

Molecular docking and in vivo studies of Aloe vera gel for their potential anti-apoptotic activity against aluminium chloride-induced neurotoxicity in mice

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Abstract

Neurotoxicity resulting from aluminium chloride (AlCl_3) exposure has been linked to increased apoptosis in neuronal cells, contributing to various neurodegenerative diseases. On the other hand, the use of alternative medicines has been practiced for years and formed part of our tradition around the world. This study investigated the impact of Aloe vera gel on brain apoptotic and pro-apoptotic markers in mice subjected to aluminium chloride-induced neurotoxicity via experimental and computational models. Twenty mice were divided into four groups as control, AlCl_3 , *Aloe vera* and AlCl_3 + *Aloe vera* respectively. Following a two-week treatment period, brain tissues were harvested for quantitative determination of apoptotic markers, employing standard methods. Molecular docking was done on all identified ligands and proteins using a computational approach. The results demonstrated a significant increase in Caspase-3 and Bax levels in the AlCl_3 group compared to both the control and *Aloe vera* groups. Conversely, Bcl-2 levels were significantly reduced in the AlCl_3 group. Notably, treatment with *Aloe vera* gel led to decreased Casp-3 and Bax levels in the AlCl_3 + *Aloe vera* group compared to the AlCl_3 group, while Bcl-2 levels increased. The molecular docking analysis of the present study indicated that Aloe resin C had the best binding score for all the proteins sampled with scores of -8.180, -6.908 and -9.811 for Bax, Bcl-2 and Casp-3 respectively. These findings thus, highlight the potentials of *Aloe vera* as a therapeutic agent in stabilizing neuronal membrane and mitigating apoptotic processes associated with aluminium chloride exposure by promoting anti-apoptotic signaling.

Introduction

Neurotoxicity, a term that refers to the condition in which the nervous system is directly or indirectly exposed to chemicals either naturally occurring or man-made, thereby impairing the nervous system's normal functioning in both man and animals [1], [2]. As reported by [3], [4], the brain is an important organ that is more susceptible to exogenous stimuli than other organs of the body because of numerous polyunsaturated fatty acid contents which makes the neural tissues very sensitive to peroxidation. Several chemicals can elicit neurotoxic disruptions in man, and also many are employed in experimental models for neurotoxicity in animals, such as aluminium chloride.

Aluminium chloride is an abundant metal on earth both in the environment and in food, with easy access to the human body via different means [5], [6]. It is a well-established neurotoxicant involved in the etiology of neurodegenerative diseases [7]. For instance, it has been reported by several researchers that it is a major neurotoxin, disrupter of neurological functions and accelerator of oxidative stress, plaque formation and amyloid beta ($\text{A}\beta$) deposition in animal models, humans and cell lines [8]–[11]. According to [11], apoptosis is the final step in the pathway of toxicity induced by aluminium leading to neurodegeneration. Apoptosis is a controlled form of physiological cell death involving cascades of degenerative events [12], [13]. Accordingly, experimental and clinical evidence have established that neurological insults, including chemical exposures, can trigger aberrant apoptosis in the brain in vitro or in vivo [7], [13], [14]. For instance, various apoptotic markers (Bcl-2 and caspase families) have been reported to be expressed following aluminium exposure indicating programmed cell death [15]. The specific mechanisms of apoptosis induction vary between exposure paradigms. However, apoptosis is triggered generally by increasing pro-apoptotic and/or decreasing anti-apoptotic markers.

Alternative medicine usage has been in practiced for years as still being used today, even in a more advanced way, including *Aloe vera*. According to [16], alternative medicine remains a constituent part of many cultural and technological development around the world. *Aloe vera* also referred to as *Aloe Barbadensis Miller*, belonging to the *Liliaceae* family is a plant with long-standing reputation majorly for its health, skincare and other benefits [17]. Research has shown that *Aloe vera* contains several phytochemicals and about 200 bioactive components, with the inner gel reported to possess most of the components [17]. The plant has been reported to possess various pharmacological properties, including antioxidant, antidiabetic, wound healing, anticancer, immune system regulations and memory-enhancing properties [18]–[21]. These potentials were attributed to its bioactive components such as phenolic, anthraquinone, flavonoids, terpenoids and saponins [16]. Thus, emphasizing its potential as a valuable natural therapeutic agent. Despite all the numerous biological potentials attributed to *Aloe vera*, no docking-in vivo work has reported on the possible role of *Aloe vera* in ameliorating apoptosis induced by aluminium chloride in the brain. Following the recent enhancements in search algorithms and energy function, computational designing of a therapeutic agent and molecular docking strategies has become valuable tools in exploring the interaction between proteins and ligands, coupled with inexpensive and streamlined techniques aiding potential therapeutic targets discoveries in specific pathophysiological situations [22], [23]. This study therefore, aims to investigate the impact of *Aloe vera* gel on brain apoptotic and proapoptotic markers of aluminium induced neurotoxicity-mice and explore the biological mechanisms through molecular docking studies.

Materials and methods

In vivo study

Chemical Material

Aluminium Chloride (AlCl_3) was obtained from Sigma-Aldrich (Sigma-Aldrich Cooperation, USA). Every other reagent utilized was of high quality and analytical grade. The reporting of this study as well conforms to ARRIVE 2.0 guidelines [24].

Ethical statement

Authors declare that the study protocol was approved by the Ethics and Animal Handling Committee of the Faculty of Basic Medical Sciences, Alex Ekwueme Federal University, Ndufu-Alike, Nigeria (approval number: AE-FUNAI/FBMS/EAHC/25/012).

Plant Material and extraction

Leaves of Aloe vera plant were obtained from Ikwo in Ebonyi State. The leaves were identified and authenticated by Mr. C.B. Udechukwu, a botanist in the Department of Biological Sciences, assigned a voucher specimen number, *AE-FUNAI/H/1220* and was deposited in the AE-FUNAI Herbarium. Extraction was done by selecting the matured Aloe vera leaves from the base of the plant. The leaves were cleaned and washed of dusts. Then, the thick green skin on both sides was removed thereby exposing the clear gel. The fresh gel was collected by scraping and squeezing into a container. The extraction was freshly done each time of the administration.

Experimental Animals

Twenty male Swiss mice (weighing 20-30 grams) were procured from University of Uyo, Akwa Ibom State. The mice were acclimatized for three weeks prior to the study and housed in plastic cages. The animals were exposed to 12-hour light and 12-hour dark cycles. The study was conducted with the animals cared for and humanely treated in accordance with the Guide for the Care and Use of Laboratory Animals.

Experimental Design

The mice were randomly allocated to four groups of five rats each (n=5) as follows:

Control Group: Mice received no treatment (0.5 mL normal saline)

Aluminium Chloride-Induced Toxicity Group: Mice received aluminium chloride (100 mg/kg body weight, orally) throughout the experimental period

Aloe vera Group: Mice were treated with Aloe vera gel (200 mg/kg body weight) daily throughout the experimental period via oral gavage

Aluminium Chloride + Aloe vera Group: Mice were exposed to aluminium chloride (100mg/kg) and treated with Aloe vera (200 mg/kg). The treatment protocols lasted for two weeks.

Sample collection

On the last day of experimental period, the mice were humanely sacrificed and euthanized by employing ketamine/xylazine (0.1 mL/100 g.bw, intraperitoneally). Following euthanasia, their brains were removed and put in 0.25M cold sucrose buffer solution and were later homogenized for biochemical assays.

Biochemical assessment

Estimation of caspase-3, Bcl-2 and Bax were done quantitatively by standard methods following the manufacturer's guidelines using Caspase Assay Kit; G-Bioscience), (BCL Assay Kit; G-Bioscience) and Bax assay Kit respectively. Results were expressed as $\mu\text{mol/mg}$ protein.

In silico study

Preparation of Target Protein and Ligands

In the present study, the forcefield employed for ligand preparation, protein preparation, and molecular docking was OPLS4. The protein databank (PDB) (<http://www.pdb.org>) was used to retrieve the crystal structures of proteins, viz., Bax (PDB ID: 5W62), Bcl-2 (PDB ID: P10417) and Casp-3 (PDB ID: P70677). Preparation of the proteins was carried out at a physiological pH range of 7.0 ± 0.4 . The structure of the ligands of Aloe vera which included the Arachidonic acid (PubChem CID: 444899), Beta-carotene (PubChem CID: 5280489), 3-Epi-beta-sitosterol (PubChem CID: 12303645), Aloe-emodin (PubChem CID: 10207), Campesterol (PubChem CID: 173183), Aloe resin C (PubChem CID: 11972360), Cholesterol (PubChem CID: 5997), Quercetin (PubChem CID: 5280343), and Aloin (PubChem CID: 14989), were retrieved from the PubChem database from NCBI (www.pubchem.ncbi.nlm.nih.gov/). Preparation and protonation of ligands were done at a physiological pH of 7.2. Also, the retrieved structures of the ligands were minimized for their potential interactions with the target protein.

Molecular docking

Molecular docking analysis employed extra precision docking (XP) which was used for the retrieved ligands with their corresponding target proteins (BAX, BCL2, CASP3) retrieved from the protein data bank (PDB). The 3D crystal structure of the mouse ligands was complexed with an inhibitor molecule which was eliminated and docking with the ligands was performed. The proteins were energetically minimized and active sites

Target proteins	Ligand	PubChem_ CID	Docking Score	Hydrogen Bond	Glide energy
BAX (mouse)	Aloe resin C	11972360	-8.18	-4.76	-47.071
	Quercetin	5280343	-7.626	-3.019	-36.329
	Aloin	14989	-4.32	-2.128	-33.171
	Aloe-emodin	10207	-3.613	-1.39	-24.227
	Cholesterol	5997	-2.22	-0.35	-22.836
	3-Epi-beta-sitosterol	12303645	-2.166	0	-20.759
	Campesterol	173183	-2.145	-0.35	-20.834
Bcl-2 (mouse)	Aloe resin C	11972360	-6.908	-2.534	-48.76
	Aloe-emodin	10207	-6.496	-1.44	-35.466
	Aloin	14989	-6.296	-1.92	-40.55
	Quercetin	5280343	-6.24	-2.4	-33.105
	Campesterol	173183	-5.011	-0.239	-19.288
	Arachidonic acid	444899	-4.681	-0.35	-29.683
	Cholesterol	5997	-4.366	0	-20.848
	3-Epi-beta-sitosterol	12303645	-3.879	-0.7	-24.55
	Beta-carotene	5280489	-2.67	0	-37.395
Casp-3 (mouse)	Aloe resin C	11972360	-9.811	-6.074	-53.796
	Aloin	14989	-7.068	-2.971	-40.587
	Quercetin	5280343	-6.988	-2.718	-44.023
	Arachidonic acid	444899	-5.738	-2.35	-35.585
	Aloe-emodin	10207	-5.271	-1.84	-30.506
	Cholesterol	5997	-4.432	-0.514	-26.583
	3-Epi-beta-sitosterol	12303645	-3.916	-1.187	-24.196
	Campesterol	173183	-2.599	-0.7	-22.002
	Beta-carotene	5280489	-0.693	0	-38.753

Discussion

In vivo study

Neurotoxicity exposure has been linked to increased apoptosis in neuronal cells, contributing to various neurodegenerative diseases. For instance, various apoptotic markers have been reported to be expressed following aluminium exposure, indicating programmed cell death. [11] also reported that apoptosis is the final pathway of toxicity induced by aluminium thereby leading to neurodegeneration. Apoptosis plays an important roles in development and tissue homeostasis, and its altered regulation is implicated in degenerative diseases such as Alzheimers' [25].

Data from our present study reveals elevated concentration of pro-apoptotic proteins- caspase-3 and Bax in the brain tissues of aluminium chloride-induced $AlCl_3$ - induced neurotoxic rats with decrease of the anti-apoptotic protein Bcl-2, an indication of enhanced apoptotic signaling and reduced cellular protection against apoptosis following $AlCl_3$ exposure. Conversely, these results also showed that treatment of neurotoxicant rats with Aloe vera gel reversed the altered Bcl-2 and Bax levels induced by aluminium chloride thereby restoring the balance between regulating proteins of apoptosis.

These findings align with those of previous studies. For instance, a study by [10], reported an aluminium chloride-induced apoptosis within the brain of Wistar rats through the activation of apoptotic caspase-3. Aluminium has been suggested to accelerate deposition of amyloid beta,

plaque formation and oxidative stress in rats brain [10]. Similarly, earlier reports by [26] noted that intracisternal infusion of aluminium into the brain of rabbit decreased Bcl-2 and decreased Bax and caspase-3 levels. This also agrees with the reports of [27] in the hippocampal tissues. Increased activation of caspase as reported by [28] confirmed that Aluminium dose-dependently induces apoptosis in brain of rats.

Treatment with Aloe vera however, decreased the pro-apoptotic markers and increased the anti-apoptotic as seen in table 1. This also agrees with the study of [4] who reported that Aloe vera gel ameliorated apoptosis together with oxidative stress and hippocampal neuronal loss, in a study aimed at evaluating the protective effects of Aloe vera gel on cisplatin-induced apoptosis in the hippocampus of rats. Thus, resulting in the down-regulation of Casp-3 and Bax, and up-regulation of Bcl-2. Earlier reports indicated that aloe-emodin, one of the active components of Aloe vera could suppress NMDA- induced apoptosis of retinal ganglion cells, thus suggesting its possible role in glaucoma management [29]. Also, recent reports highlighted the capability of aloe sterols to counteracting apoptosis [30], [31]. However, [17] reported the efficacy of Aloe vera in inducing apoptosis in cancer cells and exhibiting immunomodulatory potentials. According to [32], they appear to initiate apoptosis via up-regulation and down-regulation of the expression of P53 and Bcl-2 gene respectively. Another report by [33], also suggested that an extract of Aloe vera exerts anticancer effects on human breast and cervical cancer cells by inhibiting cancer cell growth and inducing apoptosis.

The fate of cell is determined by the measure of balance between pro-apoptotic and anti-apoptotic proteins [34]. When death is favoured by the balance, anti-apoptotic- Bcl-2 inhibits cytochrome c release within the mitochondrial membrane while Bax monitors apoptotic processes by controlling cytochrome c release into the cytoplasm thereby resulting to activation of casp-3 cascade that cleave downstream substrates leading to apoptosis [35], [36]. Chemicals typically cause apoptosis by enhancing pro-apoptotic and/or decreasing anti-apoptotic signaling resulting from oxidative stress, elevated intracellular Ca^{2+} levels, or Zn^{2+} dyshomeostasis, albeit the precise mechanisms of apoptosis induction differ depending on the exposure paradigm.

Molecular docking

According to [37], computational screening of natural products have become a necessity due to its easier and cheaper and directional approach. The study involved molecular docking studies of several Aloe vera ligands on proteins involved in apoptosis (Casp-3, Bax and Bcl-2), to assess the binding affinity in terms of binding energy and interaction. In the present study, nine active ligand molecules derived from Aloe vera were performed against the apoptotic proteins. However, five top ligands (aloe emodin, aloin, quercetin, aloe resin C and arachidonic acid; see figure 1) were selected based on their binding affinity and patterns indicated by higher negative docking scores. However, aloe resin C exhibited highest level of interactions with Casp-3, Bax and Bcl-2 active sites. The Bcl-2 family of proteins are key regulators of intracellular apoptotic signal transduction that negate damaging effects of reactive oxygen species and the key biochemical event that defines apoptosis is the activation of caspases [15], [38], [39]. Results of the molecular docking showed that aloe resin C exhibited a H-bonding interactions with Casp3 active sites of GLY 122, ASP 253, SER 205, ARG 207, SER, 63 and SER 120; Bax active sites of LYS 21, ASP 53, GLN 18, PRO 13 and TRP 158; and Bcl2 active site of ALA 146. From molecular docking results, it can be concluded that aloe resin C, aloe emodin, aloin, quercetin, and arachidonic acid interfere with the functions of Casp3, Bax and Bcl2 through H-bonding and hydrophobic interactions, which might suppress the neurodegenerative disease progression. Thereby, portraying the potentials of *Aloe vera* as a therapeutic agent in enhancing cellular protection and stabilizing neuronal membrane against apoptosis.

Conclusion

In silico molecular docking study of active ingredients of *Aloe vera* with apoptotic proteins together with higher binding energy with all biomarker proteins gave a strong hypothesis to its anti-apoptotic potentials. Thus, the findings of this study demonstrated the potentials of *Aloe vera* as a therapeutic agent in enhancing cellular protection and stabilizing neuronal membrane against apoptotic processes associated with aluminium chloride exposure by enhancing and promoting anti-apoptotic signaling.

Declarations

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Author contributions: Study conception and design was done by ARN. Material preparation, data collection and analysis were performed by all the authors (ARN, RCN, CSA, EON, AOO, IAA and AEO). The first draft of the manuscript was written and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability statement: The authors declare that the data supporting the findings of the study are available within the article

Declaration of Competing Interest: Authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Figures

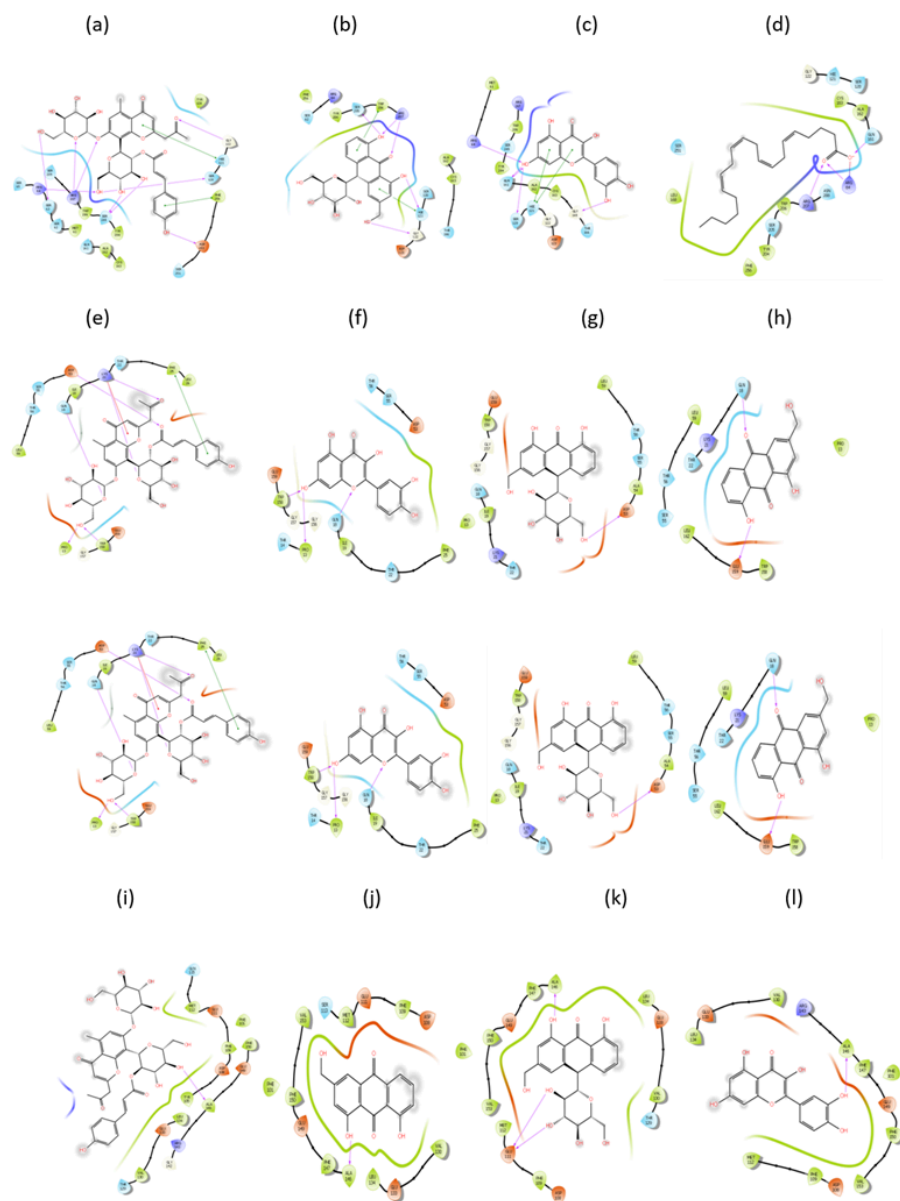


Fig. 1: 2D diagrams of ligand-protein complexes: (a) Casp3-aloe resin C (b) Casp3- aloin (c) Casp3-quercetin (d) Casp3- arachidonic acid (e) Bax- aloe resin C (f) Bax-quercetin (g) Bax-aloin (h) Bax-aloe emodin (i) Bcl2-aloe resin C (j) Bcl2-aloe emodin (k) Bcl2-aloin (l) Bcl2-quercetin



Figure 1

See image above for figure legend