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Quercetin/Donepezil co-administration mitigates Aluminium chloride induced changes in open field novelty induced behaviours and cerebral cortex histomorphology in rats

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ABSTRACT

Aluminium chloride ($AlCl_3$) occurs ubiquitously in the environment contaminating water and food sources. Although donepezil enhances cognitive function in Alzheimer's disease, it does not rectify structural damage. Quercetin, recognised for its ability to mitigate oxidative stress, is inadequately researched regarding its effects in isolation or in conjunction with donepezil. Therefore, this study investigated the effects of quercetin and donepezil co-administration on $AlCl_3$-induced alterations in rat cerebral cortex. Seventy female rats (120–150g) were divided into seven groups (10 rats each). Group A (control) received normal saline (10ml/kg). Groups B and C received quercetin (200mg/kg) and donepezil (3mg/kg) orally. Group D received $AlCl_3$ (100mg/kg). Groups E, F, and G received $AlCl_3$ plus quercetin, donepezil, or their combination. $AlCl_3$ was administered on days 1–14, while quercetin and/or donepezil were given from days 15–28. Normal saline was given to the control group throughout. The results showed a significant decrease in body weight in groups D-G compared to A ($p<0.005$). There was also a significant increase in locomotion and rearing in groups E and F compared to D, while self-grooming increased significantly in groups E and G compared to D. Levels of IL-1β and IL-6 decreased significantly in groups E, F and G compared to D. Result of cerebrocortical histomorphology revealed variable degrees of preservation of the neurons in group E, F and G compared to D. The results show that the combination of quercetin and donepezil could give protection against $AlCl_3$-induced toxicity, necessitating more investigation for the management of human neurodegeneration.

KEYWORDS: Aluminium Chloride; Donepezil; Neurotoxicity; Neuroinflammation; Neuroprotection; Oxidative stress

1. Introduction

Aluminium chloride ($AlCl_3$), a common compound derived from aluminium, is ubiquitously present in the environment due to the abundance of aluminium in the earth crust at about 8%, earning it a position of the third most abundant element in the earth crust [1]. This extensive availability, combined with $AlCl_3$'s widespread industrial and commercial use, results in significant human exposure [2]. $AlCl_3$ exposure can occur through multiple pathways, including occupational settings (such as defence industries, automobile manufacturing, and

firearms production) and everyday products like cooking utensils, food additives, antacids, and deodorants, according to the World Health Organisation [2]. Additionally, soluble aluminium compounds, including $AlCl_3$, are frequently used in water purification and food packaging, exposing humans to potential health risks [3]. Various studies have shown that Al compounds can penetrate the body through dermal absorption, ingestion, or even direct injection, eventually entering systemic circulation [4].

One of the most concerning effects of $AlCl_3$ exposure is its neurotoxicity, with clinical and preclinical studies linking it to cognitive dysfunction and other central nervous system (CNS) disturbances [2]. Once inside the body, $AlCl_3$ can cross the blood-brain barrier (BBB) and accumulate in different brain regions, such as the cerebral cortex, hippocampus, and cerebellar cortex [5]. These areas play crucial roles in memory, cognition, language, and physical movement. Aluminium's neurotoxicity is thought to result from interactions with critical metabolic enzymes and the disruption of processes vital to brain health [6]. Specifically, $AlCl_3$ has been associated with neuropathological changes like oxidative stress, neuroinflammation, neuronal degeneration, impaired neurotransmission, and the development of tau hyperphosphorylation and amyloid-β (Aβ) protein deposits; which are characteristic features of Alzheimer's disease. Research indicates that $AlCl_3$'s presence in the brain may stimulate free radical production, contributing to oxidative stress and the progression of neurodegenerative diseases, including Alzheimer's [7]. In Alzheimer's pathology, both neurofibrillary tangles (NFTs) made up of hyperphosphorylated tau protein and Aβ plaques disrupt cognitive function and are associated with psychological disturbances and neurotransmission impairment [7, 8]. The build-up of $AlCl_3$ in the brain, particularly in aged individuals, could exacerbate these pathological hallmarks, advancing the development of Alzheimer's-like symptoms and other neurological disorders [8]. $AlCl_3$ has even been implicated in rare neurological disorders, such as the Guamanian Parkinsonian-Amyotrophic Lateral Sclerosis (GP-ALS) complex and Hallervorden-Spatz syndrome, suggesting a broader neurotoxic potential beyond Alzheimer's disease [2, 9]. Considering the neurodegenerative potential of $AlCl_3$ and its pervasive presence in the environment and everyday items, there is an urgent need to explore therapies that can mitigate its harmful effects. Pharmaceutical treatments, like donepezil, provide some cognitive benefit in Alzheimer's disease but do not address the structural and biochemical changes in the brain caused by $AlCl_3$ exposure. Quercetin, a potent antioxidant known for its neuroprotective properties, presents an alternative approach, though research on its effectiveness in $AlCl_3$-induced neurotoxicity remains limited. This study examined the potential benefits of quercetin in combination with donepezil to combat $AlCl_3$-induced cognitive and structural brain damage, aiming to provide insight into therapeutic options for managing $AlCl_3$-related neurodegeneration.

The objectives of this study were to assess the effects of quercetin and donepezil coadministration on body weight, food intake and open field novelty induced behaviours. The impact on lipid peroxidation, total antioxidant capacity, and pro-inflammatory cytokines including interleukin (IL)-1β and IL-6. Furthermore, we evaluated the effect of quercetin/donepezil coadministration on $AlCl_3$ induced changes in the rat cerebral cortex.

2. Materials and Methodology

2.1 Chemicals and Drugs

Donepezil (10mg, procured from a Local Pharmacy), Aluminium-chloride (Sigma-Aldrich Corporation, USA), Quercetin (500 mg, MRM Nutrition, USA), Assay kits for interleukin-1β and interleukin-6 (Biovision Inc., Milpitas, CA, USA).

2.2 Animals

Healthy Wistar rats utilised in this investigation were sourced from Empire Breeders, located in Osogbo, Osun State, Nigeria. Rats were housed in hardwood cages measuring 20 x 10 x 12 inches at room temperature (25°C ±2.5°C), with lights on at 7:00 am and off at 7 pm. Rats were granted unrestricted access to feed and water. All procedures were executed in compliance with the protocols of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology, adhering to the regulations for animal care and use outlined in the European Council Directive (EU2010/63) on scientific procedures involving living animals.

2.3 Experimental Methods

Seventy (70) female rats (120-150g each) were divided into seven (7) groups (n=10 each). Group A (control) were fed standard rat chow, administered saline by gavage at 10 ml/kg body weight. Rats in group B (quercetin) were administered quercetin (200 mg/kg) incorporated in rodent chow, saline was also administered by gavage. Animals in group C (donepezil) were fed standard chow with donepezil administered by gavage at 3 mg/kg body weight. Group D ($AlCl_3$) received aluminium chloride by gavage at 100 mg/kg and were fed rodent chow. Group E received $AlCl_3$ and quercetin, rats in group F were administered $AlCl_3$ and donepezil while those in group G were administered $AlCl_3$, quercetin, and donepezil. Standard diet and quercetin supplemented diet were administered daily for 14

days in corroboration with a study done by [10], and Donepezil and $AlCl_3$ orally as reported by [11] [12] respectively for 14 days. After treatment, animals underwent locomotion and exploratory behavioural tests using the open field box. Twenty-four hours post-testing, rats were euthanized by cervical dislocation, and blood was drawn for analysis of interleukins (IL-6 and IL-1β). Brains were excised, fixed in 10% neutral buffered formol-saline, and cerebral cortex sections were processed, embedded in paraffin, and stained for histological evaluation.

2.4 Behavioural Testing

2.4.1 Open field Novelty induced Behaviours

Open-field responses in rats assesses arousal, inhibitory, and inspective exploratory behaviours, as well as anxiety behaviours. Stereotypic behaviours, including as grooming, have also been measured using this paradigm. These behaviours are typically considered fundamental and signify a rodent's capacity for exploration. Ten minutes of behaviours in an open field, including grooming, rearing, and horizontal locomotion, were observed and recorded in the open field apparatus as previously described by [13]. The open-field paradigm consisted of a square enclosure with a rigid floor, measuring 36 x 36 x 26 cm. The wood was painted white, and the floor was segmented by permanent blue markings into 16 equal squares. Horizontal locomotion (number of floor units traversed by all paws), rearing frequency (number of instances the rat stood on its hind legs, either with its forelimbs against the walls of the observation cage or freely in the air), and grooming frequency (number of body-cleaning actions involving paws, licking of the body and pubis with the mouth, and face-washing behaviours indicative of stereotypic activity) within a 10-minute interval were documented as previously described [14].

2.5 Biochemical Test

2.5.1 Lipid Peroxidation

Lipid peroxidation levels were assessed by determining the malondialdehyde content, which assays the levels of thiobarbituric acid reactive substance in samples. Thiobarbituric acid reactive substance combine with free malondialdehyde present in samples to form a coloured complex. Concentration of which is expressed as μmol [15].

2.5.2. Antioxidant Status

Total antioxidant capacity was measured using the Trolox Equivalent Antioxidant Capacity Assay that is based on the ability of antioxidants within a sample to react with oxidized products as previously described by [14].

2.5.3 Interleukin (IL) -1β and Interleukin-6

Interleukin (IL)- 1β and Interleukin-6 levels were measured using the enzyme-linked immunosorbent assay methods with commercially available kits procured from Biovision Inc., Milpitas, CA, USA.

2.6 Tissue Histology

Rat brains were dissected, sectioned and fixed in neutral-buffered formolsaline. The cerebral cortex was then processed for paraffin-embedding, cut at 5 μm and stained with haematoxylin and eosin and cresyl fast violet for general histological study.

2.7 Photomicrography

Histological slides of the cerebral cortex were examined under an Olympus binocular light microscope. Images were captured using a Canon PowerShot 2500 Digital camera.

2.8 Statistical Analysis

Data was analysed using Chris Rorden's ANOVA for Windows (version 0.98). Analysis of data was by One-way analysis of variance (ANOVA) and a post-hoc test (Tukey HSD) used comparisons. All results were expressed as mean ± S.E.M. and $p < 0.05$ was taken as the accepted level of significant difference from control.

3. Results

3.1 Effect of quercetin and donepezil on body weight and food intake

Figure 1 (upper panel) shows the effect of quercetin and donepezil on body weight measured as relative change in body weight. There was a significant ($p < 0.001$) decrease in body weight in the groups administered $AlCl_3$, $AlCl_3$/Done and $AlCl_3$/Quer/Done compared to control. Compared to $AlCl_3$, an increase in body weight was observed with $AlCl_3$/Quer and $AlCl_3$/Quer/Done.

Figure 1 (lower panel) shows the effect of quercetin and donepezil on food intake measured as relative change in food intake. There was a significant ($p < 0.001$) increase in food intake with Quer, Done, $AlCl_3$/Quer and $AlCl_3$/Quer/Done and a decrease with $AlCl_3$ and $AlCl_3$/Done compared to control. Compared to $AlCl_3$, food intake decreased with $AlCl_3$/Done and increased with $AlCl_3$/Quer, and $AlCl_3$/Quer/Done respectively.

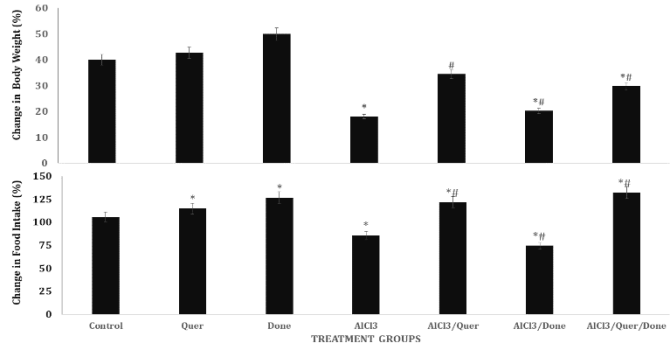

Figure 1: Effect of Quercetin and Donepezil on Relative change in body weight (upper panel) and feed intake (lower panel). Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from $AlCl_3$. Number of rats per treatment group =10. $AlCl_3$: Aluminium chloride, Done: Donepezil, Quer: Quercetin.

3.2 Effect of quercetin and donepezil on horizontal locomotion and rearing activity.

Figure 2 (upper panel) shows the effect of quercetin and donepezil on horizontal locomotion measured as line-crossing. There was a significant ($p < 0.001$) increase in line crossing with Quer, Done, and $AlCl_3$/Quer and a decrease with $AlCl_3$, compared to control. Compared to $AlCl_3$, line crossing increased significantly with $AlCl_3$/Quer, and $AlCl_3$/Quer/Done.

Figure 2 (lower pane) shows the effect of quercetin and donepezil on rearing activity There was a significant ($p < 0.003$) increase in rearing with Quer, Done, $AlCl_3$/Quer and $AlCl_3$/Quer/Done and a decrease with $AlCl_3$ compared to control. Compared to $AlCl_3$, rearing increased with $AlCl_3$/Quer, $AlCl_3$/Done and $AlCl_3$/Quer/Done.

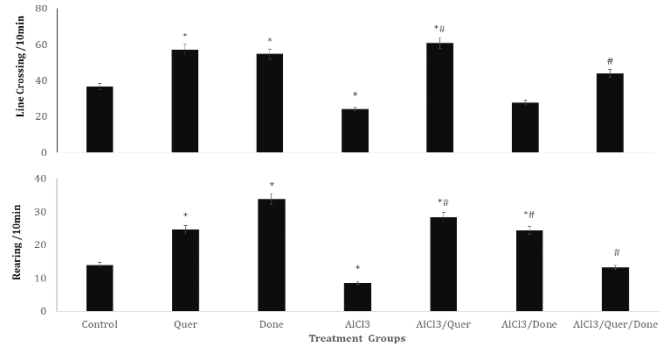

Figure 2: Effect of Quercetin and Donepezil on horizontal locomotion (upper panel) and rearing (lower panel). Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from $AlCl_3$. Number of rats per treatment group =10. $AlCl_3$: Aluminium chloride, Done: Donepezil, Quer: Quercetin.

3.3 Effect of quercetin and donepezil on self-grooming behaviour

Figure 3 shows the effect of quercetin and donepezil on self-grooming behaviour. There was a significant increase in self-grooming with Quer, Done, $AlCl_3$/Quer/Done and a decrease with $AlCl_3$, $AlCl_3$/Quer and $AlCl_3$/Done compared to control. Compared to $AlCl_3$, self-grooming increased significantly with $AlCl_3$/Quer, $AlCl_3$/Done and $AlCl_3$/Quer/Done.

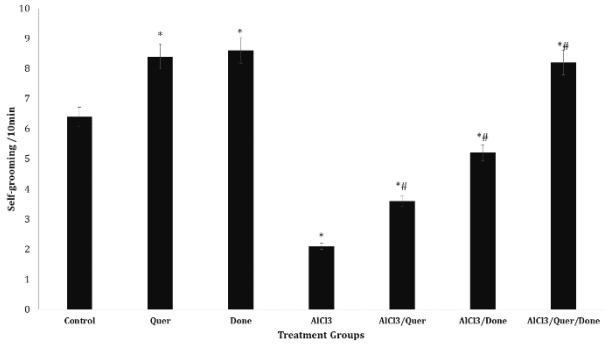

Figure 3: Effect of Quercetin and Donepezil on self-grooming behaviour. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from $AlCl_3$. Number of rats per treatment group =10. $AlCl_3$: Aluminium chloride, Done: Donepezil, Quer: Quercetin.

3.4 Effect of quercetin and donepezil on the inflammatory cytokine.

Table 1 shows the effect of quercetin and donepezil on lipid peroxidation levels measured as malondialdehyde (MDA) content, Total antioxidant capacity (TAC) and inflammatory marker (interleukin-1β, and interleukin-6). Lipid peroxidation decreased with Quer, $AlCl_3$/Quer/Done and increased with $AlCl_3$, and $AlCl_3$/Done compared to control. Compared to $AlCl_3$, MDA levels decreased significantly with $AlCl_3$/Quer, $AlCl_3$/Done, and $AlCl_3$/Quer/Done.

Total antioxidant capacity (TAC) increased significantly with Quer, $AlCl_3$/Quer, $AlCl_3$/Done, and $AlCl_3$/Quer/Done and decreased with $AlCl_3$ compared to control. Compared to $AlCl_3$, TAC levels increased significantly with $AlCl_3$/Quer, $AlCl_3$/Done, and $AlCl_3$/Quer/Done.

Interleukin-1β (IL-1β) showed no significant difference in any of the groups compared to control or $AlCl_3$. Interleukin 6 (IL-6) decreased significantly with Quer, Done and $AlCl_3$/Quer/Done and increased with $AlCl_3$ compared to control. Compared to $AlCl_3$, IL-6 levels decreased significantly with $AlCl_3$/Quer, $AlCl_3$/Done, and $AlCl_3$/Quer/Done.

3.5 Effect of quercetin and donepezil on the cerebral cortex histomorphology

Figure 4(a - g) and figure 5(a - g) are representative slides of haematoxylin and eosin (H&E) and cresyl fast violet (CFV) stained sections of the rat cerebral cortex respectively. Examination of the H&E-stained slides of rats in the control group revealed characteristic outer granular layer of the cerebral cortex. Scattered within the neuropil were multipolar shaped pyramidal cells with large vesicular nucleus, granule neurons with large open-faced nuclei and scanty cytoplasm and small

sized neuroglial were also observed (Figure 4a). The neuropil, which was pink staining in the H & E slides was also well preserved in the CFV stained slides (Figure 5a).

Table 1: Effect of quercetin and donepezil on oxidative stress and proinflammatory parameters

GROUPS	TAC (mM)	MDA (µM)	IL-1β (pg/ml)	IL-6 (pg/ml)
Control	10.08 ± 0.4	7.6 ± 0.09	42.33 ± 2.95	6.19 ± 0.24
Quer	16.72 ± 5.74 *	5.74 ± 0.04*	54.35 ± 8.32	4.25 ± 0.88*
Done	10 ± 0.72	6.68 ± 0.07	45.7 ± 15.68	4.68 ± 0.41*
$AlCl_3$	6.51 ± 7.93 *	18.58 ± 0.01*	67.78 ± 6.78	10.94 ± 0.35*
$AlCl_3$ / Quer	21.78 ± 2.69 *#	8.26 ± 0.08 #	61.22 ± 9.02	6.84 ± 1.4#
$AlCl_3$/Done	21.42 ± 0.97 *#	11.76 ± 0.06*#	53.56 ± 8.28	7.51 ± 0.48#
$AlCl_3$ / Quer / Done	15.78 ± 2.9 *#	5.94 ± 0.07 *#	54.45 ± 15.79	3.65 ± 0.64*#

Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from $AlCl_3$. Number of rats per treatment group =10. $AlCl_3$: Aluminium chloride, Done: Donepezil, Quer: Quercetin.

The staining revealed the characteristic arrangement of the cerebral cortex with well-delineated multipolar pyramidal cells (PC), deeply stained granule cells (GC), neuroglia (NG), and prominent Nissl bodies in (Figure 4 & 5 a-c). However, degenerating pyramidal cells with pale-staining nuclei and reduced Nissl substance were observed in group (Figure 4 & 5D), while protection against neuronal injury (Figure 4 e & f), and better preservation of Nissl bodies (Figure 5 e & f) was observed. These changes were more pronounced in group (Figure 4 & 5g).

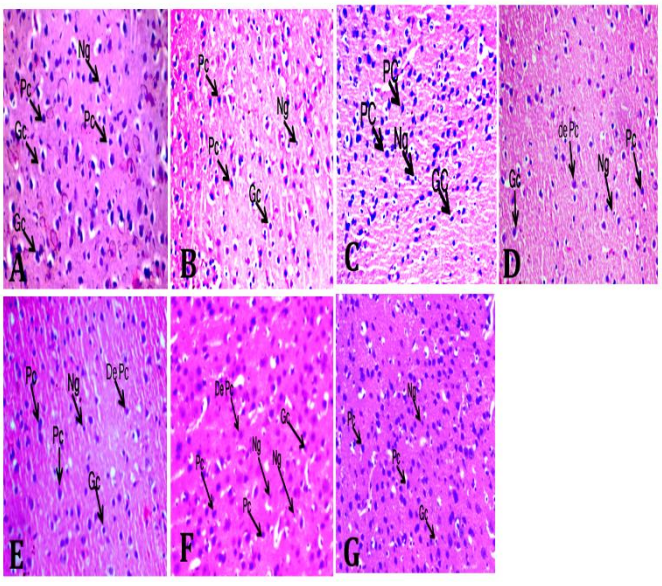

Figure 4: Representative photomicrograph of haematoxylin and Eosin-stained sections of the rat cerebral cortex. Photomicrographs revealed distinct layers of the cerebral cortex with presence of numerous granule cells (GC), pyramidal cells (PC), and neuroglial cells (NG). Also observed are degenerating pyramidal cell (De PC). Magnification: x100

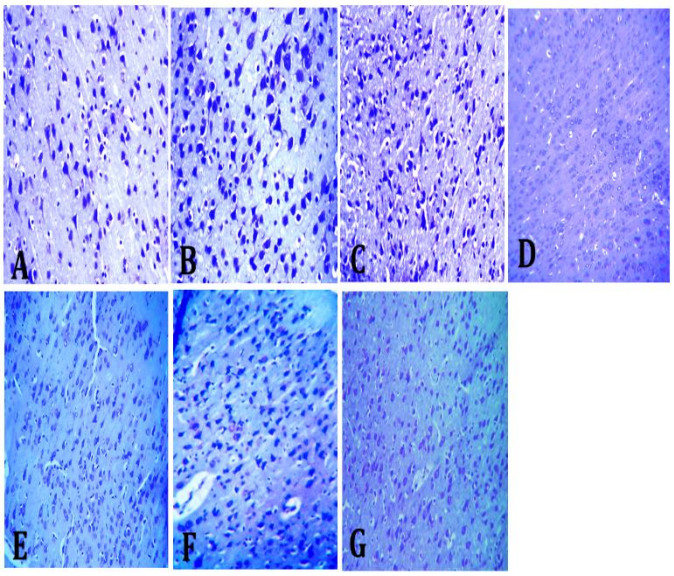

Figure 5: Photomicrograph of cresyl violet stained sections of the rat cerebral cortex section by cresyl fast violet X100. The photomicrographs show the neuronal cell scattered within the Nissl substance. Magnificationx100.

4 Discussion

This study explored the neuroprotective potential of co-administering quercetin and donepezil in Wistar rats exposed to aluminium chloride ($AlCl_3$)-induced neurotoxicity, which is known to impair cognition, reduce motor and exploratory behaviours, and heighten neuroinflammation. The findings reveal that $AlCl_3$ exposure negatively impacted body weight, feed intake, motor activity (locomotor and exploratory), and caused anxiety-like behaviours alongside, inflammatory response, and histological brain neuronal damage. However, both quercetin and donepezil, individually and especially when combined, mitigated these adverse effects, demonstrating an additive neuroprotective benefit. $AlCl_3$ exposure led to decreased body weight and feed intake, confirming similar findings from prior studies [16, 17]. The reductions were reversed by treatment with quercetin and donepezil, with quercetin demonstrating slightly greater effectiveness than donepezil when administered alone [18]. The observed weight and dietary recovery indicate improved metabolic stability and health specifically in the treated rats, reflecting the potential therapeutic effects of the administered interventions.

Additionally, behavioural assays indicated that $AlCl_3$ impaired locomotion, self-grooming, and induced anxiety-like symptoms. $AlCl_3$'s interference with dopamine and acetylcholine systems appears to play a role in these symptoms, as dopaminergic and cholinergic dysfunction are key to motor and self-maintenance deficits [19, 20, 21]. Quercetin's antioxidative properties and donepezil's cholinergic activity, however, facilitated the recovery of motor functions and

reduced anxiety behaviours, aligning with findings from previous studies on these compounds [22] [12].

Treatment with $AlCl_3$ significantly elevated brain concentrations of the pro-inflammatory cytokines IL-1β and IL-6. However, these elevations were mitigated by quercetin and donepezil. Consistent with the current findings, Milnerowicz *et al.*[23] reported that exposure to metals such as aluminium increases the levels of TNF-α, IL-6, and IL-1β, which are key pro-inflammatory cytokines. The upregulation of these cytokines promotes leukocyte recruitment, further intensifying the inflammatory response through the release of additional pro-inflammatory mediators. Accumulation of $AlCl_3$ has been shown to trigger the release of cytochrome C from mitochondria, leading to increased free radical production and elevated pro-inflammatory cytokine levels. This process also enhances the gene expression of IL-1β and TNF-α, contributing to the inflammatory cascade. $AlCl_3$-induced neurotoxicity is characterized by heightened variability in inflammatory markers, such as IL-1β and TNF-α, as reported by [24]. Quercetin has been identified as a potent modulator of neuroinflammation, a critical factor in the pathogenesis of $AlCl_3$-induced neurotoxicity and related disorders, such as Alzheimer's disease [25]. By inhibiting the production of inflammatory chemokines and cytokines [26], quercetin reduces neuroinflammatory processes, particularly through the suppression of inflammatory gene expression in microglia. In the present study, quercetin significantly reduced levels of IL-1β and IL-6, with coadministration of quercetin and donepezil producing effects comparable to those observed in the control group.

Histopathological analysis using H&E and cresyl fast violet staining further corroborated these findings. $AlCl_3$-exposed rats showed notable cortical degeneration, including a loss of neuronal structure and depletion of Nissl bodies, indicative of disrupted protein synthesis and neuronal function. Quercetin and donepezil treatment preserved brain architecture, with the combination providing the most protection, nearly restoring normal pyramidal cell morphology and Nissl body presence. This suggests that while $AlCl_3$-induced neuronal damage is severe, exhibiting shrunken neurons, pyknotic nuclei, and loss of Nissl substances, co-treatment offers robust neuroprotection that enhances structural recovery. Overall, the study underscores that co-administering quercetin, and donepezil provides more substantial neuroprotective benefits against $AlCl_3$-induced neurotoxicity than either treatment alone. Their combined antioxidative and anti-inflammatory properties counteract $AlCl_3$'s effects, protecting motor function, cognitive performance, and brain structure. These findings underscore the potential therapeutic benefits of combining both compounds to mitigate neurotoxicity-related conditions, including neurodegenerative disorders like Alzheimer's disease.

Conclusion

The combination of quercetin and donepezil demonstrates considerable therapeutic potential in alleviating the behavioural and histological effects of aluminium chloride-exposure. Enhancements in open-field behaviours, including heightened locomotion and diminished anxiety, coupled with the maintenance of cerebral cortex integrity, underscore the potential of this dual treatment. This combined approach targets oxidative stress and cholinergic dysfunction, providing a comprehensive strategy for addressing neurodegenerative conditions associated with these mechanisms. These findings indicate that the coadministration of quercetin and donepezil may be a viable strategy for addressing neurotoxicity-related behavioural and cognitive impairments, highlighting the significance of an integrative therapeutic approach.

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None

Availability of data and materials

Data generated during and analysed during the course of this study are available from the corresponding author on request.

Declarations Ethics approval

Ethical approval for this study was granted by the Ethical Committee of the Faculty of Basic Medical Sciences (ERC/FBMS/016/2024).

Competing interests

All authors of this paper declare that there is no conflict of interest related to the content of this manuscript.

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