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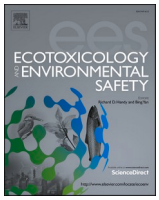

Nephroprotective effects of *Acacia senegal* against aflatoxicosis via targeting inflammatory and apoptotic signaling pathways

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ABSTRACT

Aflatoxin B_1 (AFB1) is a common environmental pollutant that poses a major hazard to both humans and animals. *Acacia senegal* (Gum) is well-known for having antioxidant and anti-inflammatory bioactive compounds. Our study aimed to scout the nephroprotective effects of Acacia gum (Gum) against AFB1-induced renal damage. Four groups of rats were designed: Control, Gum (7.5 mg/kg), AFB1 (200 μg/kg b.w) and AFB1-Gum, rats were co-treated with both Gum and AFB1. Gas chromatography-mass spectrometry (GC/MS) analysis was done to determine the phytochemical constituents in Gum. AFB1 triggered profound alterations in kidney function parameters (urea, creatinine, uric acid, and alkaline phosphatase) and renal histological architecture. Additionally, AFB1 exposure evoked up-regulation of mRNA expression levels of inflammatory cytokines, including interleukin-6 (IL-6), tumor necrosis factor α (TNFα), inducible nitric oxide synthase (iNOS), and nuclear factor kB p65 (NF-κB/P65) in renal tissue. The oxidative distress and apoptotic cascade are also instigated by AFB1 intoxication as depicted in down-regulated protein expression of the nuclear factor erythroid 2–related factor 2 (Nrf2) and superoxide dismutase type 1 (SOD1) along with upregulation of cytochrome c (Cyto c), and cleaved Caspase3 (Casp3–17 and 19) in renal tissue. In conclusion, current study obviously confirms the alleviating

Abbreviations: AFB1, aflatoxin B_1; AFBO, aflatoxin-exo-8,9-epoxide; Gum, *Acacia senegal*; ALP, alkaline phosphatase; Cl. Casp3–17/19, cleaved caspase3–17/19; Cyto c, cytochrome c; GC/MS, Gas chromatography-mass spectrometry; GSH, glutathione; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; NF-κB/P65, nuclear factor kappa-B transcription factor/P65; Nrf2, nuclear factor erythroid2–related factor2; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; TNF-α, tumor necrosis factor-α.

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effects of Gum supplementation against AFB1-induced renal dysfunction, oxidative harm, inflammation, and cell death. These mitigating effects are suggested to be attributed to Gum's antioxidant and anti-inflammatory activities. Our results recommend Gum supplementation as add-on agents to food that might aid in protection from AFB1-induced nephrotoxicity.

1. Introduction

Aflatoxins are secondary metabolites produced by certain *Aspergillus* fungi (*Aspergillus flavus* and *A. parasiticus*), and possess a bisdifuran ring structure (Gao et al., 2021). They are inescapable environmental contaminants due to their pervasiveness in the food chain and can cause serious health consequences. Among them, aflatoxin B_1 (AFB1) is the most ubiquitous poisonous one and exhibits immunosuppressive, neurotoxic, reprotoxic, teratogenic, genotoxic, and carcinogenic activities and is designated as a class 1 carcinogen (Yilmaz and Bag, 2022; Zhang et al., 2022; Wang et al., 2022; Karamkhani et al., 2020).

The toxicity of AFB1 is mainly owing to its biotransformation to AFB1-exo-8,9-epoxide (AFBO) via hepatic cytochrome-P450. AFBO is a highly reactive toxic intermediate that attacks the guanine residues of DNA, creating adducts that lead to well-renowned mutations (Wang et al., 2022). Subsequently, AFBO is detoxified by phase 2 glutathione (GSH) system to less toxic GSH-complex that is ready to excreted from cells via the mercapturic acid pathway (Dlamini et al., 2021). In addition to liver, kidney is another potential target for AFB1 toxicity. AFBO are selectively absorbed and concentrated by tubular cells and accumulated in the renal medulla prior to being excreted in the urine and causing direct toxic damage to renal tubules (Wang et al., 2022).

There is a plethora of evidence indicating that oxidative stress and apoptotic pathways are the pathological foundation of AFB1-prompted renal damage. Depletion of antioxidant enzymes as well as formation of reactive oxygen species (ROS), provoking tissue injury such as DNA adducts, mitochondrial perturbation, protein misfolding, and eventually necroptosis (Dlamini et al., 2021; Meki et al., 2001; Owumi et al., 2020; Li et al., 2022). Therefore, antioxidants supplementation could be a feasible therapeutic strategy to halt AFB1 -induced renal damage.

Over the last few decades, considerable studies have recognized plant-based natural ingredients as potential sources of drugs, including *Acacia senegal* (Gum). Gum is a natural emulsifier exuded by incision of the branches and stems of *A. senegal* tree (Ashour et al., 2022). It has been certified by the Food and Drug Administration (FDA) procuration as a safe dietary fiber (Hassanien, 2019; Elshama, 2018). It comprises arabinogalactan polysaccharides, proteins, and minerals (Abdin et al., 2022). Thus, Gum is exploited in medicinal activities because of its therapeutic potential owing to its antioxidant (Hassanien, 2019), immune-modulatory (Ali et al., 2020), anti-inflammatory (Elshama, 2018), and antibacterial activities (Elshama, 2018). Gum antioxidant capability could be ascribed to its amino acids, which have robust potential to quinch ROS and promote the oxidant scavenging system (Ali et al., 2020; Avelino et al., 2022). Additionally, it has anti-inflammatory and immunomodulatory properties owing to its potential to form short chains of fatty acids, which alter the inflammatory mediators release (Eslick et al., 2022). Accordingly, there is a growing body of literature has highlighted the effectiveness of Gum against renal diseases and various toxicants, including; chronic kidney disease (Ali et al., 2020), gentamicin (Ahmed et al., 2022; Ali et al., 2003), mercuric chloride (Gado and Aldahmash, 2013), and cisplatin (Al-Majed et al., 2003).

Consequently, this study was done to evaluate the mitigating modulatory impacts of Gum toward the nephrotoxicity induced by AFB1 exposure. Kidney function parameters, levels of expression of oxidative stress and inflammation-related genes, apoptosis signaling pathways, and renal histology were evaluated.

2. Materials and Methods

2.1. Phytochemical analysis of Acacia senegal extract

2.1.1. Preparation of Acacia senegal extract

The methanolic extract of the Gum was made by mixing 10 g of Gum with 100 mL 85% methanol and maintained at ambient temperature (30 ± 2 ℃) for 24 h. Then, this extract was filtered and concentrated under vacuum at 40 ℃ by a rotatory evaporator to provide crude extract. Methanol was used to reconstitute the crude extract for further analysis.

2.1.2. Gas chromatography-mass spectrometry (GC/MS) analysis of Acacia senegal extract

The phytoconstituents of Gum were identified by using GC/MS analysis (GC-Trace Ultra-ISQ mass spectrometer, Thermo Scientific, Austin, USA). The sample was injected to a capillary column (30 m × 0.2 mm × 0.25 μm) fused with silica. The injector temperature was maintained at 250 ℃ while the oven temperature of the GC was adjusted with an initial temperature of 60 ℃/min and further increased at the rate of 10 ℃/min until 280 ℃ with an overall holding time of 36.5 min. Helium (99.9% purity) was used as a carrier gas system with a regular flow rate of 1.0 mL/min. The solvent delay was 4 min and diluted specimens of 1 μl were injected automatically by autosampler (AS3000) coupled with GC and calibrated in the split mode. Within 40–650 m/z spectrum, electron ionization voltage was 70 eV at a full scan mode. The ion source temperature and GC–MS interface were maintained at 200 ℃ and 250 °C, respectively. The identity of active constituents was based on matching the retention times of identified compounds in the mass spectra with renowned compounds kept in the National Institute Standard and Technology (NIST) and WILEY mass spectral libraries. The obtained compounds have been tabulated. The percentage of composition was determined by area normalization.

2.2. Animal study and ethical endorsement

Wister albino rats (120 ± 10 g body weight) were procured from the Center of Laboratory Animals, Faculty of Veterinary Medicine, Assiut University, Egypt. Rats were housed in appropriately adjusted environments (22.5 ± 2 ℃, 50–60% humidity) for two weeks beforehand the experiment. All rats were fed on a conventional baseline diet with free access to water throughout the experiment. This experiment was granted by the Institutional Animal Care and Use Committee of the Faculty of Veterinary Medicine, South Valley University (Approval no. 31B/14.04.2022).

After two weeks, rats were equally allocated to 4 groupings: (1) Control group, rats were received saline; (2) Gum group, in which rats was given gum by oral gavage at dose of 7.5 g/kg b.w once daily (Gado and Aldahmash, 2013); (3) AFB1 group, rats were exposed to AFB1 at a dose of 200 μg/kg b.w, orally, every alternate day (Tang et al., 2007); (4) AFB1-Gum, rats were co-treated with both gum and AFB1 as the doses mentioned above. Notably, AFB1 was given 5 h following gum administration.

After 4 weeks, the trial was terminated, the blood sample was gathered from the retro-orbital venous plexus, and the plasma was harvested and stored at − 20 °C for further biochemical testing. Following, all animals were euthanized under inhalation of isoflurane and the kidney was swiftly removed and rinsed out with cold physiological saline to remove any clots, thereafter, sliced into several pieces. For subsequent histological inspection, one part was fixed in 10%

Table 1
The phytochemical compounds identified in Gum extract by GC-MS analysis.

No	Chemical name	Bioactive Compounds	Retention time (min)	Peak area (%)	Molecular formula	Molecular weight
1	L-Gala-L-ido-octose	Octose (Monosaccharide)	11.74	0.36	C8H16O8	240
2	1,4-Benzenediol, 2-(1,1-dimethylethyl)− 5-(2-propenyl)-	Phenylpropanes	14.83	1.05	C13H18O2	206
3	Benzoic acid, 3,5-bis (1,1-dimethylethyl)− 4-hydroxy -, ethyl ester	Benzoic acid	15.16	0.43	C17H26O3	278
4	Trans-Z-à-Bisabolene epoxide	Sesquiterpenoids	15.41	0.25	C15H24O	220
5	10,13-Octadecadiynoic acid, methyl ester	Linoleic acids	17.73	0.8	C19H30O2	290
6	(1-Methylundecyl)benzene	Fatty acid	20.69	0.81	C18H30	358
7	Dodecanoic acid, 2,3-bis(acetyloxy)propyl ester	Triacylglycerols	21.20	0.63	C19H34O6	358
8	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	Benzoic acid (Carboxylic acid)	23.01	55.26	C16H22O4	278
9	Hexadecanoic acid, methyl ester	Palmitic acid	23.43	6.75	C17H34O2	270
10	Phthalic acid, butyl undecyl ester	Phthalic acid	24.09	0.52	C23H36O4	334
11	Hexadecanoic acid	Palmitic acid	24.83	3.66	C16H32O2	256
12	1,25-Dihydroxyvitamin D3, TMS derivative	Vitamin D_3	25.33	0.34	C30H52O3Si	488
13	Cyclopropane octanoic acid, 2-[[2-[(2-ethylcyclopropyl) methyl] cyclopropyl] methyl]-, methyl ester	Cyclopropane fatty acid	26.35	1.53	C22H38O2	334
14	Octadecanoic acid, methyl ester (Methyl stearate)	Stearic acid	26.96	4.17	C19H38O2	298
15	Hexadecanoic acid, 1,1-dimethylethyl ester	Palmitic acid	27.22	1.23	C20H40O2	312
16	9- Octadecenoic acid	Oleic acid (Omega-9)	28.18	19.81	C18H34O2	282
17	Oxirane undecanoic acid, 3-pentyl-, methyl ester, cis	Fatty acid	30.29	0.61	C19H36O3	312
18	2,2,3,3,4,4 hexadeutero octadecanal	Fatty aldehydes	30.55	0.54	C18H30D6O	274
19	Methyl-9,9,10,10-d4-octadecanoate	Stearic acid	33.42	0.61	C19H34D4O2	302
20	3′,8,8′-Trimethoxy-3-piperidyl-2,2′-b inaphthalene-1,1′,4,4′-tetrone	Alkaloid compound	33.70	0.31	C28H25NO7	487

neutral buffered formalin. Other tissue portions were used for RNA and protein extraction and maintained at − 80 °C.

2.3. Estimation of kidney function parameters

Kidney function parameters, including urea, creatinine, uric acid, and alkaline phosphatase (ALP) were evaluated in the plasma. All procedures were carried out in accordance with the manufacturer's (Laboratory Biodiagnostics Co., Giza, Egypt) protocols.

2.4. RNA isolation with reverse transcription-PCR

According to the manufacturer's instructions, total RNA was isolated from kidney homogenate using QIAzol Lysis Reagent (QIAzolTM, QIAGEN®, USA). Using a spectrophotometer, the samples' total RNA concentration and quality were evaluated (NanoDrop ND-1000 Spectrophotometer, Thermo Scientific, USA). The ratio of 260–280 nm absorbance was used to determine the RNA quality. The miScript II RT kit (QIAGEN®, USA) was used to reverse-transcribe the extracted total RNA into cDNA. The cDNA was created from 1 μg RNA utilizing a primer (oligo (dT) primers, PrimeScript™, TaKaRa Bio Inc, CA, USA). The PCR using the primers (interleukin-6 (IL-6), tumor necrosis factor α (TNFα), inducible nitric oxide synthase (iNOS), and nuclear factor kB p65 (NF-κB/P65)) given in Table S1 was carried out using a thermal cycler (A200 Gradient Thermal cycler, LongGene®, Hangzhou, China). The PCR products were then electrophoretically separated 1.5% agarose gel stained in ethidium bromide (Scientific Limited, Northampton, UK) in tris-borate-EDTA (TBE) buffer. The isolated bands were spotted by a gel recording system (Bio-Rad, USA) and band intensity was measured and normalized against β-actin by using the NIH Image J v1.47 program.

2.5. Western blotting assessment

Protein fraction was isolated from the organic phase fatty tissue samples processed with QIAzol Reagent-(QIAGEN®, QIAzol™) in accord to the manufacturer's instructions, and it was then treated with a proteinase inhibitor cocktail (Sigma-Aldrich, Germany) and phosphatase inhibitor tablet (PhosStop™, Roche Diagnostics, USA). Protein samples were loaded in equivalent proportions, isolated using SDS-poly acrylamide gel (SDS-PAGE) electrophoresis, and then blotted on a polyvinylidene difluoride membrane (PVDF, Immobilon-P, Millipore). The membranes were probed with the diluted primary antibodies (the nuclear factor erythroid 2–related factor 2 (Nrf2), IL-6, superoxide dismutase type 1 (SOD1), cytochrome c (Cyto c), and cleaved Caspase3 (Cl. Casp3–17/19)) after being blocked in PBS-Tween (0.1%) with 1% BSA (Table S2). The bands were detected using the BioRAD chemidoc and the Roche Lumi-light Plus kit. Bands intensities were quantified with the NIH Image J software.

2.6. Histological inspection and scoring

The formalin-fixed kidney tissue specimens were first dehydrated in ascending alcohol grades. Then xylene clearing was done before being embedded in paraffin. The tissue was sliced into 5 μm thick sections then stained with H&E for histoarchitecture inspection and scanned using a camera-integrated digital imaging system (DM300, Leica, Germany). According to Qi and Wu (Qi and Wu, 2013), the tubular injury was defined as tubular epithelial necrosis, lymphocytic infiltrations, cytoplasmic vacuolization, tubular dilatation and the loss of the brush border. Tubular injury was scored by grading the percentage of damaged renal tubules under ten randomly selected, non-overlapping fields at magnification of X200) as follows: 0, 0%; 1, ≤ 10%; 2, 11–25%; 3, 26–45%; 4, 46–75%; and 5, 76–100%. To score injured tubules, whole tubule numbers per field were considered as standard at same scale. The grading percentage was calculated in each field as follows:

$$\text{Injury } \textit{score}\ (\%) = \frac{\text{number of injured } \textit{tubules}}{\text{total number of } \textit{tubules}} \times 100$$

2.7. Data analyses

One-way analysis of variance (ANOVA) was used to analyze the data, and Duncan's post hoc test was used to compare the treatment means (SPSS software, version 21; Inc., Chicago, IL, United States). All values are regarded as statistically significant at $p \leq 0.05$ and expressed as the mean and 95% confidence interval. The OriginPro software (version 2019b) was used to for univariate data visualization. The MetaboAnalyst program was also used to create the dendrogram and a correlation heatmap.

CRediT authorship contribution statement

Obeid Shanab: Conceptualization, Methodology, Investigation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration. **Samir M. El-Rayes:** Conceptualization, Methodology, Validation, Writing – original draft. **Waleed F. Khalil:** Conceptualization, Validation, Writing – original draft. **Noha Ahmed**: Conceptualization, Methodology, Investigation, Writing – original draft. **Afaf Abdelkader:** Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Nashwa H. Aborayah:** Methodology, Formal analysis, Data curation, Writing – original draft. **Ahmed M. Atwa:** Validation, Data curation, Writing – original draft, Visualization. **Faten I. Mohammed:** Methodology, Investigation, Formal analysis, Data curation, Writing – original draft, Visualization. **Hend E. Nasr:** Methodology, Investigation, Data curation, Writing – original draft, Visualization. Samah F. Ibrahim: Software, Resources, Writing – original draft, Visualization. **Amr M. Khattab:** Software, Resources, Writing – original draft, Visualization. **Mohammed Alsieni:** Software, Validation, Resources, Writing – original draft. **Ali Behairy:** Investigation, Formal analysis, Data curation, Writing – original draft. **Liana Fericean:** Software, Formal analysis, Resources, Writing – original draft, Writing – review & editing. **Lina A. Mohammed:** Methodology, Investigation, Formal analysis, Writing – original draft, Visualization. **Ahmed Abdeen:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Visualization, Supervision.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Samah F. Ibrahim reports financial support was provided by Princess Nourah bint Abdulrahman University. Liana Fericean reports financial support was provided by University of Life Sciences.

Data Availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ecoenv.2023.115194.

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