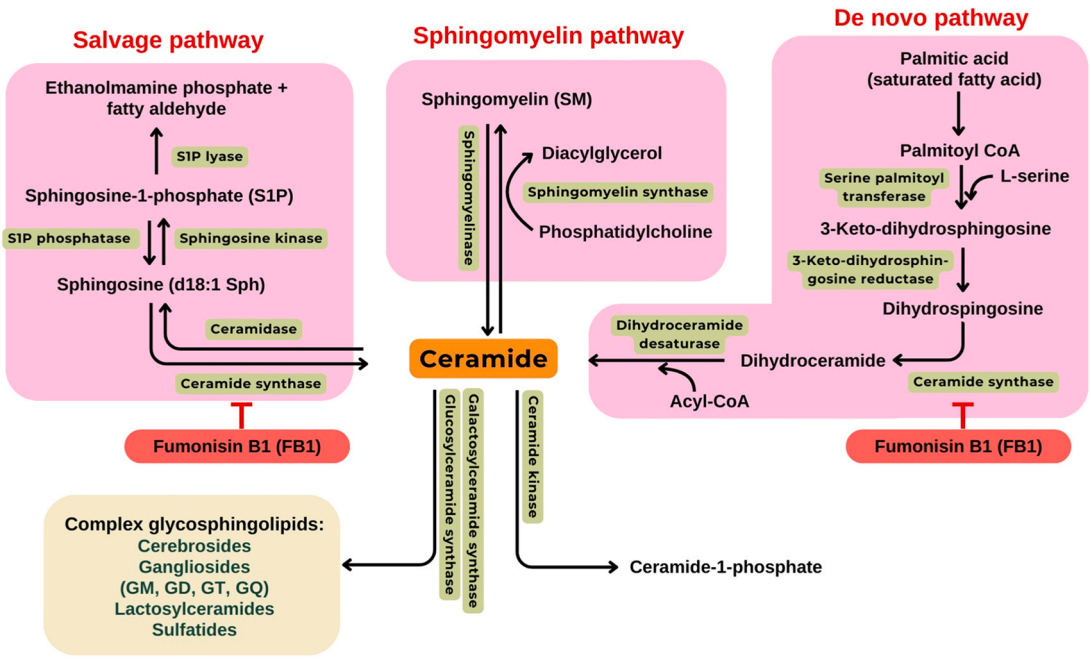

Fig. 2. Biosynthetic pathways of Sphingolipids. FB1 inhibits ceramide synthase in both the de novo and salvage pathways of sphingolipid biosynthesis. FB1 inhibits ceramide synthase in both the de novo and salvage pathways of sphingolipid biosynthesis, hence reducing ceramide synthesis. This indicates FB1 has the potential to dysregulate neuronal development, cause neuronal cell death, culminating in its neurotoxic effect.

changes in brain FB1 levels, even though FB1 was not detected in their brain [16]. It was also revealed that the passage of FB1 across the blood-brain barrier is effectively inhibited, thereby preventing its cerebral accumulation [35]. It could be proposed that the conflicting reports on the penetration of the blood-brain barrier by FB1, like its inhibition of ceramide synthase, is species-specific. Studies to delineate this the activity of FB1 in this regard are therefore required.

3. Fumonisin B_1: from the farm to our plates

FB1 has been demonstrated to contaminate crops such as cereals [36, 37], sugarcane [38,39], legumes [40,41], plants utilized for therapeutic purposes, beverages, [42], and comestibles generally [43], however, maize and value-added products of maize are more susceptible to FB1 poisoning [13,44,45]. The change in global climate, generation of new phenotypes in plants, and poor harvesting or storage practices have been suggested to facilitate the growth of FB1 on farm products [46,47].

Contamination of food products by FB1 has been reported in different parts of the world. According to previous studies, the exposure level of FB1 varies with country. It was found to be as low as 0.087 ng/kg body weight per day in South Korea and as high as 4.12 μg/kg body weight per day in Mexico [28]. In a 2002 report on studies across continents by the International Agency for Research on Cancer, it was reported that the average percentage occurrence of FB1 in maize-based products were 63.6%, 74.9%, 61.7%, 76.2% and 49.6% respectively for North America, Latin America, Europe, Africa, Asia and Oceania [19]. It was also earlier reported that FB1 contamination of food is more prevalent in temperate tropical regions because FB1 is better adapted to hot and humid environments [28]. In 2001, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) assigned a provisional maximum tolerable daily intake (PMTDI) of 2 μg/kg for FB1, FB2 and FB3, either alone or in combination. Subsequent meetings of the committee in 2011 and 2016 have retained the value [48].

The concentrations of fumonisin in maize feed have been estimated to be as high as 300 mg/kg in Hungary and the United States of America [19,49]. In São Paulo, Brazil, the concentrations of FB1 in 120 samples of corn and corn-based products were assessed and coarse corn was shown to have 474.6 μg/kg, with the highest concentration in all the assessed corn products [50]. Furthermore, processing techniques such as milling have been shown to influence the concentration of FB1 in corn and corn-based products. Corn meal and corn grits which are usually milled showed the highest concentration of FB1and FB2 when compared with corn grain and corn flour [51].

Previous studies have suggested that exposure of humans to FB1 varies with level of urbanization as well as level of maize consumption [52]. Exposure to FB1 tends to be higher in regions where high level of maize and its products are consumed, such as was observed in Central and South Americas, northern provinces of China, as well as some parts of southern Africa [21]. FB1 was found in very high concentrations in 80 out of 388 samples in maize and maize based products assessed in the Shamva, (with a median concentration of 292.15 μg/kg FB1) and Makoni (with a median concentration of 360 μg/kg FB1), which are rural areas in Zimbabwe. In addition, the evaluated average probable daily intake (APDI) of FB1 in these maize products had values greater than the provisional maximum tolerable daily intake (PMTDI) by the World Health Organization [53].

In some areas of Guatemala, average FB1 content in tortilla, a commonly consumed maize product, ranged between 8 – 27 μg/g dry weight, with over 60% of tortillas containing at least 10 μg FB1/g dry weight [54]. A retrospective study on the prevalence of NTD in Guatemala in 2000 revealed 106 NTD cases per 10,000 live births, a significantly higher rate than about 3 NTD cases per 10,000 live births recorded for the general population in USA [55]. High incidences of NTD in the Transkei region of South Africa and northern provinces of China were associated with consumption of maize contaminated by fungi while NTD incidences in Texas and Guatemala were associated with high consumption of tortillas [21]. In contrast, low levels of FB1 were observed in 120 samples of corn tortillas collected within two years in Veracruz, Mexico. These FB1 concentrations were lower than regulatory limits for fumonisin in edible foods in the United States of America (2000–4000 μg/kg) and in the European Union (1000 μg/kg) [56]. High concentration of FB1 was also discovered in corn-based infant formula in Germany in 1999 but the concentration reduced in the latter years [57]. This suggests that the levels of fumonisins in similar foods may differ in countries depending on time and the processing technique utilized.

4. Toxicokinetic of Fumonisin B1

The toxicokinetic of FB1 encompasses absorption, distribution, metabolism and excretion (ADME). Absorption of FB1 occurs principally in the gastrointestinal tract (the stomach and small intestine). The rate of absorption depends on the concentration of the mycotoxin, the route of administration and the time of administration [58]. The absorption of FB1 is minimal, as an insignificant amount is noted in the systemic circulation after oral exposure in cows and hens [19]. Studies have earlier reported a rapid decline in the level of FB1 or its metabolites in the systemic circulation after an intravenous injection [59,60]. While reasons for the weak absorption of FB1 are still being investigated, its poor transport across the gastrointestinal tract, especially in the intestine, as well as its hydrolysis by the intestinal epithelium, have been suggested to be partly responsible [61,62].

The major site of metabolism of FB1 is the liver; however, FB1 can also be metabolized by enzymes located in the digestive tract and rumen of ruminants [63]. Both *in vivo* and *in vitro* studies have shown that FB1 is metabolized by ceramide synthase to N-acyl-FB1 derivatives, majorly in the liver, but also in the kidney [64]. Hydrolysis of FB1 has been shown to result in the formation of HFB1, a slightly less potent ceramide synthase inhibitor [65]. A study indicated that in the intestinal microbiota of piglets, FB1 is partially hydrolyzed to HFB1 or aminophenol, which is a more toxic metabolite [66]. This metabolic reaction is yet unconfirmed in other animal species [10], though documented in experiments with human cell lines and rats [64,65]. However, metabolism of FB1 did not occur in bovine liver microsomal preparations [67]. Fumonisin B1 is poorly distributed in tissues due to its hydrophilic properties and high solubility in water [68]. The distribution and accumulation of FB1 has been shown to be higher in tissues than in circulation [69]. The distribution and excretion of FB1 have been well reported in literature [59,70–73].

5. Molecular comparison of ceramide synthases

We analyzed the similarity between ceramide synthase proteins, ceramide synthases (CerS) 1 and 2 between two organisms *Mus musculus* (MOUSE) and *Homo sapiens* (HUMAN). The CerS1 is expressed preferentially in the brain, and the CerS2 preferentially is expressed in the liver and kidneys [74]. These enzymes were analyzed because this review shows FB1 inhibits the activity of ceramide synthase, hence altering the metabolism of sphingolipids.

The selected protein sequences were extracted from the public database, UniProt www.uniprot.org [75], with the following codes: P27545, Q924Z4 to CerS1 and CerS2, respectively in *Mus musculus* and P27544, Q96G23 to CerS1 and CerS2, respectively in *Homo sapiens* (*CERS1 - Ceramide Synthase 1 - Homo sapiens (Human)* | *UniProtKB* | *UniProt*, n.d.; *Cers1 - Ceramide Synthase 1 - Mus musculus (Mouse)* | *UniProtKB* | *UniProt*, n.d.; *CERS2 - Ceramide Synthase 2 - Homo sapiens (Human)* | *UniProtKB* | *UniProt*, n.d.; *Cers2 - Ceramide Synthase 2 - Mus musculus (Mouse)* | *UniProtKB* | *UniProt*, n.d.) [76,77]. The basic local alignment search tool (BLAST) was used to search for similarity between ceramide synthases [78]. First, the enzymes in the same organism were analyzed, searching through the alignment tool for the percentage of identity and similarity of the amino acid sequence of the structures [79].

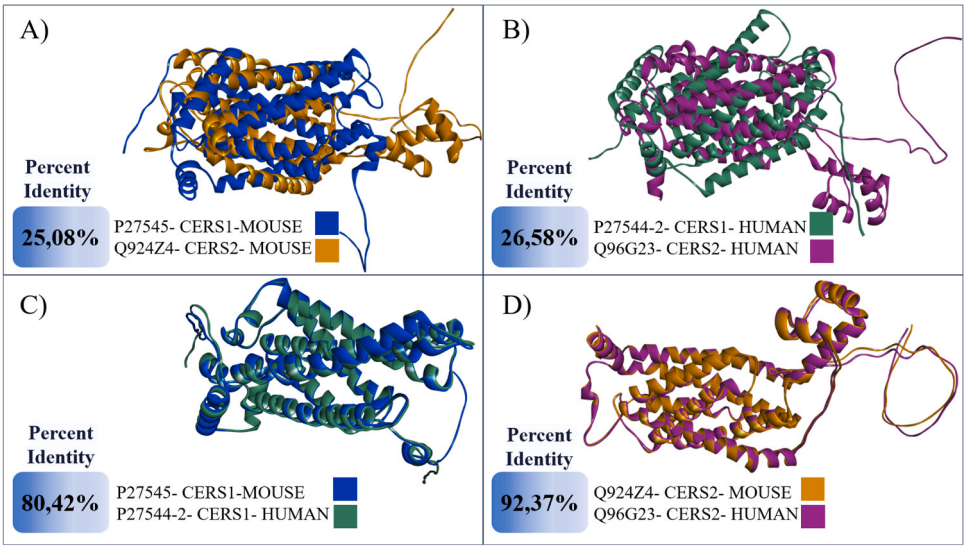

Fig. 3. Ceramide Synthase I and II in mouse and humans. There is percentage identity of 25.08% between Cers1 and Cers2 of mouse (A); and 26.58% between Cers1 and Cers2 of human (B). However, the percentage identity of Cers1 is 80.42% between mouse and human (C), while the percentage identity of Cers2 between mouse and human is 92.37% (D).

Secondly, similarities were analyzed by comparing the same enzymes between the two organisms.

To analyze the similarity of the three-dimensional structures of the proteins covered, the superimpose tool contained in the Discovery Studio Visualizer program was used (*BIOVIA Discovery Studio - BIOVIA - Dassault Systèmes®*, n.d.) [80]. The files in PDB (protein data bank) format were extracted from the same code as the UniProt database, however all the structures analyzed were generated by a predicted method. To date, no crystals have been analyzed and deposited from experiments for these organisms. Most of the ceramide synthase structures analyzed have high model confidence, which allowed greater accuracy in superimpositions. In the Discovery Studio Visualizer Program, the structures were overlaid using the "Molecular Overlay" tool, with the alignment parameters 50 % steric and 50 % electrostatic based on the consensus. Four studies were carried out, the first two, aligning different ceramide synthase, based on the same organism, and the last two, comparing the same enzyme, between different organisms.

6. Similarities between mouse and human ceramide synthases

Ceramides are a class of lipids that play crucial roles in diverse cellular processes, including regulation of cell growth, differentiation, apoptosis, and stress response. In ceramide metabolism, ceramide synthases (CerSs) are key enzymes responsible for the generation of ceramides from sphingosine and acyl-CoA [74,81,82]. In mammals, the ceramide synthase family is composed of six distinct members (CerS1 to CerS6), each with unique specificity for different acyl-CoAs and therefore producing ceramides with different fatty acid chains [74]. This functional and structural diversity allows ceramides to participate in a wide range of biological functions [83]. Dysregulation of ceramide synthases, and consequently, ceramide metabolism, is associated with several diseases, including cancer, neurodegenerative diseases, diabetes and cardiovascular diseases.

Therefore, understanding the specific function of each CerS offers potential therapeutic targets for pharmacological interventions [82, 84–87]. The CerS1 preferentially synthesizes ceramides containing stearic acid (C18:0) and is highly expressed in the brain. It has been shown that the CerS2 preferentially synthesizes long-chain ceramides (C20-C26) and is widely expressed in the liver and kidneys [74,81]. For this reason, these ceramide synthases were selected for the present study, seeking to analyze the similarity of the structures of CerS 1 and CerS 2 between *Mus musculus* (mouse) and *Homo sapiens* (human), to further understand the similarity between the ceramide synthase structures in these mammals, and understand their roles in the metabolism of FB1.

Using the CerS 1 and 2 structures of these organisms, deposited in UniProt (uniprot.org), a structural and percentage of identity comparison was carried out, using the amino acid sequence of each enzyme, together with the predicted three-dimensional structures. Using the UniProt tool, Basic Local Alignment Search Tool (BLAST), comparisons were made between enzymes from the same organism, and between different organisms, maintaining the same type of ceramide synthase, as shown in Fig. 3. There is 25.08% identity between Cers1 and Cers2 of mouse; and 26.58% identity between Cers1 and Cers2 of human. However, the percentage identity of Cers1 is 80.42% between mouse and human, while the percentage identity of Cers2 between mouse and human is 92.37%.

7. Preclinical models of Fumonisin B1- mediated neurotoxicity

Due to the limitation of human brain tissue availability, direct assessment of biomarkers is usually not possible. Therefore, neurobehavioural evaluations are mostly used as surrogate markers for impairments to the functions of the human brain, including neurotoxicity [88,89]. Conventionally, experimental animals are utilized for evaluating general neurotoxicity, developmental neurotoxicity as well as mechanisms of neurotoxicity of compounds because they mimic the biochemical and physiological environments in humans. I*n vitro* models are also utilized to complement animal studies because they circumvent the ethical issues associated with animal studies, and they produce consistent results given that they are generated from a single ancestor cell thereby generating cell populations that are homogeneous in nature. More importantly, cell lines derived from human sources, such as the SH-SY5Y human neuroblastoma cell line, eradicate issues about differences across species [90,91].

7.1. Cell studies on Fumonisin-B1 induced neurotoxicity

Cell studies can be instrumental to study the mechanisms of action of several toxic agents that possess the ability to alter cellular homeostasis. The somewhat contrasting results about the cytotoxicity of FB1 can be linked to factors such as cell source or type, species, tissue used and the

Table 1
Salient mechanisms of Fumonisin B1(FB1) induced neurotoxicity observed in cell-based studies.

Model	Experiment	Estimated Assays	Principal Results	References
Hippocampal cultures	100, 50 or 20 μM FB1 for 11 days	Viability, RONS, apoptosis, Proteome changes	Increase in cell death and RONS. Upregulation of ornithine aminotransferase, nucleophosmin 1, valosin containing protein, peroxiredoxin 6, prohibitin, prolyl 4-hydroxylase, Atp5b protein.	[34]
Aggregating cell cultures of fetal rat telencephalon	40 μM FB1for 10 days	Monitoring the effects of FB1 at different developmental stages of cell culture.	Delayed oligodendrocyte development and impaired myelin formation and deposition but did not cause cell loss and had no effects on neurons.	[85]
Rat astrocytes	10, 50 and 100 μM for 48, 72 h and 6 days	Oxygen free radicals, caspase−3 activity and DNA damage in cell death	DNA damage of apoptotic type and genotoxicity confirmed.	[86]
Rat C6 glioma cells	2.5–54 μM FB1 for 2 h	Cell viability, protein and DNA syntheses and cellular cycle	Cytotoxicity and cell death, protein and DNA syntheses inhibition, cell cycle arrest.	[87]
Human U−118MG glioblastoma cells	0.01–100 μM FB1 for 0.5–144 h	Reactive oxygen species (ROS), lipid peroxidation, intracellular reduced glutathione (GSH) levels, cell viability, caspase−3-like protease activity and DNA fragmentation.	Increased lipid peroxidation, ROS, caspase−3-like protease activity and internucleosomal DNA fragmentation; decreased GSH levels and cell viability.	[88]
Human SH-SY5Y neuroblastoma, rat C6 glioblastoma and mouse GT1–7 hypothalamic cells	0.1 and 100 μM FB1 for 0–144 h	ROS, lipid peroxidation and cell viability.	Increasd ROS production in C6 glioblastoma and GT1–7 hypothalamic cells but not in SH-SY5Y cells. Decreased GSH levels, increased MDA-formation and necrotic cell death in all cell lines.	[89]
SH-SY5Y neuroblastoma cells	50 μM FB1 for up to 48 h	Evaluation of mitochondrial dysfunction, endoplasmic reticulum stress and cell death	Increased ER stress, elevated caspase-independent cell death, mitochondrial dysfunction	[90]
Astrocytes and oligodendrocytes in primary cultures of rat cerebrum	0. 5–75 FB1 for 5, 10 and 15 days	Sphingosine and sphinganine levels	Diminished sphingosine levels, increased sphinganine levels and sphinganine/ sphingosine ratios.	[91]
microglial (BV−2) and neuroblastoma (N2A) cell lines, primary astrocytes and cortical neurons.	25 and 50 μM FB1 for 4 days (BV−2 and N2A) or 25 and 50 μM FB1 for 4 and 8 (astrocytes and cortical neurons)	Sphingosine and sphinganine levels, cell viability.	25 μM decreased viability in BV−2 cells, 50 μM caused necrotic but not apoptotic cell death in both BV−2 and primary astrocytes. Increased TNFalpha and IL−1beta in BV−2 cells and primary astrocytes. Accumulation of free sphinganine and decrease in free sphingosine levels in all cell types.	[92]
Neurulating mouse embryo on 9th day of gestation	2.0 – 100 μM FB1 for 26 h, 50 μM FB1 for 2 h	Neural tube defects	Failure of neural fold fusion in several brain regions, hypoplasia of frontonasal prominence	[93]

duration of incubation [92]. *In vitro* study using FB1 (10–100 μM) was demonstrated to increase the basal activity of neurons and neuronal networks in cell cultures or in hippocampal slices from 18-day-old rats. This study indicated that hippocampal cells exposed to 20–100 μM FB1 displayed fluctuations in the excitability of the neurons as seen in c-fos activation and reduction in the spread of labelled neurons in the hippocampus which ultimately resulted to increased cell death [35]. Further *in vitro* studies have shown that the exposure of brain cells assembled from embryonic rat telencephalon to FB1 at concentrations between 3 and 40 μMol/L for 10 days were neurotoxic, disrupted myelin formation and decreased oligodendrocyte maturation. However, FB1 was non-cytotoxic to glial cells [93]. This was further supported by another study which showed that there was no alteration in cell viability in rat primary astrocytes exposed to 50 μMol/L FB1 for 6 days [94]. Nonetheless, several studies have suggested the ability of FB1 to induce programmed cell death in glial cells. Mobio et al. (2000) showed that FB1 at 3 μMol/L and 54 μMol/L for 1 day reduced the cell survival of C6 glioblastoma to about 65 %, although this was not concentration-dependent because concentrations greater than 9 μMol/L did not induce programmed cell death [95]. Furthermore, human U-118MG glioblastoma cells exposed to FB1 at 0.1 μMol/L and 100 μMol/L for 12–144 h had diminished cell survival at only the highest concentration of 100 μMol/L after 72 and 144 h post incubation. Also, increased caspase-3-like protease activity and internucleosomal DNA fragmentation were observed in the cells [96].

Another study showed that cell viability was diminished by 20% on exposure of human SH-SY5Y neuroblastoma cells and mouse GT1–7 hypothalamic cells to 100 μMol/L FB1 after 48 hours, with further reduction of cell viability by 30% observed after 72 hours and 144 hours [97]. In addition, 50 μM FB1 was reported to exert its neurotoxic effect on SH-SY5Y neuroblastoma cells via activation of poly (ADP-ribose) polymerase (PARP)-associated and caspase-independent cell death. The study showed that FB1 instigated increased expression of Bax, a pro-apoptotic protein, and cytochrome C, an indication of the involvement of mitochondria in FB1 neurotoxicity. Moreover, the study revealed that FB1 elicited endoplasmic reticulum stress as shown by increased expression of inositol requiring enzyme-1-α (IRE1-α) and protein kinase R-like endoplasmic reticulum kinase (PERK); increased activation of C/EBP homologous protein (CHOP); and higher intracellular level of Ca^{2+}. Translocation of apoptosis inducing factor (AIF) from mitochondria to nucleus and accumulation of PAR, which is a product of PARP-1 activation as well as mitochondrial and cellular accumulation of reactive oxygen species, were also reported in the study [98].

Studies have shown that exposure of primary cultures containing astrocytes and oligodendrocytes from 2-day old Sprague Dawley rats to relatively high concentrations of 0.5, 5, 10, 25, and 75 μM FB1 for 10 days resulted in disruptions in levels and ratio of the sphingoid bases. In addition, FB1 increased the number of process-bearing cells and activity of 2′,3′-cyclic nucleotide 3′-phosphohydrolase. This is an indication of the potential of FB1 to alter the differentiation or proliferation of cultured cells [99]. Using two different cells, murine neuroblastoma Neuro2a cells (N2a) and microglial cells (BV-2), as well as two different FB1 exposure times - 0.625–50 μM for 4 days; and 25 μM FB1 for 24 hours, representing long- and short-term exposure respectively, it was observed that FB1 caused necrotic cell death in the cells, altered sphingolipid metabolism, increased levels of sphinganine and lowered free sphingosine (So) levels. Furthermore, the expression of cytokines, such as TNFα and IL-1β was reduced in BV-2 cells but not N2a cells [100]. Sadler et al. (2002) reported that FB1 caused NTD in neurulating mouse embryo in a dose-dependent manner. Using mouse embryo on

Table 2
Salient mechanisms of Fumonisin B1(FB1) induced neurotoxicity observed in animal-based studies.

Model	Experiment	Estimated assays	Principal Results	References
Horses	Filly - 59.5 mg/kg FB1 for 33 days; and colt - 44.3 mg/kg FB1for 29 days	Nervous signs	Apathy, changes in temperament, loss of coordination, paralysis of the lips and tongue.	[94]
Postnatal rats	0.4 or 0.8 mg/kg/day FB1 subcutaneous from postnatal days (PND) 3 to PND 12	Sphingolipid metabolism	Increased sphinganine (Sa) levels and Sa/sphingosine (So) ratios, hypomyelination	[95]
Pregnant LM/Bc and SWV mice on embryonic day 7.5–8.5	20 mg/kg for 1 day	Sphinganiine−1-phosphate level	Elevated sphinganine−1-phosphate levels	[96]
Male Wistar rats	1 and 4 mg/kg FB1 + FB2	Neuronal density, brain mitochondrial oxygen consumption	Reduction of neuronal density and cell body area of myenteric and nitergic neurons, reduced isolated mitochondrial oxygen consumption (respiratory activity)	[14]
Male and female Wistar rats	15, 50 and 150 ppm in feed for 4 weeks	Neurotransmitters	Stable levels of norepinephrine, dopamine and dopamine metabolites in both sexes of rats. Stable levels of norepinephrine, serotonin and its metabolites in the pineal body	[99]
C. elegans	200 μg/mL of FB1 for 24 h and > 100 μg/mL for 48	Serotonin, GABAergic neurotransmission	Destruction of GABAergic and serotogenic neurons, altered expression of genes involved in GABAergic and serotogenic neurotransmission	[100]
Fischer rats	70 % black mold + 1 mg FB1 per kg of diet for 17 days	Neurotransmission	Reduced brain acetylcholinesterase activity	[101]
6-week-old Balb/c mice	5 mg/kg FB1 and 2.8 mg/kg HFB1 via gavage for 21 days	Brain structure, oxidative stress, sphinganine/sphingosine ratio, exploratory behavious	Altered brain structure and exploratory behaviour, increased oxidative stress, disturbed glutamate/GABA ratio	[102]
Male C57BL/6 mice	8 mg/kg FB1 (single dose) + pentylenetetrazol	Brain excitability and mitochondrial function	Higher mitochondrial membrane potential, increased Na^+/K^+ ATPase in cerebral cortex	[103]
Male Large White weanling pigs	0.2, 5.0, 10.0 and 15.0 mg FB1/kg of feed for 6–10 weeks	Evaluation of regional brain and hypophyseal activities of AChE	Decreased activity of AChE in pons, amygdala, hypothalamus and the medulla oblongata	[104]
Female BALB/c mice	10 or 100 μg FB1 for 7 days (intracerebroventricular and subcutaneous)	Sphinganine levels, inflammation, neuronal health	Intracerebroventricular administration: cortical neurodegeneration, asctocytes activation, sphinganine accumulation and increased expression of TNF-α, IL−1β, and interferon-γ. Subcutaneous administration: mild cortical sphinganine build-up	[105]
Cyprinus carpio L	100 mg kg−1 or 10 mg kg−1 of FB1 in feed for 42 days	Histopathology, cerebral oedema, experimental toxicosis	Vacuolated, degenerate, or necrotic neural cells scattered around damaged blood capillaries and in the periventricular area.	[22]

day 9 of gestation, cultured in medium for both long-term exposure (2.0 – 100 μM FB1 for 26 h) and short-term exposure (50 μM FB1 for 2 h), FB1 generated NTD as evidenced by failure of neural folds fusion in the midline in different brain regions of the midbrain, forebrain and hindbrain. This is accompanied by hypoplasia of frontonasal prominence as well as reduced growth of maxillary and mandibular regions, in both long-term exposure and short-term exposure. This effect was however prevented with folinic acid supplementation [101].

Some of the mechanisms of FB1-induced neurotoxicity observed in cell-based studies are shown in Table 1.

7.2. Animal studies on Fumonisin B1-induced neurotoxicity

Animal studies have demonstrated FB1-induced neurotoxicity via damage to neurons in the brain of experimental animals. One of the earliest studies on the neurotoxicity of FB1 was equine leukoencephalomalacia (ELEM) in horses intravenously exposed to 125 mg/kg bw FB1 for 7 days. The horses showed lesions identified as features of ELEM; oedema of the brain and focal necrosis in the medulla oblongata [102]. Increased levels of sphinganine and sphinganine/sphingosine ratios were also observed in the brain of post-natal day rats (PND 3 - PND 12) subcutaneously exposed to 0.4 and 0.8 mg/kg FB1. This was accompanied by hypomyelination in the corpus callosum of experimental animals, suggesting that FB1 affects both sphingolipid metabolism and myelin deposition in developing rats [103]. Moreover, elevated levels of sphinganine-1-phosphate was observed in blood, plasma and embryonic tissue of pregnant LM/Bc and SWV mice on embryonic day 9.5 following intraperitoneal administration of FB1 (20 mg/kg/day) on embryonic day 7.5–8.5. The study correlated the high levels of sphinganine-1-phosphate via activation of its receptor signaling pathways with NTD [104].

A previous study reported that exposure of male Wistar rats (21 and 63 days old) to 1 and 4 mg/kg FB1 led to reduction of neuronal density of metabolically active jejunal myenteric neurons and a reduction in the cell body area of both jejunal myenteric and nitrergic neurons. Furthermore, FB1 at 50 μM also lowered oxygen consumption in brain mitochondrial isolates of experimental animals, an indication of reduced respiratory activity of the neurons, with attendant negative effect on the enteric nervous system [14]. The doses of FB1 in this study correspond to those present in heavily contaminated maize-based food utilized for human and animal feeding [105].

Disruption of neurotransmission has been identified as one of the mechanisms of neurotoxicity of FB1. A study with rats that consumed rodent diet containing *F. verticilloides* and corn contaminated with *F. verticilloides* reported an increase in the brain level of 5-hydroxyindoleacetic acid (H-HIAA), which is a major metabolite of serotonin without altering serotonin level [106]. A subsequent study by the same authors on the brain and pineal body of male and female rats did report that there were no alterations in brain levels of norepinephrine, dopamine, 5-hydroxyindoleacetic acid (5HIAA) and 5HIAA:serotonin ratio in either gender of experimental animals after exposure to feed containing purified FB1 (15, 50 and 150 ppm) for 4 weeks. The levels of norepinephrine, serotonin and its metabolites also remained stable in the pineal body [107]. Using the *C. elegans* as a model organism, a more recent study reported damaging effects of FB1 on serotonin neurotransmission. Exposure of *C. elegans* to 200 μg/mL of FB1 for 24 h and > 100 μg/mL for 48 h destroyed GABAergic and serotonergic neurons, with an accompanying decrease in GABA and serotonin levels. In addition, FB1 exposure altered the expression of genes associated with both serotonin and GABA neurotransmission. However, FB1 was found not to affect

dopaminergic, glutamtergic and cholinergic neurons [108]. It could be suggested that the observed differences in the neurotoxic effects of *F. verticilloides*-contaminated feed and purified FB1 in the above-described studies were due to the activities of other mycotoxins produced by *F. verticilloides*. This suggestion has been corroborated by the FAO/WHO report in 2017, which stated that the toxicity profile of pure fumonisins, cultured fumonisins and natural fumonisin-contaminated maize are different due to the differences in chemical composition of the test compounds [48].

A study described the prospect of synergistic interaction between FB1 and a phytopathogenic mold referred to as black mold (*Ustilago maydis*- Mexican truffle). In the study, a group of Fischer rats were exposed to diet containing 70 % black mold and the other group 70 % black mold + 1 mg FB1 per kg of diet for 17 days. The results from the study highlighted the synergistic neurotoxicity of *U. maydis* and FB1 in the latter experimental group as seen in 63 % decrease in AChE activity in the brain of the animals [109]. A study with 6-week-old Balb/c mice exposed to 5 mg/kg FB1 and 2.8 mg/kg HFB1 via gavage for 21 days demonstrated altered brain structure in the mice concomitant with alterations in exploratory behavior, reduction in speed, distance covered, movement time, learning abilities as well as increased distorted and irrelevant circuit. Furthermore, increased oxidative stress, sphinganine to sphingosine ratio, and alterations in amino acid metabolism and disturbance in glutamate and gamma aminobutyric acid (GABA) ratio were observed in the FB1 treated mice [110]. Exposure of adult male C57BL/6 mice to 8 mg/kg FB1 (single dose) via intraperitoneal injection 30 minutes before injecting pentylenetetrazol (PTZ) resulted in brain hyperexcitability, decrease of reaction time to myoclonic jerks, increased mitochondrial membrane potential and α1 sodium potassium ATPase activity in the cerebral cortex suggesting mitochondrial dysfunction as a potential mechanism of FB1 induced neurotoxicity [111]. Exposure of weanling pigs to formulated feed of autoclaved maize cultured with toxigenic strain of *F. verticillioides* caused deleterious effects in the brain of the animals. The pigs were divided into three feeding phases (weanling, pre-pubertal and pubertal) with different concentrations of FB1. Specifically, the animals were exposed to 0.2, 5.10, 10.0 and 15.0 mg/kg FB1 for 6 weeks (weanling feeding phase), for 8 weeks (pre-pubertal feeding phase) and for 10 weeks (pubertal feeding phase). The results from the study showed decline in both activity and specific activity of acetylcholinesterase in various brain regions - pons, amygdala, cerebellum, hippocampus, hypothalamus, cerebral cortex, midbrain, medulla oblongata, adenohypophysis, and neurohypophysis. This suggests that FB1 interfered with the production of neurotransmitters in these brain regions [112].

Administration of 10 or 100 μg FB1 to female BALB/c mice for 7 days via intracerebroventricular (icv) and subcutaneous (sc) routes was reported to have different neurotoxic effects. In the icv administration of 100 μg FB1, there was cortical neurodegeneration, hippocampal activation of astrocytes and sphinganine accumulation in all brain regions. These were accompanied by elevated expressions of TNF-α, IL-1β, and interferon-γ. However, sc administration caused only slight build-up of sphinganine in the cortex. The higher degree of FB1 neurotoxicity in the icv route, when compared with the sc route, could be due to its direct introduction to the brain [113]. The study with carp (*Cyprinus carpio* L.) fed on diet containing 100 mg/kg or 10 mg/kg FB1 for 42 days showed vacuolated and neurotic neurons which were scattered around destroyed blood capillaries [22]. Some of the main mechanisms of FB1-induced neurotoxicity observed in animal-based studies are shown Table 2.

8. Mechanism of bioactive compounds against Fumonisin B1 neurotoxicity

It has been earlier suggested that inhibition of oxidative stress is an important means of achieving detoxification of fumonisins. Both biological and synthetic antioxidants have been considered relevant in this regard [114].

A study involving the use of silver juvenile catfish has shown that inclusion of diphenyl diselenide $(PhSe)_2$ in diet can ameliorate neurotoxicity induced by FB1. The healthy animals were divided into four treatment groups: basal diet, 3 mg $(PhSe)_2$/kg of feed alone, 6.2 mg FB1/kg of feed alone and 3 mg $(PhSe)_2$/kg + 6.2 mg FB1/kg for 30 days. The results showed that $(PhSe)_2$ attenuated the brain lesion (alteration of the oligodendrocyte and myelin sheath) generated by FB1 and prevented oxidative damage to the brain of the animals as indicated in the increased activities of catalase (CAT), glutathione S-transferase (GST) glutathione peroxidase (GPx), and glutathione reductase (GR) [115]. Reports have shown that apocynin (4-hydroxy 3-methoxy acetophenone), a phenolic compound with potent antioxidant properties, ameliorated the neurotoxicity induced by FB1 in treated animals. Pretreatment of Balb/c mice with apocynin (25, 50 and 100 mg/kg) for 7 days before subcutaneously injection of FB1 (6.75 mg/kg bwt) at the cervical region resulted in apocynin-mediated restoration of serotonin levels to normal and abatement of oxidative injury by diminishing ROS production, malondialdehyde formation, protein carbonylation and activation of caspase-3 and caspase-8 [116]. Similarly, treatment of astrocyte-like C6 cells exposed to 15 μM FB1 with 80 μM magnolol, a plant-derived lignan, resulted in reduction of oxidative stress. This was evident in the amelioration of levels of malondialdehyde (MDA), superoxide dismutase (SOD), CAT, and total glutathione (GSH). Moreover, magnolol inhibited the phosphorylation of MAPK signaling pathway intermediates such as p38, JNK and ERK [117].

In a study with male Balb/c mice subcutaneously administered 6.75 mg/kg/bwt FB1 for 5 days, it was observed that apocynin (25,50,100 mg/kg/bwt) pre-treatment of experimental animals for 7 days prevented FB1-induced oxidative brain damage depicted by lowered GSH, increased ROS and lipid peroxidation. In addition, apocynin pretreatment lowered mRNA levels of CAT, GPx, caspase-3 and caspase-8. In an i*n vitro* study by the same authors, pretreatment of SH-SY5Y with apocynin (100 μM) followed by FB1 (150 μM) exposure for 24 h prevented FB1-induced cell cytotoxicity and inhibited the expression of CAT, GPx as well as caspases 3 and 8 [118]. Research has identified several enzymes which act as biological detoxicants for FB1. These enzymes degrade FB1 to its less toxic hydrolyzed form (HFB1), thereby offering a means of detoxifying agricultural products and feeds that are contaminated with FB1. Among these enzymes, FumD, a carboxylesterase which is obtained from *Sphingopyxis* sp, MTA144, is the most widely studied. It is commercially available as FUM*zyme*®. FumDSB, another caboxylesterase is obtained from *Sphingomonas bacteria*. Both enzymes degrade FB1 to its less toxic hydrolyzed fumonisin B1 (HFB1). Using the sphinganine/sphingosine ratio as endpoint, a previous study with piglets indicated that FUM*zyme*® reduced the ratio by 48.8 % while Fum DSB had a reducing effect of 8.2 % [119,120]. The ability of these enzymes to degrade FB1 is an indication of their potential to prevent neurotoxicity that may arise from consuming FB1-contaminated food/feed.

While considering the therapeutic potential of neuroprotective compounds against FB1-induced neurotoxicity, it is essential to appraise their probable side effects and toxicity as oftentimes, the distinction between safe and toxic doses of therapeutic compounds, is blurred [121]. Apocynin is generally considered safe based on outcomes of toxicity studies for extended periods in experimental animals. A previous study with mice showed that apocynin when orally administered has a very low toxicity profile [122,123]. In addition, previous studies also established the safety of magnonol [124-126]. Studies commissioned by the European Food Safety Authority (EFSA) showed that FUM*zyme*® is non-genotoxic, non-clastogenic and non-mutagenic. Moreover, a sub-chronic toxicity study with OECD guideline 408 also supports its non-toxicity [127]. FumDSB has been reported to be stable across a wide range of pH (4.0 – 9.0), with modest thermal stability. However, its safety is yet to be fully delineated [120].

A summary of potential mechanisms of therapeutic agents against

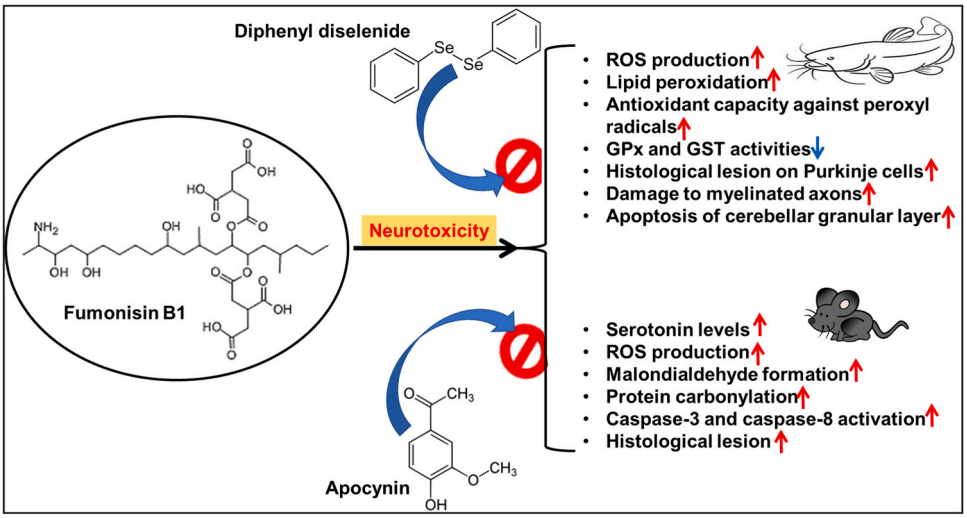

Fig. 4. Potential mechanisms associated with therapeutic agents against FB1 neurotoxicity in animal models. Diphenyl diselenide and Apocynin inhibits FB1 neurotoxicity by preventing neuronal oxidative stress and apoptosis, while also improving neurotransmission and histological lesions.

FB1 neurotoxicity in animal models are depicted in Fig. 4.

9. Conclusion and future perspectives

Altogether, FB1 is of great concern as it poses a huge threat to the populace because it contaminates cereal based products, most especially maize, which is a principal source of food for humans and animals. The available data have demonstrated the potential neurotoxicity of FB1 *in vitro* and *in vivo*, however there is a dearth of information on how to ameliorate the neurotoxicity induced by FB1. Moreover, the relevance of a few bioactive natural or synthetic compounds in ameliorating the toxic effects of FB1 was briefly highlighted. It is hoped that this review would serve as a basis for further research, not only into prevention of human and animal exposure to FB1-contaminated plant produce, but also into further elucidating the toxicodynamic and toxicokinetics of this neurotoxin. Localized and global longitudinal studies are also required to elucidate the trend of human exposure to FB1. Such studies will better inform public health policies aimed at mitigating the health challenges associated with FB1 exposure in both humans and animals.

CRediT authorship contribution statement

Delgado Cássia Pereira: Software, Methodology, Data curation. **Obafemi Olabisi T.:** Writing – review & editing, Methodology, Investigation, Data curation. **Obafemi Blessing Ariyo:** Writing – original draft, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adedara Isaac A.:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Aschner Michael:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Rocha Joao B. T.:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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