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Review Article

Bentonite Clays as Adsorbent Material for Mycotoxins and the Hematological Parameters Involved in Tilapia Species: A Systematic Review

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Aquaculture allows sustainable fish farming to meet global demand; however, fish feed can contain mycotoxins and contaminate animals and humans. Bentonites are clayey materials composed mainly of montmorillonite and are used to reduce or diminish the toxicity of aflatoxins to animals and humans. In this sense, new cheap technologies from natural resources are necessary for controlling fungi and mycotoxins in food. However, information on the potential adverse effects on fish health and performance caused by adding bentonite clays to reduce mycotoxin exposure is scarce. Thus, this systematic review aims to analyze recent studies focusing on the use of bentonite clays as adsorbent materials for mycotoxins in fish feed. In this systematic evaluation of the literature on the subject, which was conducted in Cochrane, Science Direct, PubMed, and Scopus, 1,878 publications from the last 10 years were found, but 1,871 of them were excluded, leading to the selection of only seven for this study. The articles were classified according to the main theme of fish detoxification, the use of natural or chemically modified bentonite clays through adsorbents to remove mycotoxins. The results of the risk of bias analysis of the included studies (seven) were carried out according to the Down and Black criteria. The studies showed that hematological parameters such as total serum protein, albumin, alanine aminotransferase, aspartate aminotransferase, N-urea, and creatinine were altered in some fish species due to contamination by aflatoxin B1 in the diet. On the other hand, the use of bentonite reveals that it has the potential to reduce the effects of aflatoxicosis in fish, causing an increase in body weight, changes in serum enzymes related to humoral immunity, and changes in gill morphology and liver tissue. Contamination of fish diets (especially tilapia) by aflatoxins B1 produces severe changes in all investigated parameters and is extremely dangerous for fish productivity and public health. It was observed that adding clays to tilapia diets reduces the effects of aflatoxicosis while improving economic output and lowering health hazards by adsorbing aflatoxins B1. Thus, the use of bentonite clays is one of the most promising decontamination techniques that can be used by pisciculture.

1. Introduction

The presence of aflatoxins in food has been a concern of the World Health Organization and the Food and Agriculture Organization of the United Nations in recent years [1]. In fact, aflatoxins can damage DNA and cause cancer in animal species and humans. Aflatoxins (AFs) are an important group of mycotoxins produced by *Aspergillus flavus*, *Aspergillus parasiticus*, and *Aspergillus nomius*, which are classified as B1 (AFB1), B2 (AFB2), G1 (AFG1), and G2 (AFG2) [2, 3]. Epidemiological studies with animal experiments have categorized AFB1 as a potent human carcinogen [3]. However, aflatoxin B1 is the most toxic and abundant of the aflatoxins, as it develops toxic actions in humans and animals [4].

The world production of fish had an enormous growth in production; global fish production is estimated to have reached about 178 million tons in 2020 [5]. In addition, in the same year (2020), China was the largest producer of aquaculture, followed by India, Indonesia, Vietnam, and Peru [5]. However, successful fish production is still hampered due to various problems, such as the high costs incurred in producing fish feed borne by farmers conforming to regulations and requirements, including consumer standards, as well as the contamination of feeds with aflatoxins produced by pathogens is a significant problem among producers [6, 7]. According to Sotolu et al. [6], aflatoxins caused by *A. flavus* and *A. parasiticus* are capable of affecting high mortalities of fish and, consequently, heavy economic loss to farmers. In fact, fish on aquaculture farms are often fed different plant foods such as soybean meal and various cereal grains, all of which can represent a source of mycotoxins [7, 8, 9]. However, feed additives can reduce the toxicity of aflatoxin in animal feed, for example, by adsorbing more AFB_1 from aqueous corn flour than feed additives that were less effective [4]. In fact, studies on the toxic effects of aflatoxin B1 on Nile tilapia *Oreochromisniloticus* and detoxification of the drastic effects using ozone treatment and supplementation of natural clay (bentonite) and coumarin in the diet showed that there is a decrease in residual aflatoxin [9]. Although bentonite clay has a high aflatoxin sorption capacity, feed for aquatic organisms, types, and forms of processing and inputs are factors that must be taken into consideration for better production and animal health [10, 11, 12, 13, 14, 15, 16, 17, 18].

Although Jaynes and Zartman [4] and Jawahar et al. [18] in their study emphasize that clays can reduce the toxicity of aflatoxins, there are no complete information on the hematological parameters of contaminated fish. Thus, based on the works published in [8, 19, 20, 21, 22], which emphasize that there is little information on the production of aquatic feed, the present study aims to present new information in research with an emphasis on the use of bentonite clays as adsorbent material for mycotoxins and the hematological parameters involved in fish of the tilapia and other species [8, 19, 20, 21, 22].

2. Materials and Methods

A systematic review was conducted using articles from Pubmed, Web of Science, Scopus, Cochrane Library, Science Direct, and PubMed. The search period was from 2013 to 2020, in which the following keywords were used in the study: aflatoxins, mycotoxins, fish, carcinogenic, bentonite clays, mutagenic, and teratogenic. Selected papers were evaluated for information and methodological quality using the Downs and Black checklist. We consider the following checklists as activities that aid in optimizing the process:

(i) Reporting (0–10 items)—the information provided in the selected paper was sufficient to allow a reader to make an unbiased assessment of the findings of the study [17].

(ii) External validity (0–3 items)—refers to how well the outcome of a study can be expected to apply to the population from which the study subjects were derived [23].

(iii) Internal validity (0–7 items)—establishes a trustworthy cause-and-effect relationship between a treatment and an outcome [24].

(iv) Confounding (6 items)—which considered bias in the selection of study subjects. Thus, the association between intervention and outcome differs from its causal effect.

(v) Power (1 item)—refers to the attempt to assess when the negative findings of a study may be due to chance [17].

(vi) Total score—total methodological quality scores were calculated by summing the individual criterion scores of each study.

The following criteria were used for the selection of published articles: contain all descriptors in full or in part in the title of the article; written in Portuguese and English; have been carried out with the methodology in experimental studies with fish and published in the last 10 years; articles which have considered the use of detoxification processes in fish with an emphasis on the use of natural or chemically modified bentonite clays as adsorbents to remove mycotoxins or associated with other materials; and have a simple and low-cost production process, without need for intensive use of labor, high efficiency using a small amount of product and minimal waste generation.

3. Results

Initially, 1,878 articles were identified in this study, of which 325 were removed because they were not related to the topic of the review or because they were duplicates or did not have an abstract. In total, 1,546 of the articles were excluded for not using natural or chemically modified bentonite clays through adsorbents to remove mycotoxins and those that did not perform simple, low-cost, high-efficiency production processes using a small amount of minimal products and waste generation. As explained in the flowchart (Figure 1), only seven studies met all the inclusion criteria and were included in this systematic review.

Table 1 presents the results on the risk of bias analysis of included studies (seven) in accordance with Down and Black

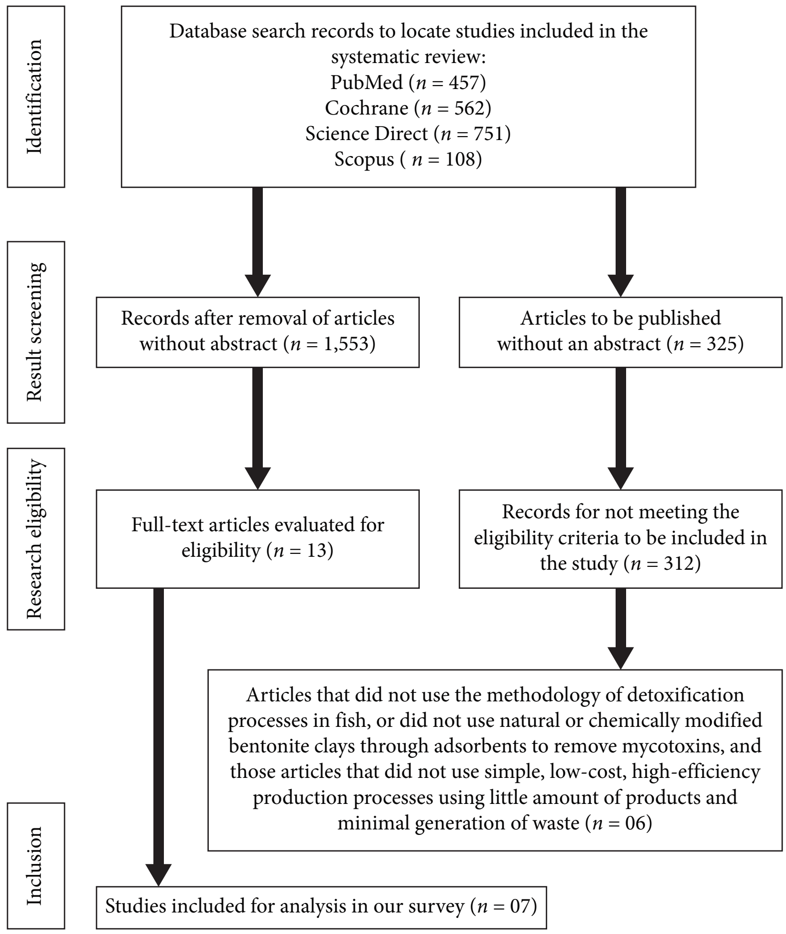

Figure 1: Flowchart showing the selection process of articles included in the current study [9, 25–30].

Table 1: Analysis of included studies in accordance with Down and Black criteria.

Article included in the study	Reporting (0–10)	External validity (0–3)	Internal validity (bias) (0–7)	Confounding (selection bias) (0–6)	Power (1)	Total scores
Neeratanaphan and Tengjaroenkul [25]	10	3	4	4	1	22
Li et al. [27]	9	3	4	4	1	21
Selim et al. [28]	9	3	5	3	1	21
Ayyat et al. [9]	9	3	4	4	1	21
Zahran et al. [29]	9	3	5	3	1	21
Hassaan et al. [26]	10	3	4	4	1	22
Zychowski et al. [30]	9	3	4	4	1	21

Note: A low number is poor, and a high number is excellent.

criteria. Neeratanaphan and Tengjaroenkul (article 1) [25], Hassan et al. (article 6) [26] scored 22 points and are classified as excellent. On the other hand, articles published by authors Li et al. (article 2) [27], Selim et al. (article 3) [28], Ayyat et al. (article 4) [9], Zahran et al. (article 5) [29], and Zychowski et al. (article 7) [30] presented a total of 21 points at the end of the evaluation in relation to the evaluation of the quality of the study (Table 1).

Results in Table 2 show the country that carried out the studies, as well as the characterization of the population profile of evaluated fish that used diets added with clay-based adsorbents in the period from 2013 to 2020. In addition, the seven articles were classified according to the main theme of fish detoxification, the use of natural or chemically modified bentonite clays through adsorbents to remove mycotoxins, as well as a simple and low-cost production process, high efficiency using a small amount of products and minimal waste generation (Table 2). In general, the included studies were carried out with Nile tilapia fingerlings fed a basal diet contaminated with aflatoxins and a basal diet contaminated with

Table 2: Information from the articles included in the study, countries of study, and characterization of the population profile of the evaluated fish.

Articles included in the study	Countries of study	Fish population profile
Neeratanaphan and Tengjaroenkul [25]	Thailand	Used young tilapia
Li et al. [27]	China	Used young tilapia
Selim et al. [28]	Egypt	Nile tilapia fingerlings were used
Ayyat et al. [9]	Egypt	Nile tilapia fingerlings were used
Zahran et al. [29]	Egypt	Used young Nile tilapia
Hassaan et al. [26]	Egypt	Nile tilapia fingerlings were used
Zychowski et al. [30]	USA	Used young Texas tilapia

clays, with the exception of one study that used trout fish in the experiment. Regarding the methodology used, it appears that the seven articles are quantitative. Among the countries shown in Table 2, the country that had the highest percentage of studies on the term was Egypt ($n = 4$, 57.4%) [9, 26, 28, 29].

The effectiveness of clays in reducing the level of mycotoxin contamination in fish meat and the results of the detrimental effects of AFB_1 in Nile tilapia fish diets were examined in the seven publications contained in Table 3. Three studies presented the fish population studied using a basal diet based on bentonite (coumarin bentonite, 2% sodium bentonite, Thai sodium bentonite); the other used studies a basal diet based on sepiolite, calcium aluminosilicate with sodium hydration, and esterified gluomannone; clinoptilolite; and nanozeolite.

Studies from 2013 to 2020 that were included in the analysis revealed that there is a relationship between clay use and aflatoxicosis in trout and tilapia, whose symptoms include pale gills, abnormal blood clotting, anemia, general weakness, and slow growth. Based on the review's findings, it is confirmed that the presence of a baseline diet with clays in the fish feed results in an increase in weight gain, an improvement in the fish's immune system, and an improvement in blood parameters in addition to a decrease in the adsorption of aflatoxins. In addition, it was found that of the seven studies, only in four of them the fish were fed diets contaminated with aflatoxins and had a reduction in body weight gain. The studies included in Table 3 showed that in fish treated with diets supplemented with natural clays, there was a performance in blood parameters, liver enzymes, creatinine, plasma proteins, and immune status. A basal diet with a daily concentration of 200 μg/kg of AFB_1 for 10 weeks led to a mortality rate of 34.34% in Nile tilapia, in addition to having levels of AFB_1 accumulation ranging from 23 to 94 mg/kg in the musculature. As explicit in Table 3, the studies demonstrated that the levels of aflatoxins, even at concentrations allowed in the diets, could induce immunotoxicity and significant histopathological changes in the liver and kidneys of Nile tilapia.

4. Discussion

In the current study, only seven articles were selected and classified into two thematic axes to be analyzed in our review based on the flowchart checklist (Figure 1). Regarding the judgment of the items present for evaluation (Down and Black) in Table 1, the dilemmas found were those related to the type of population samples used in the experimental studies and the average toxic level found in the meat of the evaluated fish, so it was possible to evaluate at external validity, internal validity (bias) and confounding (selection bias). The design of the quality of the selected articles (Table 1) presented an average for the total score of 21 points (with SD = 1.02) according to the Down and Black instrument. In addition, in Table 2, it is noted that the studies were mostly carried out in Nile tilapia.

According to the analysis of the efficiency of clays in reducing toxicity in fish meat and results of adverse effects of AFB_1 in diets for Nile tilapia fish, it was possible to see in the study by Neeratanaphan and Tengjaroenkul [25] that the use of Thai bentonite reduced the effects of aflatoxicosis in terms of body weight, as the fish analyzed in the study lost weight and displayed low indicators of serum enzymes related to humoral, followed by significant changes such as in gill morphology and liver tissue of Nile tilapia (Table 3). Additionally, Neeratanaphan and Tengjaroenkul [25] discovered that using Thai sodium bentonite clay reduces the toxic effects brought by aflatoxicosis. In fact, a significant decrease in AFB_1 contamination was observed in other fish species, such as rainbow trout, using sodium bentonite [31]. Therefore, sodium bentonite can be used as a feed additive to stimulate immunity and for disease resistance in the effective production of freshwater catfish [18]. In addition, these findings also revealed changes in fish body growth with changes in the production of antibodies, as well as serum liver enzymes and histopathological changes using contaminated foods [25]. The study showed a significant rise in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) production. According to the findings of this study, Thai sodium bentonite can lessen the danger of human intake of fish as a rich source of protein and diminish aflatoxicosis in tilapia [9, 25, 27, 28].

Aflatoxins (AFB_1) can be cumulative in fish tissues, i.e., the diets for fish with AFB_1 levels (10–40 mg/kg) cause the gills of the fish developed lesions with balloon aspect at the tip of the gills, development of vascular congestion, sinusoidal increases and infiltration of leukocytes. In fact, fish-fed AFB_1 (20–40 mg/kg) showed irregular formation of cell nuclei and mitochondria, dissociation of endoplasmic reticulum, and vacuolar degeneration [25]. Therefore, the use of toxin absorbents is one of the main methods to reduce aflatoxin amount in fishes. Indeed, the use of Thai sodium bentonite

Table 3: Analysis of the efficiency of clays in reducing toxicity in fish meat and results of adverse effects of AFB_1 in diets for Nile tilapia fish found in the articles included in the study.

Article included in study	Treatment AFB_1 + clay	Weight gain	Liver enzymes AST/ALT	Fish mortality	Immunity	Observation of results/hematological parameters
Neeratanaphan and Tengjaroenkul [25]	AFB_1[a] + 1% TB[b]	53.67 g	114 54	Reduced	Reduced	(1) Aflatoxicosis symptoms were less severe in Nile tilapia in terms of body weight, blood enzyme indicators, humoral immunity, and gill and liver morphology when 1% Thai bentonite was used
Li et al. [27]	—	—	—	—	—	(1) Given that it was able to eliminate AFB_1 from feed or food, this study hypothesized that the adsorption of raw clay minerals from samples from Nanyang (China) was greater than that from other samples. Furthermore, ion-dipole interactions between AFB_1 and exchangeable cations of montmorillonite play a significant role in the adsorption of AFB1 in the presence of montmorillonite (MMT) on raw clay minerals
Selim et al. [28]	AFB_1[a] + 0.5 HSCAS[c] AFB_1[a] + 0.25 CS[d] AFB_1[a] + 025 EGM[e]	23.83 g 19.33 g 17.03 g	Reduced Reduced Reduced	Reduced Reduced Reduced	Increased Increased Increased	(1) The death rate of 34.34% in Nile tilapia was confirmed by the data. Additionally, AFB_1 has a significant negative impact on the quantity of leukocytes, hemoglobin content, and erythrocytes. The harmful impact of AFB_1 on the kidneys was confirmed by the raised levels of creatinine. Serum ALT and AST values significantly increased, which indicates hepatotoxicity. (2) AFB_1 decreased the quantities of protein, albumin, and globulin in the serum. The plasma protein in *Labeorohita* that was most vulnerable to aflatoxin exposure was globin. In Nile tilapia flesh, AFB_1 concentrations varied from 23×10^{-3} to 94×10^{-3} mg (kg). Growth performance, blood parameters, liver enzymes, creatinine, plasma proteins, and immune state in fish treated with S.C. and EGM were all better than in fish exposed to AFB_1
Ayyat et al. [9]	0.000 mg (kg) AFB_1[a] + 20 g Clay 0.025 mg (kg) AFB_1[a] + 20 g Clay	38.180 g 35.381 g	Reduced −14.9583 Reduced 20,867	—	—	(1) According to the findings, AFB_1 contamination caused a decrease in feed conversion and hematocrit count, which led to an increase in the mortality rate. This also caused a decrease in fish growth rate. Weight increase, feed efficiency, and hepatosomatic index in tilapia were all significantly ($P < 0.05$) reduced when AFB_1 was present at concentrations of 1.5 and 3.0 mg (kg). Aflatoxin toxicity can be decreased by using ozone. A group of fish, in this instance, demonstrated noticeably improved growth, feed conversion, rate, and tissue aflatoxin levels. (2) Natural clay (Tafla, which contains 80% bentonite) performed well in terms of growth indices. Aflatoxin residues were further reabsorb by fish. As they lessen the toxic effects of meals contaminated with AFB_1, treatment with ozone as an oxidizing agent and natural clay are utilized to diminish the detrimental effect of aflatoxins
Zahran et al. [29]	16 μg (kg) AFs [f] + 2 g (kg) Minazel-plus®[g]	45.50 g– 54.17 g	—	—	Increased bactericidal activity and lysozyme activity	(1) The findings show that Nile tilapia can develop immunotoxicity and significant histopathological abnormalities in the liver and kidney when aflatoxin levels are lower than those permitted in feed. Aflatoxins may bioaccumulate in the liver and musculature of Nile tilapia samples at low concentrations. Aflatoxin's general detrimental effects on fish health were successfully mitigated by supplementing with Minazel-Plus® in the aflatoxin-contaminated diet. In fact, fish showed improved antioxidant and immunological responses when Minazel Plus® was used as a supplement

Table 3: Continued.

Article included in study	Treatment AFB_1 + clay	Weight gain	Liver enzymes AST/ALT	Fish mortality	Immunity	Observation of results/hematological parameters
Hassaan et al. [26]	3 mg (kg) AFB_1 3 mg (kg) AFB_1 + 5 g nano-zeolite 3 mg (kg) AFB_1 + 10 g nano-zeolite	28.03 g 35.38 g 38.44 g	24.50 147.50 14.50 98.00 15.00 94.00	Reduced	Increases activity of oxidizing enzymes	(1) The study's findings were as follows: AFB_1 reduced Nile tilapia growth, decreased feed utilization, digestive enzyme activity, antioxidant enzyme activity, increased liver enzyme activity, caused DNA damage, and left residual aflatoxin in the Nile tilapia musculature. Nano zeolite alleviated AFB_1 toxicity in *O. niloticus* in addition to having positive effects to eliminate AFB_1 detrimental effects on tilapia health. (2) Growth performance and feed consumption were much better after 84 days. As seen, the diet of fish fed with 3 mg (kg) AFB_1 and supplemented with Nano zeolite inclusion (5 g (kg)) secreted more endogenous amylase and chymotrypsin than other treatment diets. Fish from the group fed a meal with 10 g (kg) Nano zeolite had considerably greater levels of hemoglobin, hematocrit, red blood cells, and white blood cells. Fish samples showed lower levels of the blood enzymes alanine and aspartate aminotransferase, alkaline phosphatase, total protein, albumin, and globulin than were animals exposed to AFB_1 without nano-zeolite. (3) The same effects and trends were also created by the antioxidant activities of MAD, SOD, CAT, DNA fragmentation, and lysis. The results showed that there was a lingering reduction of AFB_1 in fish muscle
Zychowski et al. [30]	1.5 mg (kg) AFB_1 + 0% NS[h] 1.5 mg (kg) AFB_1 + 0.5% NS[h] 1.5 mg (kg) AFB_1 + 1% NS[h] 3 mg (kg) AFB_1 + 0% NS[h] 3 mg (kg) AFB_1 + 0.5% NS[h] 3 mg (kg) AFB_1 + 1% NS[h]	550% 449% 627% 375% 522% 451%	—	—	—	(1) High dosages of AFB_1 resulted in decreased weight gain and decreased feed efficiency. In addition, fish exposed to 3 mg (kg) AFB_1 performed worse than fish in the control group subjected to 1.5 mg (kg) AFB_1. Within 10 weeks, which is a little period when compared to a whole development cycle, tilapia exposed to relatively low amounts of AFB_1 (3 mg (kg)) might experience harmful consequences. (2) In the groups exposed to AFB_1, the hepatosomatic change index (HSI) was significantly reduced. Additionally, histological examinations at levels of $AFB_1 < 1.5$ mg (kg) revealed liver damage. Reduced HSI and histopathological alterations in the liver point to the development of AFB_1-induced heptocarcinogenesis. The amount of superoxide anion produced extracellularly by macrophages decreased. The extracellular superoxide anion increased following treatment with 0 mg (kg) AFB_1 + 1% NovaSil clay (NS) compared to the control group ($P < 0.05$), indicating that NS alone may have a beneficial effect on the tilapia immune system

AFB1[a] (Aflatoxin B1); TB[b] (Thai bentonite); HSCAS[c] (hydrated sodium calcium aluminosilicates); SC[d] (*Saccharomyces cerevisiae*); EGM[e] (esterified glucomannan), AFs[f] mix of aflatoxins (AFB1 and 2, AFG1 and 2); Minazel-plus®[g] is a product based on organic modification of mineral clinoptilolite surface, effective against polar and less polar mycotoxins; NS[h] (NovaSil) is a calcium montmorillonite clay.

acts as a filter, reduces aflatoxicosis in tilapia, and influences the decrease in the risk of contamination when fish protein is used for human consumption [9, 25, 26, 28]. Ellis et al. [31] evaluated sodic bentonite in trout (*Oncorhynchus mykiss*) fed diets containing aflatoxins (20 μg/kg) and came to the conclusion that adding 2% sodic bentonite to the meal considerably lowers the fishes to absorb aflatoxins. According to this study, results suggest that 2% bentonite considerably lowers the quantity of AFB_1 absorbed from the digestive tract after trout meals contaminated with 20 μg/kg AFB1 have been consumed [31].

According to Dilkin [32], contamination by aflatoxins leads to decreases in growth rate, feed efficiency, and weight gain loss caused by reduced protein metabolism and absorption of fats even at low levels of aflatoxins, in addition interfering with the immune response, which makes animals more susceptible to infections and parasitic diseases, also causing failures in response to vaccinations [32]. Weight reduction in tilapia (*Oreochromisniloticus*) was observed by authors such as Tuan et al. [33] with inclusion levels of 100 mg/kg of AFB_1 kg^{-1} in the animals' diet, Arana et al. [34], who used 80 μgAFkg^{-1} in the diet, and Deng et al. [35] who observed that due to exposure for 20 weeks and high concentrations of AFB_1 (1,641 μg/kg), such animals had less weight gain, that is, tilapia exposed to the highest concentration of AFB_1 were the most affected [35]. Results of other studies on Nile tilapia intoxication with diets containing AFB_1 at concentrations of 0.25, 2.5, 10, or 100 mg/kg of feed showed that these animals also presented difficulties with weight gain, problems of blood cell reduction and appearance of liver lesions, which may trigger in the death of the animal [33]. According to Dilkin [32], aflatoxins affect multiple enzymatic systems (amylase, pancreas, trypsin, lipase, RNAse, and DNAse), interfering with the digestion of starches, proteins, lipids, and nucleic acids, which results in decreased animal production. In addition, there is a reduction in the detoxification function of toxins and drugs, exerted by the liver. It causes a considerable reduction in the production of plasma proteins, influencing the production of hemoglobin, on the mechanism of blood coagulation and on the synthesis of important enzymatic systems that, associated with increased capillary fragility, causes generalized hemorrhages. The main clinical signs in animals intoxicated by aflatoxins are anorexia, reduced weight gain, hemorrhages, poor carcass quality, embryotoxicity, and teratogen [36, 37]. Experiments in domestic birds and other animals pointed out the following effects of immunosuppression: aplasia of the thymus and bursa of Fabricius, reduction of the number and activity of T cells, decrease in antibody response, reduction of humoral components and immunoglobulins [18, 38]. According to Rosmaninho et al. [39], the association of these factors associated with the exposure of animals to rations contaminated with aflatoxins can lead to the appearance of concomitant infections, especially by viral and bacterial agents [39].

Although the values of concentrations of AFB_1 influence the health of fish, the addition of other compounds to AFB_1 must also be considered. Hussain and Mateen [40] used inclusion levels of AFB_1 (2 and 4 mg/kg) associated with calcium bentonite clay (4TX) (0.5% and 1%) added in the form of dry powder mixture (PM) and dispersed in water (WD) for a period of 10 weeks in Nile tilapia (*Oreochromisniloticus*). They observed that in the muscle tissues of fish fed AFB_1 (4 mg/kg), there were residues of AFB_1. However, the addition of 4TX in the diets substantially reduced the bioaccumulation of AFB_1 in the Nile tilapia muscle, mainly when included in the dry powder mixture form (PM) (0.43 ± 0.03 ng/g) compared to the form when dispersed in water (WD) (1.87 ± 1.32 ng/g). Note that 4TX clay has a significant efficacy in mitigating AFB_1-induced toxicity when included in dry powder form (PM). Based on this study, results suggest that aflatoxin-B1 had a detrimental effect on Nile tilapia development independent of the presence of 4TX clay. Some of the metrics studied are significantly affected by the addition of 4TX to the diets [40]. According to Caguan et al. [41], Nile tilapias exposed to aflatoxins at concentrations from 5.0×10^{-3} to 115.34×10^{-3} mg/kg for 90 days did not experience any appreciable changes in weight, size, or weight gain. However, Nile tilapias exposed to the highest concentrations displayed mortality rates above 50% [36, 41]. In fact, when analyzing 10 adult Nile tilapia (*Oreochromisniloticus*) fed a diet containing 6.3×10^{-3} mg/kg of AFB1, Souza et al. [42] verified the presence of fluid in the abdominal cavity and changes in the liver, such as yellowish pallor, appearance, and friable consistency; microscopically observed fatty degeneration and necrosis of hepatocytes [42].

Zychowski et al. [30] observed that tilapia exposed to relatively low concentrations of AFB_1 (3 mg/kg) at 10 weeks might lead to a significantly decreased hepatosomatic alteration index (HSI). Histological damage to the liver was also observed at levels below the value of 1.5 mg/kg of AFB_1. Histopathological changes in the liver and reduced HSI suggest a progression to Heptocarcinogenesis induced by AFB_1. With the use of NS, the protective effect of NS clay against the toxic effects induced by AFB_1 in Nile tilapia fish was demonstrated. Over the course of a very brief period of 10 weeks, AFB_1 generally had a detrimental effect on tilapia weight increase and feed efficiency. With both 1.5 and 3.0 mg/kg treatment levels, AFB_1 also had a substantial unfavorable influence on a number of physiological and biological parameters, including the production of HSI and extracellular superoxide anion in macrophages. However, future research should aim to mitigate aflatoxicosis in tilapia by figuring out an efficient dosage technique for NS in fish, even if NS inclusion in fish feed provides some protection in some situations. In order to allow for AFB_1 adsorption without interference from the food matrix, this technique may call for supplementation apart from the feed itself [30]. It is interesting to note that other foods and their compositions can also cause damage to the health of fish; according to studies conducted on fish exposed to mycotoxins over an extended period of time, fishes may have impaired hepatic function, decreased food efficiency, weight loss, increased susceptibility to infectious diseases, necrosis, and tumor development in the liver and other organs, and increased mortality [43].

Li et al. [27] observed in their study that the adsorption of the raw clay minerals from the Nanyang (Chine) sample was higher than other samples, since it was able to remove AFB_1

from rations or foods. In addition, the presence of montmorillonite in clay minerals plays an important role in the adsorption of AFB_1, due to ion-dipole interactions between AFB1 and exchangeable cations of montmorillonite [27]. Sepiolite is a clay mineral of the hermit group. These minerals are complex magnesium silicates, with an open channel structure, forming elongated crystals, and may present partial isomorphic substitutions of magnesium by aluminum and/or iron. These substitutions of magnesium and iron, in the octahedral layers of clay minerals, result in an excess of negative charges that make them a sorbent for some polar molecules or positive ions [44]. Therefore, the study results suggest that, due to ion-dipole interactions between AFB_1 and the exchangeable cations of montmorillonite, the presence of montmorillonite in clay minerals is crucial for the adsorption of AFB_1. The experimental findings supported the second-order kinetic model with good agreement, indicating that chemisorption dominates the adsorption process. The Freundlich isotherm model was found to suit the adsorption data, which suggests that multilayer adsorption should be the mechanism used to bind AFB_1 to three samples of clay minerals. The AFB_1 molecules penetrate the channels in addition to coating the rods' surface [27].

Selim et al. [28] while conducting a study to investigate the protective effect of three adsorbent mycotoxins, sodium hydrate calcium aluminum silicates (HSCAS), *S. cerevisiae* (SC), and an esterified galactomannan (EGM) for AFB1 diet contaminated with AFB_1 (0.2 mg/kg) in Nile tilapia observed that treatments with adsorbents associated with AFB_1 showed a decrease in AFB_1 residue muscle tissues of fish when fish treated with AFB1. HSCAS significantly reduced the AFB_1 when equated with S.C. and EGM. The results of this study thus point to the possibility that the increased rates of infectious illness mortality may be brought on by immunological dysfunction brought on by AFB_1. To distinguish if AFB_1 effects are focused on humeral immunity or particular immunity, more research is required. AFB_1 adsorbents are now better-understood thanks to this work, but further research is needed to understand how they interact with one another [28]. In the same study, the authors observed that the diet containing AFB_1 (0.2 mg/kg) resulted in a mortality rate of 34.34% in Nile tilapia. AFB_1 severely affected the number of erythrocytes, hemoglobin content, and number of leukocytes. In addition, there was an increase in creatinine levels, confirming the toxic effect of AFB_1 on the kidneys. There were significant increases in alt and AST serum levels, confirming hepatotoxicity. AFB_1 reduced serum levels of protein, albumin, and globulin, as well as accumulation of AFB_1 levels ranging from 23×10^{-3} to 94×10^{-3} mg/kg in Nile tilapia meat. Globulin was the plasma protein most susceptible to exposure to aflatoxin in *Labeorohita* [28]. In fact, Selim et al. [28], when analyzing Nile tilapia (*Oreochromisniloticus*), submitted to 200 mg AFB1 kg) for 10 weeks, presented lower values of erythrocytes, hemoglobin, and leukocytes than the control tilapias [28]. Hassaan et al. [26] and Zychowski et al. [30] demonstrated an increase in the activities of oxidizing enzymes with the use of clays, by ultra-side Zahran et al. [29] observed an increase in bactericidal and lysozyme-activated activities, both mechanisms used by the immunologic system to eliminate invasive microorganisms.

Ayyat et al. [9], in a study with a group of tilapia fish treated with clay, ozone, and coumarin, reduced residual aflatoxin when compared to the control group that showed a reduction in fish growth rate, feed conversion, weight gain, hematocrit count, feed efficiency and hepatosomatic index and increased mortality rate. Thus, treatments with natural clays or ozone can be used to depreciate the toxic effects of diets contaminated with AFB_1. This study concluded that the feeding experiment led to the conclusion that aflatoxin contamination of fish diets produced numerous severe changes in all investigated parameters and is extremely hazardous to fish productivity and public health. The most effective therapies to lessen aflatoxin's adverse effects were ozone treatment as an oxidizing agent and natural clay. The use of natural clay orozone treatments may be advised to lessen the deleterious effects of aflatoxin B1-contaminated diets [9]. The use of clays is a factor that leads to the reduction of fish death; therefore, fish treated with clay, ozone, and coumarin can further reduce death by aflatoxin [9, 25, 26, 28].

In the same way as the various results obtained by other studies, Zahran et al. [29], in their experiment, observed that AFB_1 may induce bioaccumulation in the liver and muscles of Nile tilapia. In addition, changes in immune toxicity and significant histopathological changes in the liver, spleen, and intestine corroborating the results of Hassaan et al. [26], Zychowski et al. [30], and Deng et al. [35]; all studies using Nile tilapia. Minazel-Plus® supplementation to the aflatoxin-contaminated diet was successful in mitigating the overall adverse effects of aflatoxin on fish health. The use of Minazel Plus® as supplementation alone increased antioxidant and immune responses in fish and reduced the bioaccumulation of AFB_1 in the muscles of tilapia fish. The reported findings strongly imply that feed-mill monitoring strategies for aflatoxin levels in feed ingredients must be put into place and strictly enforced, especially in light of potential illegal use of highly contaminated feed and insufficient or absent regulations regarding the safe level of aflatoxins in fish feed [29].

Hassaan et al. [26] conducted an experiment to investigate the protective effect of natural clay nanozeolite on Nile tilapia with basal diet of AFB_1 (0 and 3 mg/kg) and nanozeolite (0.5 and 10 g/kg). The results showed that AFB_1 induced reduction in growth, food use, digestive enzyme activities, and antioxidant enzyme activities; increased liver enzyme activities, DNA damage, and residual aflatoxin in Nile tilapia musculature. Nanozeolite has alleviated the toxicity of AFB_1 in fish and has beneficial effects to eliminate the negative impacts of AFB_1 on tilapia health status. After 84 days, fish-fed AFB1 (3 mg/kg) versus nanozelite (5 g/kg) growth performance and feed utilization were significantly higher. Higher secretion of endogenous amylose and chymotrypsin occurred than in other treatment diets. The use and nanozelyte (10 g/kg) biochemical parameters such as hemoglobin, hematocrit, red blood cells, and white blood cell count were significantly higher. There was a decrease in ALT, AST, alkaline phosphatase (AF), total protein, albumin, and globulin, as well as the antioxidant activities of MAD, SOD, CAT, lyses, and DNA fragmentation had the same trend [22]. Based on the study results, the toxicity of AFB_1 in *O. niloticus*was reduced by nano-zeolite, and it also had positive effects to improve the health status of tilapia, so more research is required to fully understand the remediation of nanozeolites.

AFB_1 caused reductions in growth, feed utilization, digestive enzymes, and antioxidant enzyme activities; elevated liver enzyme activities; DNA damage; and residual aflatoxin in Nile tilapia musculature. Moreover, in previous studies, it has been mentioned that bentonite can be used in the prevention of aflatoxicosis, because they are effective adsorbents of aflatoxin [44, 45]. Thus, bentonite is used as an adsorbent of mycotoxins that is capable of capturing and adsorbing toxic molecules by the ionic process that slows the entry into the blood of the gastrointestinal tract [46], because bentonite presents large areas of specific surface with high porosity, surface load and functional surface groups that qualify them as useful adsorbents, besides being abundant in nature, low cost and has environmental compatibility in their applications [29]. However, Tamames [47] points out in his study that it is erroneous to conclude that various types of clay are capable of adsorbing mycotoxins, because each clay has differences between them, just as mycotoxins are different from each other [47]. The concentration of adsorbents is a determining factor for the absorption of mycotoxins; according to Ouhida et al. [48], the use of sodic bentonite (2%) in the diet was not enough to alter weight gain and feed conversion, but when using high levels (6%), there was great absorption of mycotoxins [48].

Fish diets contaminated with AFB_1 due to the use of rations for aquaculture cause damage to the health of the fish; therefore, studies must be carried out using several types of clays. In fact, as occurred in the work by Zychowski et al. [30], which observed that the treatment with 0 mg/kg AFB_1 + 1% NS produced an increase in extracellular superoxide anion compared to the control group ($P < 0.05$), suggesting that NS alone may have a positive influence on the immune system of tilapia [30]. Similarly, growth performance and immunosuppressive effects were used to evaluate the response in yellow catfish (*Pelteobagrusfulvidraco*); it is possible to verify that with the increase of AFB_1 concentrations and by evaluating the protective effect of dietary supplementation with a bentonite-based ligate, the immunosuppressive action of AFB_1 with the use of diets in yellow catfish occurred due to lower bactericidal activity, lower lysozyme activity, reduced total protein and increased albumin/globulin ratio, i.e., binder for AFB_1 protected fish from the toxic effects of AFB_1 [45].

In Table 3, the studies by Ayyat et al. [9], Selim et al. [28], Zahran et al. [29], and Hassaan et al. [26] showed that some hematological parameters of the species were altered by aflatoxin contamination in the diet [9, 11, 26, 27, 28, 29]. Similarly, Ayyat et al. [9] observed that total serum protein, albumin, ALT, AST, urea-N, and creatinine were increased in the groups of fish-fed diets contaminated with AFB_1 [9]. This occurs, due to the bioaccumulation of AFB_1 in the entire body of the fish, while fish treated with clay, ozone, and coumarin occurred a decrease in the residues of AFB_1 when compared to the control group [9]. Thus, significant differences in production and health parameters between groups containing AFB_1 versus control and groups supplemented with Minazel-plus were observed similarly in other studies, such as a decrease in red blood cells, hemoglobin, and volume of red blood cells, changes in the dynamics of leukocyte counts, and decrease in lysozyme and bactericidal activity [35, 49].

As we saw in the text above, bentonite clays are effective in absorbing mycotoxins; in addition, it is a nontoxic and natural material that does not require additives or chemicals to be at their best. However, when used in animal feed, it has limitations due to its physicochemical properties. These properties include the cation exchange capacity, swelling capacity, pH, rheological properties, and other important properties [50]. Research involving the application of bentonite clays in the absorption of mycotoxins should be carried out considering the hematological parameters of poultry, swine, and other fish species. Thus, new results may be useful for the development of new drugs or more effective materials for the mitigation, food safety, and elimination of toxic elements such as aflatoxins present in diets supplied to humans or animals [51].

5. Conclusions

In this systematic review study, new information on fish diets using bentonite clays to reduce the effect of aflatoxins (AFB_1) was presented. According to studies, bentonite clays reduce the effects of aflatoxicosis in terms of body weight, serum enzyme indicators, humoral immunity, gill morphology, and bio-accumulation in the liver and musculature of tilapia. In addition, it was found that the hematological parameters of the analyzed species included in the studies of this systematic review undergo hematological changes with the contamination of aflatoxin in the diet; that is, there was a decrease in red blood cells, hemoglobin, and volume of red blood cells, changes in the dynamics leukocyte counts, decreased serum lysozyme and bactericidal activity.

The values of concentrations of AFB_1 influence the health of fish; however, the addition of other compounds to AFB_1 must also be considered. In addition, studies must be carried out using several types of clays.

The findings in this study show that it is necessary to invest in the search for new technologies and innovative natural means with low-cost strategies that combine high degradation efficiency, as well as safety for health and environmental character. Finally, all-natural and technological means can minimize the effects of aflatoxins on human health and lead to the creation of public health policies and the reduction of economic losses in developed and mainly developing countries.

Data Availability

Data that support the findings of the research will be made available upon request.

Disclosure

The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

Conceptualization was done by Francisco José Mendes José Mendes dos Reis and Karuppusamy Arunachalam; methodology was done by Francisco José Mendes José Mendes dos Reis and Karuppusamy Arunachalam; validation was done by Antonio Marcos Jacques Marcos Jacques Barbosa and Rita de Cássia Avellaneda Guimarães; investigation was done by Francisco José Mendes José Mendes dos Reis, Marta Aratuza Pereira Aratuza Pereira Ancel, Elaine Silva Silva de Pádua Melo, Maria Fernanda Balestieri Mariano Fernanda Balestieri Mariano de Souza, Ana Carla Pinheiro Carla Pinheiro Lima, and Rodrigo Juliano Juliano Oliveira; writing—original draft preparation was done by Francisco José Mendes José Mendes dos Reis and Karuppusamy Arunachalam; writing—review and editing was done by Valter Aragão Aragão do Nascimento and Francisco José Mendes José Mendes dos Reis; supervision was done by Valter Aragão Aragão do Nascimento; project administration was done byValter Aragão Aragão do Nascimento; funding acquisition was done by Valter Aragão Aragão do Nascimento. All authors have read and agreed to the published version of the manuscript.

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