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Review

Detoxification Methods of *Jatropha curcas* Seed Cake and Its Potential Utilization as Animal Feed

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Abstract: *Jatropha* seed cake (JSC) derived from *Jatropha curcas* seeds is a by-product of biodiesel production and, due to its high protein content, has been considered as a potential animal feed ingredient. However, the presence of toxic compounds such as phorbol esters and other anti-nutritional factors limits its use in animal feeding. Several detoxification approaches have been used to tackle these constraints and this review aims to summarize the recent advances in JSC treatment aiming to enhance its potential as an animal feedstuff. The review first provides an overview of the structure and composition of phorbol esters and other anti-nutritional compounds, discussing its toxic effects on different animal species. It then explores several detoxification methodologies giving special emphasis to its effects on the nutritional composition of JSC and on the use of the treated substrate as a feed ingredient in fish, poultry, pigs, and ruminants, highlighting their growth performance, nutrient utilization, and animal health issues. Overall, the review concludes that these treatments hold great potential for the detoxification and utilization of JSC as an animal feed ingredient. However, further research is needed to optimize the treatment conditions, evaluate the economic feasibility, and assess the long-term effects of treated JSC on animal health and product quality.

Keywords: *Jatropha curcas*; animal feed ingredient; anti-nutritional factors; detoxification methodologies

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1. Introduction

Within the industry of biodiesel production, the utilization of the residual seed cakes exists as a crucial aspect beyond mere oil extraction. *Jatropha* seed cake (JSC) is the main by-product of the *Jatropha curcas* biodiesel industry [1], which holds potential value as livestock feed [2,3]. Providing an added value to the defatted seed cake is essential to boost the sustainability, feasibility, and widespread acceptance of biodiesel production among both the scientific community and the general population [4]. Furthermore, viewing animal feed as a link connecting biodiesel and animal production, incorporating this by-product into animal feed has the capacity to enhance productivity within the biodiesel chain [5] and substantially increase the value of the cultivation system [6]. This holds particular significance considering that animal nutrition represents a considerable proportion of the total costs in animal production.

Jatropha seed cake (Figure 1) is characterized by a crude protein content of up to 60% [7], making it a promising resource for livestock feed. However, the presence of toxic compounds and anti-nutritional factors in *Jatropha* seeds [8–10] imposes cost-effective detoxification processes to unlock its full potential as feed ingredient. Although in the last three decades a large number of publications have been published, only few were

conducted to explore the removal of toxic compounds and other anti-nutritional factors. Various detoxification methodologies, including chemical, physical, and biological processes, have thus emerged as a critical area of research aimed at mitigating these challenges and unlocking the full potential of *Jatropha* seeds [7,11,12].

Figure 1. Seeds of *Jatropha curcas* and its seed cake after oil extraction (source: the authors).

Chemical methods involve treatments with solvents to neutralize or remove toxic compounds whereas physical processes, such as heat treatment or mechanical extraction, aim to alter the structure of the seed to reduce toxicity. Biological approaches utilize microorganisms or enzymes to degrade toxic components. Despite the potential of these methodologies, challenges persist in optimizing their effectiveness and scalability. Ameen et al. [11] and Azzaz et al. [12] highlighted the need for further research to evaluate the efficiency and practicality of detoxification techniques and Makkar [13] emphasized the importance of continued exploration to refine and validate these methods for widespread application. Moreover, the economic viability of detoxification processes must be considered, as they add additional costs to biodiesel production. Thus, cost-effective detoxification strategies are needed to ensure the competitiveness of *Jatropha*-derived products in the market [14]. In this way, the detoxification methodologies for JSC play a crucial role in enhancing the sustainability and economic viability of biodiesel production. Continued research and development efforts are essential for optimizing these techniques and addressing remaining challenges. By effectively detoxifying *Jatropha* products, its potential as a valuable feed ingredient while ensuring the safety and quality of animal nutrition can be maximized.

As several detoxification methodologies of Jatropha seeds have been described, either in isolated or combined methodologies, this review describes the main processes reported in the literature, giving special emphasis to the utilization of the detoxified products on animal nutrition trials.

2. Toxicity

A diverse array of biologically active compounds is widely distributed throughout the plant kingdom, particularly in species utilized as animal feed [15]. Among these plants, *Jatropha curcas* stands out for its well-documented toxicological effects across various plant tissues, with particular emphasis on its seeds as a focal point of research interest [16]. Within the possible toxic compounds present in *Jatropha*, trypsin inhibitors, lectins, phytate, saponins, and phorbol esters have been referred as the most relevant, either in concentration (Table 1) or toxic effects. The ingestion of whole *Jatropha* seeds has led to numerous cases of intoxication in humans, as evidenced by reported incidents [17,18].

Table 1. Anti-nutritional factors and toxic compounds of JSC.

Trypsin Inhibitors [1]	Lectins [2]	Phytate [3]	Saponins [4]	Phorbol Esters [5]	Reference
15.10	25.60	9.20	2.20	0.020	[19]
22.69	0.05	8.63	2.18	0.027	[20]
0.16	0.43	0.52	0.03	0.199	[21]
3.15	3.43	10.04	2.67	2.880	[22]
0.20	0.52	0.82	0.10	0.959	[21]
34.00	0.71	8.55	2.55	3.850	[8]
0.21	0.34	9.10	2.47	0.013	[10]

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g).

Furthermore, experimental studies have demonstrated adverse effects in rats following seed consumption, highlighting the potential risks associated with exposure to this plant species [17]. Similar detrimental outcomes have been observed in livestock such as cattle, sheep, and goats, further emphasizing the broad impact of *Jatropha* toxicity [17,23]. Moreover, the adverse effects of *Jatropha* extend beyond direct seed consumption, with negative repercussions observed in various animal species across different feeding regimes. For instance, poultry exposed to *Jatropha* meal have exhibited signs of toxicity, as evidenced by studies conducted on chickens [24]. Likewise, pigs fed with *Jatropha*-derived feed have displayed unfavorable physiological responses, underscoring the potential hazards associated with its use in animal husbandry practices [25]. Additionally, investigations into the effects of *Jatropha* on aquatic organisms have revealed deleterious impacts on fish populations, further highlighting the wide-ranging consequences of exposure to this plant species [18]. In ruminants, as well as in additional studies involving rats, the ingestion of *Jatropha*-derived products has been associated with adverse health outcomes, indicating a consistent pattern of toxicity across different animal models [26]. In this way, elucidating the mechanisms underlying *Jatropha* toxicity and its broader implications for animal health and welfare still remains a critical area of research.

2.1. Trypsin Inhibitors

There is a wide variety of bioactive compounds responsible for these toxic effects. Among the most relevant, *Jatropha curcas* L. is known to contain significant levels of trypsin activity inhibitors [27,28]. According to Makkar and Becker [18], JSC has trypsin inhibitory activity similar to that of soybean meal and is found in all parts of the kernel [29]. Trypsin inhibitors have been linked to pancreatic hypertrophy and hyperplasia [30], disrupting the digestive processes in monogastric animals and consequently stunting growth [8,31]. Ruminants are less sensitive to plant bioactive compounds than monogastric animals because rumen bacteria can greatly break down lectins, phytate, and trypsin inhibitors [31].

2.2. Lectins

Lectins, which belong to another class of proteins found in *Jatropha curcas* named phytohemagglutinin, have a strong anti-nutritional effect on animals due to their affinity for binding to carbohydrate molecules without altering their structure [32,33]. According to Xiao and Zhang [33], this binding ability damages the structure of the small intestine and destroys the digestive organs, which frequently results in the inhibition of animal growth [32]. While initially believed to be the primary toxic component in *Jatropha*, recent research suggests that lectins might not play a central role in its toxicity [27,34]. However, monogastric animals' performance may be negatively impacted by underheated JSC, which includes a significant amount of lectin [35].

2.3. Phytate

Phytate (inositol-hexaphosphoric acid) is a cyclic molecule with six phosphate groups that has been found to have anti-nutritional properties in cereals and legumes [32]. With its twelve ionizable protons, phytate possesses a special structure that allows it to bind proteins, minerals, and starch, creating complexes with proteins, starch, and chelates with the minerals [36]. Because it can chelate food micronutrients, making them unabsorbable and therefore having limited bioavailability, phytate is commonly referred to as an anti-nutrient [36]. According to Makkar et al. [37], JSC from different *J. curcas* genotypes contains phytates that can range from 7.2 to 10.1%, and as the digestive system of monogastric animals cannot degrade phytates, phosphorus availability might be reduced. Additionally, by forming complexes and interacting with enzymes like trypsin and pepsin, phytates have been associated with a decrease in protein digestibility [38].

2.4. Saponins

Saponins are steroid or triterpene glycoside compounds present in a variety of plants that due to their high surface-active qualities, which stem from the availability of both polar and nonpolar groups, account for many of their physiological activities [38]. In plants, saponins may serve as antifeedants or help in protecting the plant against microbes and fungi. However, saponins are often bitter and astringent in taste, and thus, when present in high concentrations, would reduce plant palatability for livestock [32]. As a defense mechanism against viruses, pests, and predators, saponins execute their principal biological effects through contact with membrane components. Characterized by their hemolytic activity and foaming properties, saponins influence the permeability of the small cells of the intestinal mucosa, thereby affecting the transport of active nutrients [31,32,39]. Since *Jatropha* saponins are non-hemolytic and are present in both poisonous and non-toxic forms of the plant at comparable concentrations, authors have suggested that they are relatively innocuous [31,40].

2.5. Phorbol Esters

Phorbol esters, discovered primarily in plant species of the *Euphorbiaceae* family [41], refer to a group of naturally occurring compounds, identified as the principal toxic agent in *Jatropha curcas* seeds and its by-products after oil extraction [37]. These compounds belong to the tigliane-type diterpenes family [32,42] and are categorized as tetracyclic diterpenoids, possessing a tigliane skeleton structure, characterized by a polycyclic framework [41–45]. The tigliane diterpenes consist of a 4-ring system labeled as A, B, C, and D [42–44]. Moreover, adjacent carbon atoms within this structure feature two esterified hydroxyl groups with fatty acids [43], and hydroxylation typically occurs at positions C_{12} and C_{13} of the tigliane skeleton [45,46]. Although phorbol esters share a common alcohol moiety, they display variations in their carboxylic acid components, primarily differing in substitutions at positions on the C ring [41,42,44]. The inherent hydroxylation capability at various positions in the fundamental structure, coupled with the potential for ester bonding to a range of acid moieties, results in the formation of diverse phorbol ester compounds [42,43,46,47].

Phorbol esters, primarily located in the seed core, exhibit varying concentrations dependent on the seed genotype [2]. According to Makkar [37], their concentration can range from 0.87 to 3.32 mg/g. By contrast, samples from Paplanta, Mexico, did not show detectable levels of phorbol esters [37]. In this way, the quantity of phorbol esters in *J. curcas* seeds can be influenced by several factors, including the geographical region of cultivation [27], soil composition, species variation, seed maturity, and in JSC, the method of oil extraction [41,46].

These compounds manifest various adverse biological effects, including inflammation [48], along with symptoms such as dizziness, vomiting, and diarrhea [32]. Additionally, several authors have reported other effects such as cell proliferation, platelet aggregation, lymphocyte mitogenesis, and prostaglandin production [4,15,41,43,49]. Other authors have also observed their tumor-promoting activity through the stimulation of protein kinase C

(PKC), which is crucial in signal transduction and the regulation of cell growth and differentiation [15,41]. Phorbol esters activate PKC by binding irreversibly to the protein, resulting in cellular damage [41]. These esters hyper-activate PKC, leading to cell proliferation and enhancing the effectiveness of carcinogens [15].

Various studies have highlighted the toxicity of phorbol esters found in the seeds and seed cake of *J. curcas*, posing risks to humans, rodents (mice and rats), domestic animals (sheep, goats, calves, chicks, and pigs), fish, and snails [13,27,28,41,50]. The symptoms of intoxication in humans were described by Makkar et al. [37] and include burning and pain in the mouth and throat, vomiting, delirium, muscle shock, decreased visual capacity, and a rapid pulse. The toxic effects observed in animals fed *J. curcas* seed fractions, attributed to phorbol esters, include reduced feed intake and weight gain, abdominal pain, diarrhea, mucosal membrane erosions, gastrointestinal tract hemorrhages, anemia, dyspnea, nervous imbalance, sunken eyes, acute necrotic liver lesions, proximal renal tubule cell damage, congested cardiac blood vessels, and death [13,16,41]. Furthermore, the topical application of isolated phorbol esters results in symptoms such as erythema, edema, necrosis, diarrhea, scaling, and thickening of the skin [41].

These negative effects have been observed using different plant materials and animal models indicating that phorbol esters may have a wide range of toxicological effects at different levels of intake, the administration method, and that animal species may also respond differently [16,41,51]. These parameters must be considered in order to implement effective risk management strategies, so that we can safeguard animal health and mitigate the adverse effects of exposure to toxic phorbol esters.

3. Detoxification Methodologies

Since the initial recognition of JSC as a potential feed ingredient, extensive research has been dedicated to exploring the feasibility of its detoxification. Over the past few decades, various detoxification techniques have been examined for the removal of anti-nutritional and/or toxic compounds. However, some of these methods may not be economically feasible, or may only address a portion of the issue, failing to fully degrade all these compounds. These methodologies encompass a spectrum of physical, chemical, biological, and combined approaches.

3.1. Physical and Chemical Treatments

Physical detoxification methods (Table 2) involve reducing toxicity through processes like heat treatment, irradiation, or deodorization. Trypsin inhibitors are deactivated by physical treatments, and its sensitivity to heat makes exposure to high temperatures necessary to partially or completely denature these compounds [8,30,32,35,38]. Nevertheless, the lipid content of JSC should be taken into account as lipids may protect trypsin inhibitors from heat inactivation [27]. From the presented results, it is also clear that phytic acid and saponins cannot be eliminated by heat treatments. Saponins are particularly heat-stable, and their biological activity cannot be diminished by typical cooking heat treatments [21,27,33]. The efficiency of heat treatments in the phorbol esters' concentrations (Table 1) is quite variable and most heat treatments show low levels of reduction on its concentrations, with studies demonstrating that roasting and other cooking treatments did not significantly affect phorbol esters' levels [19,20]. Nevertheless, when increased temperature and pressure are both applied, the increased degradation of phorbol esters is described [52].

Table 2. Physical methods utilized in JSC detoxification.

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Heat										
Dry heat [19]	14.60	ND	25.60	12.80	9.30	10.70	2.30	1.90	ND	ND
Dry heat [19]	15.10	ND	25.60	12.80	9.20	9.60	2.20	2.30	0.020	0.010
Dry heat [20]	22.69	0.65	0.05	ND	8.63	2.46	2.18	1.74	0.027	0.013
Dry heat [20]	22.69	0.00	0.05	ND	8.63	1.84	2.18	1.24	0.027	0.010
Dry heat [53]	-	-	-	-	-	-	-	-	0.350	0.068
Moist heat [54]	-	-	102	1.17	-	-	-	-	1.780	1.780
Moist heat [12]	18.89	0.65	-	-	-	-	3.50	3.33	-	-
Heat + Pressure										
3 mbar [55]	-	-	-	-	-	-	-	-	3.770	ND
1.91×10^5 mbar [52]	-	-	-	-	-	-	-	-	0.378	ND
Ionizing radiation										
50 kGy [56]	-	-	-	-	-	-	-	-	0.377	0.269
50 kGy [47]	-	-	-	-	-	-	-	-	0.290	0.041
125 kGy [47]	-	-	-	-	-	-	-	-	0.290	0.011
UV radiation [21]	0.16	0.14	0.43	0.26	0.52	0.05	0.03	0.02	0.199	0.016
UV radiation [57]	-	-	-	-	-	-	-	-	3.090	2.180
Microwave [58]	-	-	-	-	-	-	-	-	7.660	1.050
Ultrasonic [58]	-	-	-	-	-	-	-	-	7.660	0.950
Microwave and ultrasonic [58]	-	-	-	-	-	-	-	-	7.660	0.890

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g); BT—before treatment; AT—after treatment; ND—not detected.

In general, even though some heat-based methodologies showed a decrease in phorbol esters' levels, it can be inferred that heat treatments alone may not be sufficient to significantly reduce their concentration. This aligns with earlier reports by Makkar et al. [19,26] that heat treatment alone may not effectively deactivate phorbol esters. Nevertheless, treatments using a combination of heat and pressure [52,55] were able to degrade the totality of phorbol esters. Levels of reduction of up to 96% are also reported for ionizing radiation methodologies.

Chemical treatments involve the digestion of JSC with organic solvents or short-chain alcohols like ethanol or methanol, and over the past few decades, several chemical methods have been explored for JSC's detoxification (Table 3). Treatments' efficiency in decreasing trypsin inhibitors is quite low with some effects detected with the utilization of alkaline hydrolysis at high temperatures [12] or alkaline hydrolysis combined with ethanol extraction [8]. For lectins, phytic acid and saponins, ethanol extractions seem to reduce its concentrations in variable proportions depending on the treatments.

Table 3. Chemical methods utilized in JSC detoxification.

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Methanol										
50% [59]	-	-	-	-	-	-	-	-	0.210	0.080
70% [59]	-	-	-	-	-	-	-	-	0.210	0.270
90% [59]	-	-	-	-	-	-	-	-	0.210	0.360
90% [22]	3.15	3.09	3.43	1.46	10.04	7.28	2.67	1.58	2.880	0.980
99.5% [59]	-	-	-	-	-	-	-	-	0.210	0.470
Ethanol										
50% [59]	-	-	-	-	-	-	-	-	0.210	0.090
70% [59]	-	-	-	-	-	-	-	-	0.210	0.200
85% [58]	-	-	-	-	-	-	-	-	7.660	0.140
90% [59]	-	-	-	-	-	-	-	-	0.210	0.430
90% [22]	3.15	3.12	3.43	1.62	10.04	8.83	2.67	1.46	2.880	1.160
92% [60]	-	-	-	-	-	-	-	-	1.010	0.860
95% [59]	-	-	-	-	-	-	-	-	0.210	0.350
Ethanol [61]	-	-	-	-	-	-	-	-	0.656	0.023

Table 3. *Cont.*

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Methanol/ethanol										
(50:50) [58]	-	-	-	-	-	-	-	-	7.660	0.350
(50:50) [62]	-	-	-	-	-	-	-	-	3.600	0.100
Alkaline treatments										
$NaHCO_3$ [63]	-	-	70	ND	-	-	-	-	1.290	0.956
$Ca(OH)_3$ [63]	-	-	70	ND	-	-	-	-	1.290	1.285
NaOH [63]	-	-	70	ND	-	-	-	-	1.290	1.065
NaOH [64]	-	-	ND	ND	-	-	-	-	0.449	0.145
Urea [63]	-	-	70	ND	-	-	-	-	1.290	1.249
Alkaline hydrolysis + ethanol [60]	-	-	-	-	-	-	-	-	1.010	0.020
Mix treatments										
Methanol + NaOH [21]	0.20	0.10	0.52	0.90	0.82	0.84	0.10	0.10	0.959	0.860
Methanol + NaOH [12]	18.89	0.82	-	-	11.25	11.24	3.50	3.04	-	-
NaOH + methanol [58]	-	-	-	-	-	-	-	-	7.660	0.150
Hexane + methanol [65]	-	-	-	-	-	-	-	-	6.050	2.100
Combined methods										
Methanol + dry heat [54]	-	-	102	ND	-	-	-	-	1.780	0.090
Methanol + NaOH + dry heat [66]	ND	ND	ND	ND	-	-	-	-	1.800	ND
Methanol + NaOH + dry heat [67]	ND	ND	ND	ND	-	-	-	-	1.800	ND
Ethanol + $NaHCO_3$ + dry heat [8]	34.00	0.57	0.71	0.04	8.55	12.00	2.55	1.07	3.850	0.080
Methanol + NaOH + moist heat [68]	-	-	-	-	-	-	-	-	0.980	ND
Hexane + ethanol + moist heat [69]	0.22	ND	-	-	-	-	-	-	0.700	0.800
Hexane + ethanol + moist heat [70]	-	-	-	-	-	-	-	-	0.580	0.023
NaOH + dry heat [12]	18.89	0.75	-	-	11.25	10.56	3.50	3.15	-	-
$NaHCO_3$ + dry heat [8]	34.00	0.66	0.71	0.09	8.55	8.92	2.85	3.00	3.850	0.950
$NaHCO_3$ + moist heat [12]	11.89	1.33	-	-	11.25	11.25	3.50	1.75	-	-
$NaHCO_3$ + 10 kGy [8]	34.00	34.30	0.71	1.15	8.55	6.04	2.85	1.72	3.850	3.160
$NaHCO_3$ + air bubbling [56]	-	-	-	-	-	-	-	-	0.377	0.081

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g); BT—before treatment; AT—after treatment; ND—not detected.

Phorbol esters are moderately polar, and both ethanol and methanol have a strong affinity for them. The results presented in Table 2 show that its reduction after applying methanol or ethanol varies between a medium value of around 60% [59] for methanol, from 15% [60] up to 97% [61] for ethanol, and 96% for a mixture of these two solvents [58,62]. It should be noted that these differences should be attributed to different solvent concentrations and different incubation procedures, such as time and temperature of extraction. Nevertheless, both treatments are quite effective in the breakdown and degradation of phorbol esters.

Other chemical treatments, such as alkaline hydrolysis or a combination of alkaline/methanol or ethanol treatments with or without moist heat treatments, also point to efficiencies in the removal of phorbol esters of up to 98% [60]. According to Gomes et al. [43], although these physical and chemical treatments show a highly efficient removal of phorbol esters in some cases, the majority of them are considered to be aggressive to the substrates, being responsible for the degradation of proteins and functional amino acids and thus decreasing the nutritional qualities of JSC. According to the same authors [43], chemical detoxification methods with organic solvents and alkaline solutions could also alter the odor of feeds and, consequently, decrease its consumption by animals. Furthermore, methanol residual toxic components might also be present in treated substrates, thus inhibiting its utilization as an animal feed.

According to Martínez-Herrera et al. [8], due to its relatively low toxicity, ethanol offers an advantage over methanol, as any residues left in the treated meal, although improbable due to its higher volatility, are unlikely to adversely affect animals consuming it. Furthermore, while chemical treatments can rapidly degrade phorbol esters, various factors, such as the operational complexity, specialized equipment requirements, proper

disposal of solvent residues, and limitations in detoxification efficiency, all hinder the widespread adoption of such methods [43].

3.2. Biological Treatments

Biological detoxification offers a promising opportunity for converting agro-industrial waste and by-products into valuable raw materials utilizing various strains of fungi and bacteria to produce enzymes, metabolites, and other edible products, thereby providing an alternative to physical and chemical treatments. In the Kingdom of fungi, divisions such as Zygomycota, Basidiomycota, and Ascomycota are commonly employed for biological detoxification processes. The data presented in Tables 4–6 show that biodetoxification can be used to reduce potential toxic compound levels in JSC, although its contents may remain relatively high in some cases.

Trypsin inhibitors were reduced from values ranging from 60% [7] incubating with *Rhizopus oligosporus* up to 99% [71] by incubating with *Bacillus licheniformis*, respectively. Fungal treatments were able to reduce lectins by around 60% [7] when using *Trichoderma* strains, and by up to 80% [7] for *Aspergillus niger*, respectively. However, bacterial treatments were the most effective in lectin removal, attaining reduction values of up to 87% [72] using *Lactobacillus acidophilus*. For phytic acid, biological treatments using fungi showed a medium removal proportion of around 50%, with the exception of *Aspergillus* strains that were able to remove it to values of up to 93% [28]. Medium degradation values of saponins of 80% were obtained for fungal treatments with the highest removal proportion (95%) being attained for *Aspergillus niger* incubations [7,11]. While Zygomycota strains were able to reduce phorbol esters up to 75% [28], strains from Basydomycota reduced the concentrations by up to almost 100% [73], with medium removal values of around 80% for fungal and bacterial treatments.

Table 4. Biological methods utilized in JSC detoxification using Zygomycota and Basydomycota strains.

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Fungi—Zygomycota										
R. olisgosporus [7]	0.21	0.08	-	-	9.10	4.18	2.47	0.33	0.013	0.012
R. olisgosporus [70]	33.50	20.15	-	-	8.90	5.27	2.50	1.30	3.650	3.050
R. nigricans [7]	0.21	0.08	-	-	9.10	3.88	2.47	0.22	0.013	0.010
R. oryzae [28]	-	-	-	-	6.08	0.61	-	-	0.830	0.310
C. echimulata [28]	-	-	-	-	6.08	0.42	-	-	0.830	0.210
M. mucedo [11]	-	-	-	-	6.68	6.26	2.13	0.35	-	-
Fungi—Basydomycota										
B. adusta [74]	-	-	-	-	-	-	-	-	0.820	0.070
P. rufa [74]	-	-	-	-	-	-	-	-	0.820	0.020
G. resinaceum [74]	-	-	-	-	-	-	-	-	0.820	0.656
G. lucidum (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.075
G. lucidum (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.043
G. lucidum [75]	-	-	-	-	-	-	-	-	1.072	ND
P. chrysosporium [75]	-	-	-	-	-	-	-	-	1.072	0.591
T. hirsute [75]	-	-	-	-	-	-	-	-	1.072	0.197
T. zonata [75]	-	-	-	-	-	-	-	-	1.072	ND
T. gibbosa [75]	-	-	-	-	-	-	-	-	1.072	0.089
T. versicolor [75]	-	-	-	-	-	-	-	-	1.072	0.118
T. versicolor (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.214
T. versicolor (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.257
Pleurotus sp. (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.104
Pleurotus sp. (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.341
P. ostreatus (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.058
P. ostreatus (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.375

Table 4. *Cont.*

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Fungi—Basydomycota										
P. ostreatus (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.100
P. ostreatus (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.176

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g); BT—before treatment; AT—after treatment; ND—not detected; SmF—submerged fermentation; SSF—solid-state fermentation.

The data presented for the various biological treatments show that the removal of phorbol esters is within the values reported for chemical treatments. Nevertheless, it seems that certain fungal strains have the potential to completely degrade these compounds. As the incubation procedures are quite variable among the reported data (Table 4), specific methodologies should be analyzed in order to evaluate possible selection of fermentation techniques. In fact, differences within the reported values might be allocated not only to the different fungal strains used and the diverse synergism between its enzymatic complexes, but may also be due to the time of fermentation and the composition of the medium of incubation. Additionally, the combination of fungi in solid-state and submerged fermentation has been explored, with submerged fermentation generally proving to be more efficient in degrading phorbol esters [46].

Table 5. Biological methods utilized in JSC detoxification using Basydomycota and Ascomycota strains.

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Fungi—Basydomycota										
P. florida (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.163
P. florida (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.157
P. florida [75]	-	-	-	-	-	-	-	-	1.072	0.344
P. sapidus (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.150
P. sapidus (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.281
P. sapidus [75]	-	-	-	-	-	-	-	-	1.072	0.257
P. pulmonaris (SmF) [46]	-	-	-	-	-	-	-	-	1.072	ND
P. pulmonaris (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.262
P. eryngii (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.123
P. ostreatus [14]	-	-	-	-	-	-	-	-	1.090	0.002
P. ostreatus [75]	-	-	-	-	-	-	-	-	1.072	0.295
P. ostreatus [73]	-	-	-	-	3.06	0.77	-	-	1.080	ND
P. sajor-caju [75]	-	-	-	-	-	-	-	-	1.072	0.344
P. pulmonaris [72]	-	-	-	-	-	-	-	-	2.170	0.060
P. lecomtei (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.125
P. lecomtei (SSF) [46]	-	-	-	-	-	-	-	-	1.072	0.115
F. hepatica (SmF) [46]	-	-	-	-	-	-	-	-	1.072	0.043
F. hepatica (SSF) [46]									1.072	0.021
Coriolopsis sp. [76]									1.072	0.023
Fungi—Ascomycota										
T. longibrachitum [7]	0.21	0.08	0.34	0.14	9.10	4.12	2.47	0.43	0.013	0.011
T. harzianum [77]	-	-	-	-	-	-	-	-	2.780	0.060
T. harzianum [77]	-	-	-	-	-	-	-	-	2.780	0.110
P. sinensis [77]	-	-	-	-	-	-	-	-	2.780	0.160
C. cladosporioides [77]	-	-	-	-	-	-	-	-	2.780	0.220
F. chlamydosporum [77]	-	-	-	-	-	-	-	-	2.780	0.280
F. chlamydosporum [77]	-	-	-	-	-	-	-	-	2.780	0.300
F. chlamydosporum [77]	-	-	-	-	-	-	-	-	2.780	0.390

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g); BT—before treatment; AT—after treatment; ND—not detected; SmF—submerged fermentation; SSF—solid-state fermentation.

4. Utilization of Detoxified JSC in Animal Feeding

Variable detoxification efficiencies are presented in Tables 2–6 for different types of treatments. Although there are methodologies that can remove the toxic compounds of *J. curcas* at high proportions, the utilization of detoxified substrates should be carefully evaluated as the presence of some of these toxic compounds might still lead to negative results in terms of animal productivity. In fact, in the case of phorbol esters, a concentration as low as 0.021 mg/g of diet has produced lower body weights and reduced food intakes in rats [13]. Although Aregheore et al. [54] have considered a threshold of 0.09 mg of phorbol esters/g of substrate as a limit to the safe use of JSC as an animal feed, the results analyzing its incorporation in different animal species are quite variable.

Table 6. Biological methods utilized in JSC detoxification using Ascomycota and and bacteria strains.

Treatment	Trypsin Inhibitors [1]		Lectins [2]		Phytate [3]		Saponins [4]		Phorbol Esters [5]	
	BT	AT	BT	AT	BT	AT	BT	AT	BT	AT
Fungi—Ascomycota										
Penicillium sp. [7]	0.21	0.08	0.34	0.15	9.10	4.32	2.47	0.53	0.013	0.011
P. micynskii [28]	-	-	-	-	6.08	0.91	-	-	0.830	0.380
P. micynskii [28]	-	-	-	-	6.08	0.62	-	-	0.830	0.360
S. cerevisiae [28]	-	-	-	-	6.08	0.53	-	-	0.830	0.300
A. niger [78]	-	-	-	-	-	-	-	-	1.400	ND
A. niger [7]	0.21	0.07	0.34	0.08	9.10	2.70	2.47	0.13	0.013	0.003
A. niger [11]	-	-	-	-	6.67	5.92	2.13	0.48	-	-
A. niger [28]	-	-	-	-	6.08	0.21	-	-	0.830	0.250
A. versicolor [28]	-	-	-	-	6.08	2.15	-	-	0.830	0.260
A. versicolor [28,79]	0.70	0.01	0.31	0.03	6.08	1.70	-	-	0.832	0.158
A. oryzae [28]	-	-	-	-	6.08	0.43	-	-	0.830	0.350
A. terreus [28]	-	-	-	-	6.08	0.48	-	-	0.830	0.350
A. niger+N. sitophila [80]	-	-	-	-	-	-	-	-	0.007	0.002
Bacteria										
P. aeruginosa [21]	0.11	0.05	-	-	0.07	0.29	0.10	0.10	0.887	0.796
L. acidophilus [72]	23.30	4.20	55.41	7.35	6.50	2.75	4.50	2.40	-	-
Bacillus sp. [81]	1.47	0.41	-	-	8.80	0.39	-	-	-	-
Bacillus sp. [81]	1.47	0.16	-	-	8.80	0.09	-	-	-	-
B. subtilis (SmF) [82]	-	-	-	-	-	-	-	-	0.600	0.087
B. subtilis (SSF) [82]	-	-	-	-	-	-	-	-	0.600	0.180
B. licheniformis [71]	23.30	0.30	-	-	16.10	9.20	-	-	0.120	0.002
B. licheniformis [82]	-	-	-	-	-	-	-	-	0.600	0.232
B. smithii (SmF) [82]	-	-	-	-	-	-	-	-	0.600	0.252
B. smithii (SSF) [82]	-	-	-	-	-	-	-	-	0.600	0.075
B. sonorensis (SmF) [82]	-	-	-	-	-	-	-	-	0.600	0.245
B. sonorensis (SSF) [82]	-	-	-	-	-	-	-	-	0.600	0.150
B. coagulans (SmF) [82]	-	-	-	-	-	-	-	-	0.600	0.086
M. morganii [50]	-	-	-	-	-	-	-	-	7.530	1.210
M. morganii [50]	-	-	-	-	-	-	-	-	1.720	0.190
M. morganii [50]	-	-	-	-	-	-	-	-	7.750	0.560
Enterobacter sp. [83]	0.08	0.01	0.31	0.03	6.08	1.06	-	-	1.220	0.590

[1]—Contents expressed as mg trypsin inhibited/g; [2]—contents expressed as [1/(minimum amount of meal in mg/mL assay which produced hemagglutination)]; [3]—contents expressed as %; [4]—contents expressed as diosgenin equivalent; [5]—contents expressed as phorbol-12-myristate 13-acetate equivalent (mg/g); BT—before treatment; AT—after treatment; ND—not detected; SmF—submerged fermentation; SSF—solid-state fermentation.

As mentioned before, Makkar et al. [19] considered that heat treatments used for the detoxification of *J. curcas* seeds did not have the expected effect on the concentration of phorbol esters. The results reported by Agboola [84] showed that JSC inclusion in the diet of Japanese quails, obtained after roasting and the heat moisture extraction of oil, induced high mortality levels for an inclusion level above 10%, reaching 100% mortality at 20% incorporation. More recently Attia et al. [85] reported that an increase in the time period heat treatments applied to JSC can reduce the negative effects of its inclusion at 3.5% in the diet of Japanese quails, with final phorbol esters' concentrations of 0.068 mg/g of JSC. Nevertheless, animal performance parameters were still negatively influenced using this inclusion level. Similar results were obtained by El-Hack et al. [86] and Farag et al. [53],

also working with the same inclusion level in diets for Japanese quails, indicating that although the heat treatment might decrease the toxic level of JSC, some negative effects were still detected in animal performance parameters. These data indicate that the tendency to decrease JSC inclusion in the diet aiming to reduce concentrations of phorbol esters, although reducing severe effects such as animal mortality, still induce negative results on animals' performance. Another issue that should be highlighted is the duration of some of the trials, as short rearing periods may not be appropriate for measuring beneficial effects on animal health and production performances.

With respect to the implications of the inclusion of chemical-treated JSC in animals' diets, the data point to some contradicting results. A chemical treatment with 3% sodium bicarbonate was utilized in a feed trial with lambs aged between 4 to 6 months, in which JSC (containing 1.3 mg/g of phorbol esters) was included at a rate of 25% of the total diet [63]. As expected, due to the high concentrations of phorbol esters, mortality rates were high and animals' performance was negatively affected. On the other hand, petroleum benzene extraction for 60 min of JSC promoted its inclusion in carps' diets up to 25%, without adverse effects on growth and digestibility parameters [87]. According to these authors [87], the chemical treatment completely removed phorbol esters from the seed cake, that initially presented with values of 1.8 mg/g in the defatted substrate. More recently, Souza et al. [64] studied the application of an alkaline treatment using NaOH, achieving a 68% degradation of phorbol ester content up to a concentration of 0.145 mg/kg. The treated JSC was integrated into concentrate supplements for grazing dairy cows in three proportions of 10, 20, and 30% that corresponded to 0.0145, 0.029, and 0.04435 mg of phorbol esters/kg DM of diet. These inclusion levels led to a reduction in supplement intake, total-tract digestibility of nutrients, and the performance of the dairy cows. Nesseim et al. [88] employed a method of chemical extraction using petroleum ether to obtain JSC. The inclusion of the cake at 4 and 8% levels in broiler diets reduced animal performance parameters such as average daily weight gain and feed conversion ratio and the overall mortality rate showed an increase according to the levels of JSC in the diets.

Combinations of chemical and physical methods have also been studied with contrasting outcomes. Wang et al. [68], in a trial conducted with growing pigs demonstrated that JSC (containing 0.90 g/kg of phorbol esters), treated with 90% methanol-sodium hydroxide followed by a steam treatment (no phorbol esters detected after the treatment), included in diets at 25 and 50%, had no effects on animals' weight gain and feed conversion ratio. Li et al. [89] applied a method consisting of ethanol extraction and steam treatment to JSC, aiming to reduce phorbol ester contents to 0.11 mg/g. Using five inclusion levels up to 75% of soybean meal replacement in the diets of fattening pigs, these authors [90] verified that only until the 30% replacement level (corresponding to a final concentration of 5.50 mg/kg diet) no negative effects were detected. After this level, animals showed a lower average daily weight gain, average daily feed intake, and feed conversion ratio. More recently, Flora et al. [91] in a feeding trial using tilapia reported that JSC treated with chemical and extrusion techniques when included at levels up to 12% in the total diet reduced the growth performances of fish and high mortality rates were detected. In this study, the concentration of phorbol esters in the treated cake attained 0.023 mg/g and it reached 2.76 mg/kg of diet at the highest inclusion level.

Biological treatments using different strains of fungi and bacteria have been utilized as a promising strategy to degrade toxic constituents from JSC. According to Gomes et al. [43,92], these biodetoxification methods present several advantages over the other methodologies such as their potential higher efficiency, lower costs, as well as the possibility of obtaining fermented products with improved nutritive value due to the activity of certain specific enzymes during the incubation periods.

Belewu et al. [93], when evaluating the efficiency of *A. niger* and *T. longibrachitum* on the detoxification of JSC for its inclusion in goat's diets at 2 and 4%, verified that the lowest level of incorporation of JSC treated with *A. niger* could be regarded as safe, indicating that this strain is quite effective on the detoxification of the substrates. Nevertheless, the results

obtained for the highest level of inclusion and the data obtained for the diets including JSC treated with *T. longibrachitum* did not reveal such a promising outcome due to the hematological results of the animals subjected to these diets and the mortality rate that was recorded. In another study, Belewu et al. [94] demonstrated that a combination of *A. niger*-, *P. chrysogenum*-, and *T. harzanium*-treated JSC can replace 50% of the soybean cake in the diets of West African dwarf goats without any adverse effects. However, the specific phorbol ester levels in both the untreated and treated kernel meal were not reported. In a study conducted by Kasuya et al. [14], JSC treated with *P. ostreatus* for 45 days showed a decrease in the phorbol ester content of 99% to a concentration of 0.002 mg/g dry matter. The inclusion of the treated JSC on diets for goats at a rate up to 20% of incorporation for a period of 72 days showed no effects on animal performance parameters as well as on measured hematological and clinical chemistry parameters. On the other hand, studies reported by Okukpe et al. [95] showed that goats fed on diets with the inclusion of JSC treated with *T. ghanense* and *T. asperellum*, at up to 4% of the total diet, were severely affected as determined by the measured parameters for animal growth and high mortality levels after five weeks of trial. It should be noted that no data are presented for the phorbol ester concentrations of the treated JSC.

More recently, Ojediran et al. [96] evaluated the performance of Marshal strain broiler chicks fed on diets containing 10% of JSC treated with *A. niger*. Before the fermentation procedure, JSC was subjected to five different processing methods. The final concentration of phorbol esters varied between 0.550 and 0.942 mg/100 g of substrate. The data reported by these authors suggest that animals were adversely affected with the inclusion of treated JSC due to the negative effects on animals' performance as well as due to the high mortality levels. In contrast, Nesseim et al. [97] evaluated intake and growth performance of broiler chicks subjected to diets including up to 8% of JSC treated with *A. niger*, and observed no differences within the measured parameters, and even positive effects were detected in animals fed the treated JSC, for which the average daily weight gain and live weight were higher. It should be pointed that no data on phorbol ester concentration were presented. In a study evaluating the effects of hydrothermal processing and fermentation using *Bacillus* sp. and *Staphylococcus* spp. on the nutritive value of JSC, Okomoda et al. [81] verified that there was an improvement in feed conversion ratio as well as in general growth parameters of African catfish fed on diets containing approximately 30% of the treated substrates. Although these authors showed a general decrease in several anti-nutritional factors after treatments, no data were presented for the phorbol esters of JSC.

5. Conclusions

Although the detoxification treatments used on JSC to remove, degrade, or inactivate different anti-nutritional compounds present different efficiencies, depending on the methodologies used, recent approaches have pointed out the advantages of combining treatments in order to enhance their effectiveness and overcome possible limitations. In fact, although physical treatments have low implementation costs, they are less effective in reducing the content of phorbol esters and together with chemical treatments they are considered to be aggressive and may cause the degradation of other compounds such as proteins and amino acids. Some chemical methods are efficient in the removal of toxic compounds, including phorbol esters, but present the drawbacks of environmental disposal, of changing the palatability of the substrates, and the high cost of chemical reagents. However, it should be stressed that nowadays physical and chemical treatments are still considered the most adequate to process large amounts of substrates in a short period of time. Alternatively, although time consuming, the utilization of biological treatments should be considered a viable approach. On top of being environmentally friendly, they are lower in cost and possess high efficiency in the removal of toxic compounds. As biodegrading microorganisms have multifaceted enzymatic complexes that are able to reduce or eliminate anti-nutritional compounds, they are also capable of promoting changes in

their lignin structure and facilitate access to structural polysaccharides, so they are a viable assay in bioremediation.

Phorbol esters are the most impactful toxic compound in JSC and their degradation is most effective when using chemical and biological treatments. Nevertheless, animal trials have demonstrated that JSC should only be included in diets if these compounds have been completely removed.

In this way, the reported data underscore the potential of biological detoxification methods to significantly reduce phorbol esters in JSC, thereby making it a viable option for producing value-added products from agro-industrial waste and by-products. However, it is imperative to note that further research is needed to optimize the conditions and strains for achieving maximum detoxification efficiency. Through continued investigation and refinement, biological detoxification methods hold the promise of not only mitigating the toxicity of *J. curcas* but also unlocking its potential as a sustainable and valuable resource in the agricultural and industrial sectors.

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