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REVIEW ARTICLE

Potential Harmful Effects of Aflatoxin M1 in Milk and Milk Products and Novel Methods to Reduction of Aflatoxin M1: A Review

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KEYWORDS

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ABSTRACT: Dairy products are rich sources of vitamins, proteins and calcium that are vital to the human body. Aflatoxin M1 is a hydroxylated metabolite of aflatoxin B1. The presence of this toxin in milk has caused serious concern among nutritionists. Consumption of aflatoxin-contaminated milk (AFM1) may lead to serious health problems in humans. AFM1 causes various cancers such as liver cancer, damage to the nervous and DNA, as well as mutagenicity and teratogenicity. In reducing the amount of aflatoxin in the product, with does not affect the milk quality is of particular importance. Absorption and restructuring methods such as yeast, lactic acid (bacteria), enzymes, ozon, and cold plasma have been used for this purpose. In this study, they have been studied on aflatoxin M1 and toxicology besides reducing method for aflatoxin M1.

INTRODUCTION

Mycotoxins are substances that are produced naturally by poisonous fungi that grow on a number of agricultural products and are often responsible for human and animal healt. Hundreds of know types of mycotoxins, aflatoxins (AF) are the most studied and the most public health concern worldwide [1]. Food contamination with mycotoxins (aflatoxin) is a particular importance and the World Health Organization [2], Relevant international organizations (FAO and Codex) have set the maximum amount of aflatoxin contamination for different foods [3]. Aflatoxins are products of Aspergillus species including A. flavus, A. parasiticus and A. nomius. Aflatoxins G1, G2, B1 and B2 are the most important aflatoxins. AFM1 has been reported worldwide in dairy products [4]. When aflatoxin-contaminated feed is ingested with highly variable levels of AFB. However, milk has been shown to have the greatest potential for introducing AFM1 into the human diet [5, 6]. In terms of toxicity, aflatoxin M1 is

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approximately ten times less toxic than aflatoxin B1, but AFM1 is exposed to diet consumption of milk and dairy products can cause human disease such as liver cancer [7, 8]. Studies show that AFM1 is relatively stable during pasteurization. In anticipation of potential hazards, several national and international regulators have set a maximum AFM1 limit for milk and dairy products. AFM1 in milk should not exceed 0.05 µg kg^{-1} for adults and 0.025 µg kg^{-1} for foods used for infants and young children, while the amount of AFM1 in milk has been reported by the Codex Commission 0.05 µg kg-1 and by the FDA 0.5 µg kg^{-1} [9,10]. The national limit of AFM1 milk in Iran is 0.1 µg kg^{-1} [10].

Studies show that the existence of AFM1 in milk is a public health solicitude because milk plays a very important role in human diets across countries [11]. Aflatoxin causes poisoning (acute and chronic) and cancers in humans. The results indicated that aflatoxin poisoning varies with age, sex, and condition, and symptoms such as central nervous system, immunity system disorders, liver and kidney, brain injury, and death [12,13]. Given that milk is a valuable and ideal food for all age groups and is rich in essential nutrients, vitamins and amino acids and plays an important role in human health, so ensuring the quality of milk is very important. In recent years, the presence of dangerous and toxic chemicals in food, especially in milk, has increased. In this review, we discuss the presence of aflatoxin M1 in dairy products (milk) and its adverse effects on human health as well as new reducing methods that assessed in recent years.

Aflatoxin M1 in dairy products (milk and milk products)

AFM1 appearance in the milk 48-72 hours after the ingestion of AFB1. In one study, adding 1.7 to 2 micrograms of aflatoxin to milk and production of cheese, it was observed that 40% of aflatoxin remained in cheese and 60% in whey [15]. Studies show that about 0.3% - 6.2% of AFM1 can be transferred to milk. The amount of infection depends on the season, winter and genetic conditions of the animal [16-18]. Almost all samples of dry matter, baby food and yogurt in Italy and Kuwait are contaminated with aflatoxin M1, which causes health problems for Italians [15]. Detection of AFM1 derivative in milk is from 12 to 24 hours after AFB1 consumption, but there is a decrease in concentration after 72 hours of contact [19, 20]. Measurement of AFM1 in Turkey showed that high-fat cheeses containing AFM1 exceeded the standard in Turkey [21]. Researchers show that only 33% of Spanish raw milk samples contain contamination [15]. A study (in Brazil) showed that aflatoxin M1content has been 24–50 ng l^{-1} [22]. The AFM1 in raw milk samples (cow) on northern, northeastern and western China was 69 ±52 ng kg^{-1} [23]. The level of AFM1 in milk in Iran from 0.03 for Hamadan to 1293.29 for Kermanshah and from 0.03 for East Azerbaijan to 66.00 ng kg^{-1} for Qazvin were, respectively [6]. The average estimated level of AFM1 in Italian milk samples using valid ELISA method was about 35 ng kg^{-1}. Studies show that the average level of AFM1 in the milk of Middle Eastern countries was low. Meanwhile, the results of one study showed that the average level of AFM1 in Iranian raw milk (55.74 ng kg^{-1}), pasteurized (47.02 ng Kg^{-1}), UHT milk (93.61 ng kg^{-1}) [24]. Dairy products made from raw milk contaminated with AFM1, so contain AFM1. Mixing bulk milk consignments with different levels of AFM1 contamination together is the only current process applied to reduce AFM1 content in milk [25]. The mean concentration of AFM1 in raw milk samples of Alborz province was from 0.0024 to 0.231 µg kg^{-1}, the mean concentration 0.027 ± 0.018 µg kg^{-1}. According to FAO, in 2002 the annual milk consumption in Iran was 26.5 kg. Meanwhile, in the years 2010 to 2017, due to advertising and educational activities, the per capita annual consumption increased by 90 to 100 kg per person. Finally, for reasons such as the increase in dairy prices, the annual per capita consumption was reported to be 66.12 kg per Iranian. While the per capita annual milk consumption in the United States and Europe was reported to be 300-400 kg per person [12]. All these results indicate the importance of paying attention to milk and its products and aflatoxin contamination. With the advancement of the world and the acquisition of new scientific methods to identify and reduce food toxins, more global attention should be paid to this issue. Because milk, in addition to being the main food of

many sections of society, has also become the raw ingredient for other process products.

Effects of AFM1 on human health

Exposure to AFM1 is problematic for health on human and animal. The most commonly used methods recently are ELISA and fluorescence detection (FLD) liquid chromatography (LLD) [26-28]. However, other methods include thin layer chromatography (TLC), lateral flow immunoassay, and gel-based safety assays. TLC is an old technique and using HPLC with FLD is most effective. It is widely used in the diagnosis of AFM1 these days [29-31]. Daily AFM1 intake, as estimated by JECFA for Africa, the Middle East, Latin America, Europe, and the Far East, was 0.002 ng kg^{-1} bw/day, 0.1, 0.058, 0.11, and 0.20, respectively [3]. Therefore, dairy foods are particularly vulnerable to contamination by AFM1 and there are certain risks to human health [32]. Acute aflatoxin poisoning can have serious effects on human health, including as different types of kidney and liver disturbance. Studies show that people with hepatitis B are 30 times more likely to develop liver cancer, while in chronic poisoning leading to depression, neurodegenerative diseases and deficiency of vitamins A and D. Studies show that aflatoxicosis causes poisoning, disease and death in humans and animals [32]. Numerous studies on living creatures exposed to aflatoxin have shown DNA damage, with AFM1 being the destructive agent Figure 1. Therefore, acute and chronic toxicity research on living creatures, it is obvious that AFM1 is carcinogenic to living creatures and is classified in group B2 as carcinogenic according to the IARC [12].

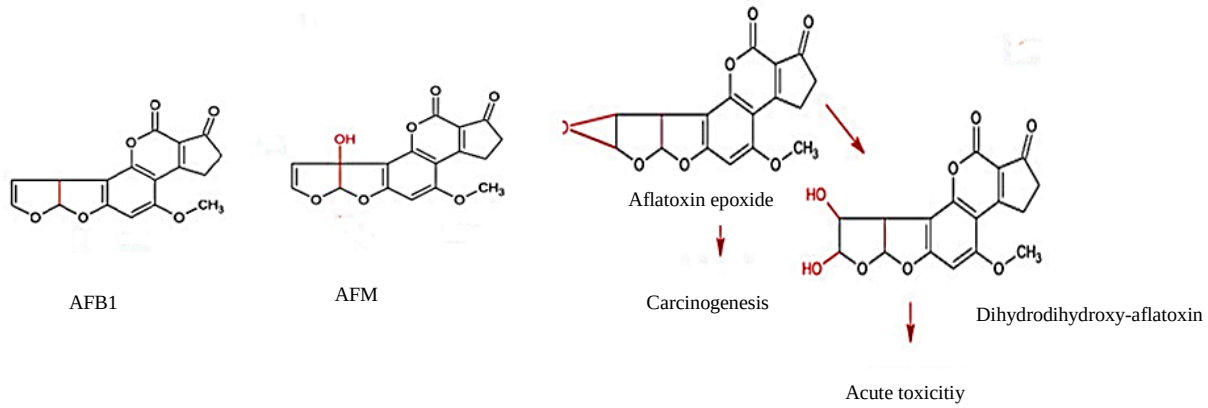

Figure 1. Aflatoxin M1 and its toxicity ways

Reduction of aflatoxin M1

Most countries have strict regulations for aflatoxins in milk, which vary from country to country. While the maximum residual rate (MRL) of AFM1 in dairy products is presented in Table 1. There are different ways to control aflatoxin levels, such as traditional methods of keeping feed dry to prevent the growth of toxin-producing fungi. However, humidity may be present in some countries based on climatic conditions. Therefore, it is necessary to study and find alternative methods.

Table 1. Regulation of aflatoxin M1 in dairy products in some countries [29]

Country	product	MRL (μg L^{-1})
USA	Milk and milk products	0.5
	cheese	0.25
EU	milk	0.05
France	infants and young children	0.25
	children <3 years	0.03
	pasteurized infant milk	0.01
Austria	butter	0.020
	cheese	0.25
	milk powder	0.4
Iran	milk	0. 1
	milk powder	0.5
	butter and butter milk	0.02
	cheese	0.2
Turkey and Switzerland	milk	0.05
	cheese	0.25

Aflatoxin reduction occurs in absorption or restructuring ways Figure 2. AFM1 was reduced by up to 100% after 60 min of treatment using *S. cerevisiae* in combination with lactic acid bacteria. *S. cerevisiae* alone reduced AFM1 by 90.3% during 30 minutes and 92.7%[33]. Heat-killed cells are used to prevent fermentation, which may affect the binding capacity of the yeast cell wall and also increase the ability of the microorganism to change its cell wall structure [33]. The use of biological filters for *S. cerevisiae* immobilized on perlite is also used [34]. In this study, the initial level of 0.23 ppb AFM1 decreased by 81.3% at 80 min. The effect of different levels of AFM1 on the binding potential of microorganisms was reduced by 0.1% AFM1 in milk (0.05 μg/L) using 0.1 μg l^{-1} *S. cerevisiae* alone or in combination with lactic acid bacteria [34].

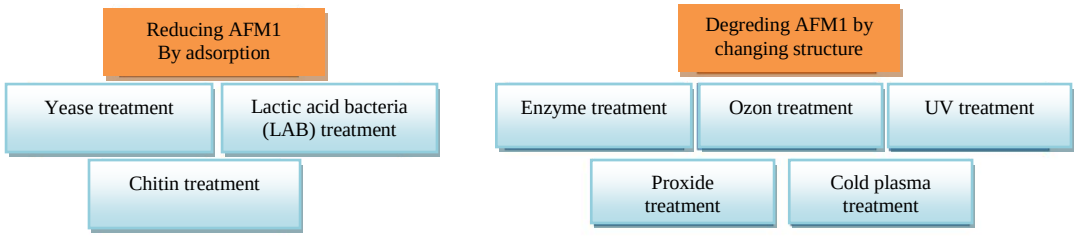

Figure 2. Reduction methods of Aflatoxin M1.

Chitin was used to bind AFM1 in milk [35]. Chitin binding capacity depends on the time of treatment, the level of chitin used, and the level of AFM1 contamination in the milk. The longer (24 hr) the binding between chitin and AFM1 was more stable compared to 30 min. Also, reducing the level of contamination, long duration and high level of chitin by using and low level of contamination of AFM1 increases the binding capacity of chitin.

The reduction of AFM1 in milk by LAB when using one strain was less than 90% [36, 37]. In other environments, such as yogurt, the binding capacity of AFM1 and lactic acid bacteria, which are also used as starters, include *L. delbrueckii* and *S. thermophilus* are less common [38]. Aflatoxin binding decreased by approximately 9% after yogurt production, which is probably related to the pH of the acid. However, Pierides et al. [39] It has been found that there is an increase in the binding ability of phosphate buffered saline at the acid pH level.

The ability of non-living microorganisms to bind has been more adaptable than that of living organisms. Therefore, to reduce the effects of fermentation, the use of heat in milk can be useful for deactivation, as has been done in yeasts [40]. In this regard, Kuharic et al. [41] isolated a higher percentage of AFM1 compared to living cells by examining non-living cells of *Lactobacillus plantarum*.

The link between aflatoxins and microbes is said to be weak, which is the reason for the connection. Although the binding mechanism is not fully understood, the binding mechanism is hydrogen bonds and vanderwaals bonds. Polysaccharides and peptidoglycans (Bacterial cell wall) are responsible for the uptake of AFM1 [42]. Different strains of bacteria have different ability to absorb aflatoxins due to changes in cell wall tissue [39,43].

The ability of bacteria and yeasts to bind aflatoxins in the short term [34]. This method suggests as a potential method for controlling aflatoxins in milk. Investigating the ability of microorganisms and environmental factors that may increase or decrease the connection capacity. Binding between the bacterial/yeast cell wall and aflatoxins is associated with AFM1 as a reversible bond, which does not degrade aflatoxins [44,45]. So evaluating the taste of milk after treatment will be necessary for future studies (Table 2).

The effect of enzymes on microbial species can be another way to control and of course the degradation of aflatoxin. In fact, instead of using the microorganisms, their enzymes are used for extraction. Degradation of aflatoxin using microbial extracts is said to depend on pH and temperature [46,47], and if destroyed, its mutagenicity is reduced [48]. In many studies, ozone has been used to reduce AFB1 in different food [49,50]. Ozone concentration, sample, time as well as moisture level inactivate aflatoxin by ozone [51]. Report the efficiency of this method has been around 50% [52]. Although ozone treatment for 5 min at 16 mg/l reduced AFM1 in milk containing 0.56 µg/kg by 50%, but it did decrease in ß-carotene content and total microbial count have seen [52].

Formation of aldehydes, organic acids, and ketones are other reactions that may occur [53]. Monozone derivatives through ozone treatment need to evaluate their effect on human health. This treatment causes reactions such as bonding between the furan and ozone. This may also be associated with reducing toxins and thus reduce the carcinogenicity and teratogenicity of aflatoxin [54].

Peroxide treatments are effective for inactivating AFM1 at a level of 0.7-1.7 µg L^{-1} in naturally contaminated raw milk of hydrogen peroxide (H_2O_2), riboflavin (Rib) or H_2O_2 and lactoperoxidase (LOP). The effectiveness of these treatments was up to 100%, but using too much H_2O_2 in food can be a risk to human health. Excessive consumption of hydrogen peroxide can cause serious gastrointestinal problems [55]. Food and Drug Administration (FDA) regulations for H_2O_2 0.5 mg L^{-1} in processed food and 0.05% by weight of milk [56]. Using ultraviolet light (UV) is another way to reduce aflatoxin. The use of high-intensity ultraviolet radiation can alter the organoleptic properties of milk in taste [34].

Cold plasma, argon, nitrogen, nitrogen containing oxygen, helium and air can also be used to degrade aflatoxins [27]. AFB1 degradation is believed to be caused by cold plasma OH radicals, which are strong oxidizing agents, increase

the reaction between ozone and the aflatoxin eruption ring [57].

Mutagenicity and toxicity of aflatoxin due to olefin double bonding in the aflatoxin catalyzed by the epoxy group by cytochrome P450. The disappearance of this double bond can prevent the formation of AFB1-exo-8,9-epoxide [58, 59] ultimately lead to a reduction in aflatoxin toxicity. Changes in this process have resulted in changes in the concentrations of butyric acid, caprylic acid [60] and stearic acid [34].Concentrations of milk fatty acids, ketones and alcohols did not change significantly while an increase in total aldehyde composition was observed [61]. Aldehyde content has also been reported to increase with increasing cold plasma exposure time [62]. Increased aldehydes can be associated with increased residual reactions. Studies have shown that medicinal plants have active compounds of medicinal and antioxidant substances can eliminate contaminants in food [63, 64] and have therapeutic effects in humans [65-74].

Table 2. Bacterial strains used to reduce Aflatoxin M1 in milk [33, 35-37, 43]

Species	Sample	Contamination level (ppb) of aflatoxin M1	Temperature (°C) and time	Reduction (%)
L. plantarum				
L. rhamnosus	Skim			
L. plantarum	milk/PBS	10	37°C- 24 h	4.13 –64.16
L. plantarum				
L. plantarum				
L. plantarum				
B. animalis	Yoghurt/PBS	0.1	42°C – 4h	49 -60
B. bifidum				
L. plantarum				
B. pumilus	-	40	37°C- 12 h	89.55
L. Plantarum				
L. acidophilus				
B. bifidum	Milk	50	37°C- 12 h	80 - 90
Kl. lactis				
S. cerevisiae				
L. rhamnosus	-	50	37°C- 18 h	63
L. helveticus	Milk	0.1	-	85
L.rhamnosus	UHT			
B. lactis	skimmed	0.5	4°C- 15 min	13-37
L. bulgaricus	milk			

CONCLUSIONS

AFM1 in dairy foods has adverse effects on alive creature (Human, infants and children) who consume large amounts of milk. Given that AFM1 has irreversible effects on human health and the highest transmission of AFM1 is through contaminated animal feed, it is concluded that to reduce the side effects of this dangerous toxin, the World Agricultural Health Organization should provide the necessary training to provide livestock feed to ranchers. Among the proposed methods, some methods are not able to completely reduce AFM1 and may pose an additional risk to food safety. Peroxide treatment requires high doses of hydrogen peroxide, which may create residues that are of

concern to human health. Microbial enzymes degrade aflatoxins and no harmful effects have been observed. But it is not used directly in milk and could be a new study.

CONFLICT OF INTERESTS

The authors declare no conflict of interest

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