Pacific Journal of Medical and Health Sciences
ISSN: 2456-7450 | Volume 2, Issue 1, January to March 2026, pp - 76 - 84

PJMHS
PACIFIC JOURNAL OF MEDICAL AND HEALTH SCIENCES

Review

Aluminum Chloride and the Hypothalamus-Pituitary-Testicular (HPT) Axis: Pathophysiology and Antioxidant Rescue

Solihu Olashile Ibrahim[1]*, Suleiman Muhammed Eze[1], Samson Opeyemi Adeleke[2] and Babatunde Joseph Dare[2]

[1]Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Alhikmah University Ilorin, Kwara State, Nigeria

[2]Department of Human Anatomy, Faculty of Basic Medical Sciences, College of Health Sciences, Osun State University, Osogbo, Osun State, Nigeria

Received : 23 October 2025
Revised : 10 November 2025
Accepted : 11 November 2025

***Corresponding Author Email:** osibrahim@alhikmah.edu.ng

ABSTRACT

Aluminum chloride ($AlCl_3$) is a common environmental and industrial product that is finally noted to be an endocrine-disrupting toxicant with dire effects on male reproductive health. Human and animal studies indicate that $AlCl_3$ interferes with the hypothalamic-pituitary-testicular (HPT) axis in a variety of ways. On the hypothalamic level, it suppresses the secretion of calcium-dependent gonadotropin-releasing hormone (GnRH) thereby causing changes in the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In testes, aluminum affects the functioning of Leydig and Sertoli cells by blocking ion-dependent ATPases, gonadotropin receptor down-regulation, and steroidogenic enzyme disturbances resulting in the decreased production of testosterone and impaired sperm production. Its toxicity is associated with oxidative stress that is marked by an overproduction of reactive oxygen species (ROS), lipid peroxidation, mitochondrial dysfunction, and the stimulation of an apoptotic response. A typical histopathological outcome is the degeneration of seminiferous tubules, loss of germ cells, atrophy of Leydig cells and the decrease in sperm count, motility and viability. Flavonoids like quercetin, rutin and naringenin have protective properties involving antioxidant, anti-inflammatory, metal-chelating and anti-apoptotic properties. These compounds restore hormonal balance, antioxidant enzyme activity, testicular architecture and sperm quality by scavengers of ROS, Nrf2 pathway activation, and NF-kB signaling. In general, flavonoid-based interventions have potential to alleviate the effect of aluminum causing reproductive toxicity.

KEYWORDS: Aluminum chloride, Hypothalamic–pituitary–testicular axis, Oxidative stress, Flavonoids, Quercetin, Naringenin, Male infertility, Endocrine disruption

Hypothalamic-Pituitary-Testicular (HPT) Axis Overview

The HPT axis, which is also known as the male hypothalamic-pituitary-gonadal axis, is a normal neuroendocrine system [Figure 1]. The hypothalamic gonadotropin-releasing hormone (GnRH) triggers the release of pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which subsequently stimulates the functions of testicular Leydig and Sertoli cells respectively, and ultimately results in the production of testosterone and sperm respectively[1,2,3]. Normal GnRH pulsatility is Ca^{2+} dependent. Any form of disruption (hypothalamus, pituitary, or testis) may disrupt the fertility in males. Exposure to industrial and dietary aluminum (Al) is now known as an endocrine disrupter that disrupts this axis. Experiments in rodents and humans have attributed increased tissue Al in the brain, testes, and sperm, to defective secretion of gonadotropin and steroidogenesis[1,4]. As an example, excess Al may accumulate in the hypothalamus and pituitary, and this may disrupt steroidogenic signaling[5].

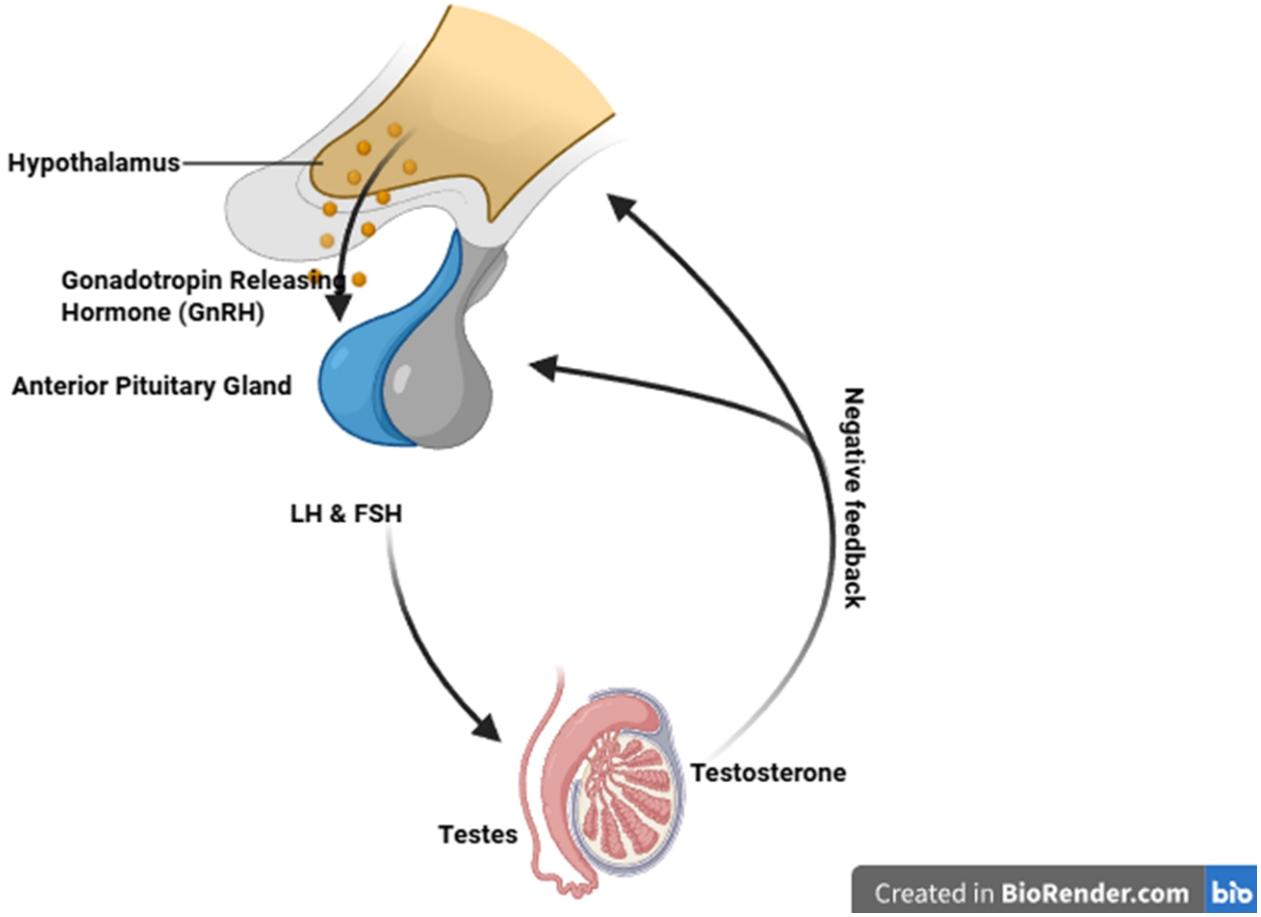

Figure 1: The Male Hypothalamic-pituitary-testicular (HPT) Axis

The GnRH neurons in the hypothalamus discharge pulses of GnRH that cause secretions of LH and FSH into the bloodstream which cause the Leydig and Sertoli cells in the testes to produce testosterone and promote spermatogenesis. Testosterone in turn has negative feedback effect on the anterior pituitary gland and hypothalamus.

In experimental models of the toxicity of Al, aluminum chloride ($AlCl_3$) is frequently employed. It has an easy ability to dissolve in body fluids to give Al^{3+} and cross the blood-brain barrier, where it gets deposited in neuroendocrine tissues. High levels of Al have been clinically linked with reproductive disorders when administered clinically[6]. The pathophysiology of $AlCl_3$ in HPT axis is important to understand, and there is a need to investigate interventions. The naturally occurring antioxidants, flavonoids in particular quercetin, rutin, naringenin, etc., are being investigated in correcting Al-induced dysfunction. This is a review of the toxic effects of $AlCl_3$ on HPT hormones, oxidative stress, apoptosis, and tissue histology, and the flavonoid-based antioxidant interventions [Tables 1].

Aluminum Toxicity and Endocrine Disruption in the HPT Axis

Hypothalamic Effects and GnRH Suppression

One of the important pathways of the $AlCl_3$ toxicity is the disruption of calcium (Ca^{2+}) signaling by the hypothalamic neurons. Al^{3+} is a strong antagonist of the voltage-sensitive calcium channels. Since the production and the pulsatile secretion of GnRH are highly Ca^{2+}-sensitive processes, the Ca^{2+} blockade induced by Al significantly inhibits the production of GnRH[7]. To illustrate, Shahraki et al, (2008) injected the rat brain with $AlCl_3$ and found that downstream gonadotropins were significantly reduced, which is expected of impaired GnRH: "GnRH synthesis, secretion and spermatogenesis: Since GnRH synthesis, secretion and spermatogenesis require calcium ion, the study in question was conducted in order to demonstrate the effect of aluminum microinjection on downstream gonadotropins. Other authors have also highlighted that $AlCl_3$ "block the calcium channel in the hypothalamus causing depletion in the GnRH secretion hence reducing FSH and LH release. Concisely, GnRH neurons in the hypothalamus are suppressed by Al^{3+} through Ca^{2+} channel blockage, and this leads to secondary reductions in LH/FSH pituitary [Figure 1][7,8].

Pituitary and Leydig Cell Effects

Although less studies directly evaluate the histology of the pituitary, less GnRH pulses inevitably result in a weakening of the activity of gonadotrope of the pituitary. As a result, serum LH and FSH tend to be low in the $AlCl_3$-exposed animals. As an example, according to Shahraki et al. (2008), the $AlCl_3$-treated rats showed significantly reduced FSH, LH, and testosterone as compared to the controls[2]. The following central suppression probably played a role: Reduced LH release level will cause the serum testosterone to reduce[7,9]. Consequently, several rodent-based studies also show hypothalamo-gonadotrophic, indicating lower LH and/or FSH, following exposure to $AlCl_3$[10]. However, responses can vary. Olanrewaju et al. (2021) found that LH declined and FSH increased in $AlCl_3$-treated rats, implying a dissimilar effect of pituitary, and the authors explained that this was because feedback was interfered with or there were direct effects of Sertoli cells[11]. Overall, the majority of the studies show that $AlCl_3$ has an adverse effect on hypothalamic-pituitary signaling, thereby causing a change in the level of gonadotropin and subsequent downstream androgen deficiency[12].

Testicular cells are also directly affected by aluminum. Both Leydig cells (LH-responsive) and Sertoli cells (FSH-responsive) attempt to use Ca^{2+} mediated signaling as well as energy dependent processes to regulate steroidogenesis and spermatogenesis. $AlCl_3$ suppressed testicular ion pumps and receptor expression. In a study on rats, the $AlCl_3$ treatment decreased Na^+/K^+, Mg^{2+}, and Ca^{2+} - ATPase activities as well as had a huge down-regulation of the FSH receptor (FSHR) and LH receptor (LHR) mRNA and protein in the testis[13]. This implies that $AlCl_3$ is responsible for inhibiting the responsiveness of the Leydig and Sertoli cells to gonadotropins. Maladaptive Ca^{2+} clearance can be used to flatten the testosterone production in Leydig cells. It is so, that numerous studies observe dose-dependent testosterone suppression during the $AlCl_3$ exposure[14,15]. Reduced testosterone can also disorient HPT feedback loops. Al-mediated enzyme inactivation is also associated with dysfunction of steroidogenic enzymes, which also leads to hypogonadism[16].

Overall, the endocrine deficits along the HPT axis are common with the use of $AlCl_3$. In vivo studies are summarized in Table 1 (below). The major patterns are: (1) low LH/ FSH release which is usually with low serum testosterone, due to low GnRH synthesis; (2) direct impairment of the Leydig/Sertoli cell functions; and (3) some cases of compensatory or strain-specific changes like isolated FSH elevation. There is less information available in human data, however, increased testicular Al has been reported to be associated with low sperm viability and disrupted hormone secretion. For example, high levels of Al in human testes and seminal fluid were associated with low quality of sperms. Altogether, the mechanism vision is that $AlCl_3$ affects the release of GnRH via Ca^{2+} and testicular signaling and leads to the breakdown of the HPT axis.

Oxidative Stress and Apoptosis in HPT Tissues

Generation of Reactive Oxygen Species (ROS)

Oxidative stress is one of the significant agents in the toxicity of $AlCl_3$. Al stimulates the synthesis of reactive oxygen species (ROS) in HPT tissues by Fenton-like reactions and damage of mitochondria. According to several reviews, it is observed that "$AlCl_3$ has its harmful actions on the male reproductive tract by causing an elevation in oxidative stress. High levels of ROS that were caused by $AlCl_3$ result in the destruction of DNA, lipid peroxidation, protein alteration, and other negative outcomes[17,18]. The biochemical indicators of redox imbalance in

vivo like elevated levels of malondialdehyde (MDA) and nitric oxide (NO), and reduced antioxidant defenses are evident in $AlCl_3$-treated animals[19,20]. Testis tissue, epididymis and even hypothalamus of rodents have been recorded to have changed after the dosage of $AlCl_3$. The overall consequence is the extensive oxidative injury of HPT tissues[19].

Apoptosis and Cell Damage

Superfluous ROS activates the death of germ cells. Germinal epithelium is very prone to oxidative damage in the testis. The oxidative stress caused by $AlCl_3$ builds up apoptotic pathways in spermatogenic cells. As an example, $AlCl_3$ increases testicular caspase-3 and Bax/Bcl-2 ratios in rats, which are suggestive of apoptosis[21]. According to Faizah *et al.,* oxidative stress, in turn, induces apoptosis in the germinal cells, which cause hypospermatogenesis[12]. In line with this, TUNEL tests in Al-treated testes show a rise in the number of apoptotic nuclei in seminiferous tubules arresting spermatogenesis[10]. Similarly, Al overload is accompanied by neuronal apoptosis in alveolar or neural studies. Altogether, the ROS burden of $AlCl_3$ does not only damage the cell membranes and DNA but promotes programmed cell death of hypothalamic and testicular cells, which compromises the integrity of HPT axis[12].

By synthesizing the results, one can come up with a mechanistic model (Figure 2). With entry of Al^{3+} into HPT tissues, oxidative cascades (high ROS, high NO, lipid peroxidation) are initiated, which overwhelms anti-oxidant defense. Consequences of resulting damage include: (a) cell membrane/ enzyme disruption in Leydig/ Sertoli cells; (b) mitochondrial damage and DNA damage in germ cells; and (c) inflammation of intrinsic apoptotic intrinsic apoptotic pathways in GnRH neurons and testicular cells. It is this multifactorial stress that destroys reproductive cells directly and indirectly acts to block endocrine signals[22].

Histological and Spermatic Alterations

Testicular Morphology

Histopathological investigations have continually demonstrated that $AlCl_3$ causes severe testicular atrophy. The atrophy of seminiferous tubules (reduced diameter), depletion of the germinal cell layer, vacuolation of Sertoli cell cytoplasm, and disorientation of the seminiferous epithelium are common in rodents[23]. Pandey and Jain (2017) also noted shrinkage of seminiferous tubules and Leydig cell nuclei in Al -treated rats in a dose-dependent manner[10]. Similarly, photomicrographs show degenerative alterations in the seminiferous tubules and the Leydig cells, as well as, interstitial edema and sloughing of the germ cells. Al withdrawal does not always decrease the number of germ cells per tubule in histomorphometry, although Al exposure initially causes a decrease[24,25]. Importantly, in the literature, several reports indicate a partial reversal of such lesions when the Al dosage was stopped, which shows the possibility of recovery[10].

Epididymal and Sperm Effects

$AlCl_3$ affects sperm parameters in addition to the testis. Several reports indicate that there are reports of oligoteratospermia - reduced sperm count, motility, and viability - after exposure to Al. In a rat experiment, $AlCl_3$ decreased the epididymal sperm count and caused an abnormal morphology of sperm[26,27]. Programmed death by apoptosis of the testicular tubules and destruction of tubules is an expected consequence of fewer developed sperm. In severe cases, Al leads to the development of so-called giant cells and Sertoli cell vacuolization[4]. Al exposure has been associated with poor sperm quality and counts in humans. Therefore, histological and functional sperm studies support the biochemical damages: $AlCl_3$ injuries the architecture of the HPT axis, which produces infertility-relevant injuries[27].

Aluminum Chloride Case Study

The summary of the main findings of the representative animal studies of the toxicity of $AlCl_3$ HPT is presented in Table 1 (below). Although models like rats, mice, doses and duration differ, there is still a pattern: exposure to $AlCl_3$ decreases testis weight and body weight, decreases LH/FSH/testosterone, increases the markers of oxidative stress, and leads to testicular degeneration. An example is that Olanrewaju et al. (2021) administered 300 mg/kg/day $AlCl_3$ (14 d) to the rats and observed a decrease in the weight of the testis, LH decreased, and degeneration of seminiferous tubules. Shahraki (2008) administered approximately 4 pmol of $AlCl_3$ ICV over 20 d on the rat and observed a significant reduction in LH, FSH, testosterone and sperm count. Rai et al. (2023) exposed mice to 10 mg/kg/day $AlCl_3$ over 62 d, and they found the loss of weight, elevated NO, and MDA, reduced antioxidant enzyme, and tubule damage. Even months of low-dose exposures may have an adverse effect on sperm quality. Overall, the endocrine and oxidative damage to the HPT axis of animal models is represented by $AlCl_3$ in a consistent manner [Table 1 below illustrate the details].

Flavonoids in Amelioration are Natural Antioxidants

Since oxidative stress and inflammation are the most significant in terms of toxicity in Al, natural antioxidants have been tested as countermeasures[28]. Particularly, polyphenolic flavonoids have great prospects because of their anti-inflammatory, anti-apoptotic, and free-radical scavenging properties. These compounds (e.g. quercetin, rutin, naringenin) are able to chelate metal ions, activate endogenous antioxidant pathways (e.g. Nrf2-mediated gene expression), suppress pro-inflammatory signaling via the NF-kB pathway, and directly quench ROS[29,30]. According to a more recent review, natural antioxidants have a tendency to alleviate heavy-metal reproductive injury by regulating the HPG axis and main signaling pathways (Nrf2, MAPK, NF-kB)[29].

Table 1: Representative animal studies of $AlCl_3$-induced HPT axis disruption ($AlCl_3$, aluminum chloride; IP, intraperitoneal; ICV, intracerebroventricular)

Study (Model)	$AlCl_3$ Dose & Duration	Hormonal Effects	Oxidative Stress / Apoptosis	Histology/ Sperm
Shahraki (2008) – ICV in rats	4.125pmol/day (ICV) ×20 days	Low LH, Low FSH, Low Testosterone	Implicit (Low GnRH = germ cell apoptosis)	Decreased Sperm count, Decreased epididymis/testis weight; germ cell loss
Olanrewaju (2021) – Oral rats	300 mg/kg/d (oral) ×14 d	Low LH, High FSH; Low Testosterone	Not reported	Degeneration of seminiferous tubules; Decreased sperm count, motility, viability
Faizah (2023) – Oral mice	100–200 mg/kg/d (oral) ×53 d	Low FSH (100 mg); minor Low Testosterone (all doses)	High MDA, High ROS; germ cell apoptosis	Atrophy of tubules; Decreased Leydig cell area
Rai (2023) – Oral mice	10 mg/kg/d (oral) ×62 d	(Hormones not measured)	High MDA, High protein carbonyls, High NO; Low SOD, CAT, GPx, GSH	Degeneration/detachment of spermatogenic cells; Decreased testis weight
Chen (2024) – Maternal mice	50–150 mg/kg (gestational)	Not measured (developmental effect)	(Not reported)	Disrupted testicular development in offspring; TJ protein alteration
Miska-Schramm (2017) – Chronic Al (3–200 mg/L in water) in voles	Approx. 66 or 175 mg/kg (IP) in cited mice studies	Low Testosterone (dose-dependent)	(High ROS expected but not given)	Decreased spermatid/sperm counts; testicular necrosis
Clinical (Dialysis patients)	High Al^{3+}(uremia)	Low LH, Low FSH, Low TSH, repro impairment	-	Variable; impaired fertility observed

Quercetin (QUE)

Quercetin is a flavonol, which is found profusely in onions, apples, berries and tea. It is a strong ROS scavenger that is reported to accumulate in the testicular tissue. Quercetin has significant improvements in the $AlCl_3$ models. Olanrewaju et al. (2021) administered 200 mg/kg/day of QUE to the $AlCl_3$-exposed rats and observed almost normalization of the testis weight, sperm parameters, and the hormone levels. $AlCl_3$ alone had a strong effect in inhibiting LH and testosterone and activating FSH in their study; quercetin co-treatment undid these effects. Histologically, QUE decreased the seminiferous degeneration and apoptosis. The authors inferred that QUE antioxidant activity had the capacity to reverse the reduction of the sperm status, hormonal action, and functional deficiency caused by aluminum chloride[11]. The action of quercetin is probably to increase testicular SOD/CAT and glutathione levels, decrease lipid peroxidation, and prevent caspase activation. In such a way, the benefits of quercetin are based on the ability to scavenge the ROS generated by Al- and enhance the survival of cells[30].

Naringenin (NAR) and Naringin

Protective effect also occurs with naringenin. Recent mouse study conducted by Rai *et al,* (2023) provided NAR (10 mg/kg/day) following chronic exposure of $AlCl_3$ (10mg/kg). NAR rectified body and testis weight and improved testicular dysfunction. NAR biochemically reduced oxidative stress - reducing MDA, protein carbonyls, NO, and restored antioxidant defense. NAR-treated testes had histopathological evidence of normalized spermatogenic epithelium with reduced apoptotic cells. The paper concludes with the finding that NAR reduced oxidative stress, it restored the antioxidant defense mechanism and it improved the change in histopathology in the testes that was treated with $AlCl_3$[19]. NF-kB and caspases have also been prevented by naringenin in other heavy-metal models[31]. Although there is little evidence on specific $AlCl_3$ + NAR data it is highly suggestive that NAR is a good testicular protectant through antioxidant effect.

Rutin and Naringin

Two flavonols that have been experimented in other studies are rutin (quercetin-3-O-rutinoside) and naringin (naringenin glycoside). A rutin and naringin study on human sperm in vitro discovered that rutin and naringin reinstated motility of the spermatozoa exposed to Aluminum[32]. Motility of sperm cells was considerably inhibited by 1 mM $AlCl_3$ in that experiment; addition of rutin or naringin (50-200 μM) greatly restored it, but quercetin unexpectedly had no effect[32]. This implies that these glycosylated flavonoids are capable of countering acute Al-induced sperm dysfunction, which may be through the protection of sperm membrane against peroxidation. When tested on animals, rutin has been demonstrated to cause glutathione, and antioxidant enzyme induction in the testis with other cadmium toxicity[13]. Despite the lack of rodent studies on $AlCl_3$ + rutin, due to the structural similarity with quercetin, rutin would also act as an ROS scavenger and Al^{3+} chelator.

Flavonoid Protection Mechanisms

Flavonoid functions as protective measures are complex. To begin with, they directly absorb free radical (superoxide, hydroxyl, peroxynitrite), inhibiting lipid and DNA oxidation. Second, flavonoids might compete with metal ions in a chelation reaction, so that Fenton reactions are inhibited; quercetin and rutin contain catechol rings that chelate Al^{3+}. Thirdly, they increase native antioxidants: most flavonoids stimulate the Nrf2 pathway by promoting genes of SOD, CAT, glutathione peroxidase, and phase-II detox enzymes. Fourth, they prevent inflammatory signaling: flavonoids suppress cytokines like IL-1β and TNF-α, increase in a metal toxicity. Lastly, they will be able to regulate apoptotic regulators: an example is quercetin which is confirmed to cause Bcl-2 and Bax and caspase-3 to decrease in testicular models, thereby inhibiting cell death. The overall result is that there is maintenance of HPT tissue integrity during Al stress[33].

Antioxidant Intervention Conclusions

The tendency of interventions of flavonoids in $AlCl_3$ testicular toxicity is evident: co-treatment with flavonoids brings the hormone levels to normal, the antioxidant activities of enzymes are restored, and the tissue histology is enhanced.

- Quercetin (200mg/kg) + $AlCl_3$ (300mg/kg) almost corrected testicular weight, sperm count/ motility and serum testosterone in rat $AlCl_3$ reduced serum LH that had been reduced, and FSH was brought down to normal. Histology revealed normal tubules[11].
- Post- $AlCl_3$ insult of naringenin (10 mg/kg) replaced the weight of the testis and antioxidant enzymes. NAR reduced oxidative markers like MDA and protein carbonyls significantly, and this was associated with almost normal spermatogenesis[19,31].
- Rutin/Naringin (20-200 μM in vitro)1 mM $AlCl_3$ The human sperm motility was preserved by Rutin/Naringin (20-200 μM in vitro). In vivo rat data are not available, but since they are effective in human sperm, they are good candidates[13,32].
- $AlCl_3$ testicular damage in rats was also prevented by the Bay leaf extract (high in flavonoids and alkaloids) that enhanced sperm count/morphology and decreased the oxidative markers[34].

In every instance, the flavonoid-treated groups were characterized by reduced lipid peroxidation, improved SOD/CAT activity, decreased apoptosis markers, and improved histology as compared to the Al-only animals. These gains were in the form of increased testosterone levels and sperm parameters. There are no clinical trials of flavonoids in men who are exposed to Al, but the animal results indicate a therapeutic effect. Notably, such compounds are usually considered to be safe and can be administered as diet or supplements. Nevertheless, dose-optimization and long-term safety require research.

CONCLUSION

Aluminum chloride is a strong disturber of the male hypothalamic-pituitary-testicular axis. Mechanistically, the $AlCl_3$ closes neuronal Ca^{2+} channels through inhibition of hypothalamic GnRH release and consequently LH/FSH. At the same time, it impairs oxidative stress on pituitary and testicular cells, leading to the loss of DNA/lipid damage and apoptosis. The sum of the effects is decreased testicular steroidogenesis and spermatogenesis: testosterone decreases, gonadotropin receptor becomes dysfunctional, and seminiferous tubules are destroyed. These are pathologies that have been consistently

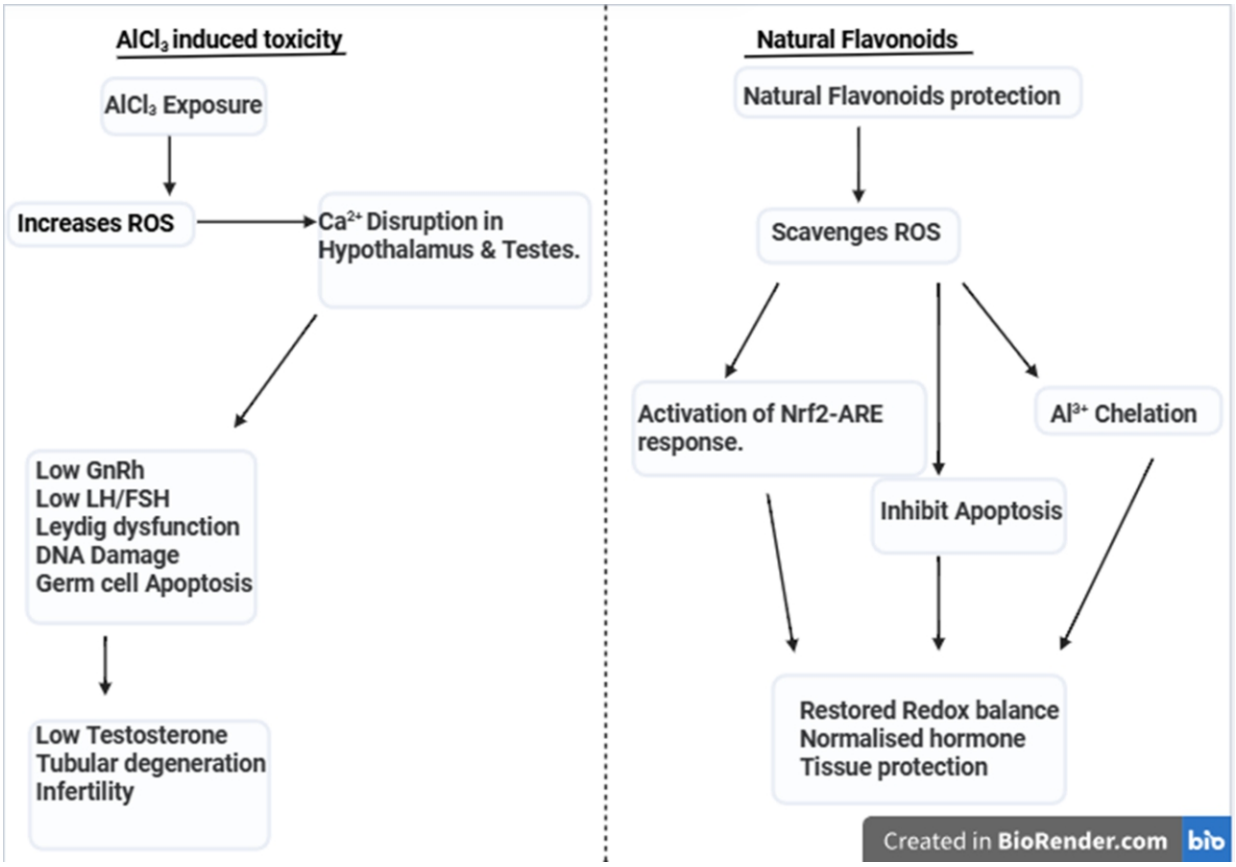

Figure 2: Schematic of $AlCl_3$-induced Testicular Toxicity and Flavonoid Protection

$AlCl_3$ (left) increases ROS and disrupts Ca^{2+} signaling in hypothalamus and testis, leading to decreased secretion of GnRH, Low LH/FSH, Leydig dysfunction, oxidative DNA/ lipid damage, and germ cell apoptosis. The result is low testosterone, tubular degeneration, and infertility. Natural flavonoids (right) scavenge ROS, activate Nrf2-ARE antioxidant responses, chelate Al^{3+}, and inhibit apoptosis. The net effect is restored redox balance, normalized hormones, and tissue protection.

found in rat and mouse models, and the increase of Al in humans is associated with like deficits.

Naturally, there is some hope of rescue through the natural antioxidants, in particular flavonoids. Quercetin, naringenin and other analogs reverse the effects of $AlCl_3$ toxicity through the scavenging of ROS, the promotion of the endogenous antioxidant response, metals chelation and pro-apoptotic activation inhibition. These agents experimentally reestablish the levels of antioxidant enzymes, hormone levels, and testicular histology in animals exposed to al-challenges. Therefore, dietary or supplemental flavonoids have therapeutic potential in overcoming the Al-induced reproductive damage. The interventions like optimal doses, delivery and combination therapies) should be improved in the future and applied to human subjects. Further clarification of molecular targets (e.g. particular signaling kinases, epigenetic alterations) in the toxicity of $AlCl_3$ is also required. On the whole, the data show that despite the high threat of aluminum to the endocrine system of men, the antioxidant therapy can be used to a great extent to reduce this load.

CONFLICT OF INTEREST: None

FINANCIAL SUPPORT: None

REFERENCES

1. Casteel CO, Singh G. Physiology, gonadotropin-releasing hormone. 2020.
2. Casati L, Ciceri S, Maggi R, Bottai D. Physiological and pharmacological overview of the gonadotropin releasing hormone. Biochemical pharmacology. 2023 Jun 1; 212:115553.
3. Adeleke OS. Hypothalamic-pituitary-testicular-axis response in Wistar rat treated with chlorpromazine, rauwolfia vomitoria leaf and combination of reserpine, ascorbate and zinc (doctoral dissertation, university of ilorin). 2021.
4. Ghosh B, Sharma RK, Yadav S. Toxic effects of aluminum on testis in presence of ethanol coexposure. Eur J Anat. 2021;25(3):359–367.
5. Miska-Schramm A, Kapusta J, Kruczek M. The effect of aluminum exposure on reproductive ability in the bank vole (Myodes glareolus). Biol Trace Elem Res. 2017;177(1):97–106. doi:10.1007/s12011-016-0848-3.
6. Yokel RA. Aluminum reproductive toxicity: a summary and interpretation of scientific reports. Crit Rev Toxicol. 2020;50(7):551–593.
7. Shahraki MR, Mony EY, Asl SZ, Sarkaki AR, Shahraki AR. Effects of aluminum chloride injection in lateral ventricle on serum gonadothropines, testosterone and spermatogenesis in rats. Journal of Medical Sciences. 2008;8(4):410.
8. Ciechanowska M, Łapot M, Malewski T, Mateusiak K, Misztal T, Przekop F. Effects of GABAA receptor modulation on the expression of GnRH gene and GnRH receptor gene in the hypothalamus and anterior pituitary gland of follicular-phase ewes. Anim Reprod Sci. 2009;111(2-4):235–248.
9. Reis LO. Variations of serum testosterone levels in prostate cancer patients under LH-releasing hormone therapy: an open question. Endocr Relat Cancer. 2012;19(3): R93–R98.
10. Pandey G, Jain GC. Aluminum chloride-induced testicular effects in rats: a histomorphometrical study. Asian J Appl Sci Technol. 2017;1(9):46–52.
11. Olanrewaju JA, Akinpade TG, Olatunji SY, Owolabi JO, Enya JI, Adelodun ST, et al. Observable protective activities of quercetin on aluminum chloride-induced testicular toxicity in adult male Wistar rat. J Hum Reprod Sci. 2021;14(2):113–120. doi: 10.4103/jhrs.jhrs_190_20.
12. Faizah Z, Hendarto H. The effect of aluminum chloride on testicular biometry, hormonal profiles, spermatozoa quality, and spermatogenic cell morphology in mice. Open Vet J. 2024;14(9):2315–2324. doi:10.5455/OVJ. 2024.v14.i9.20.
13. Sun X, Sun H, Yu K, Wang Z, Liu Y, Liu K, et al. Aluminum chloride causes the dysfunction of testes through inhibiting the ATPase enzyme activities and gonadotropin receptor expression in rats. Biol Trace Elem Res. 2018;183(2):296–304.
14. Seifi R, Karami M, Jalali-Nadoushan M. AlCl3-induced Alzheimer's in rats: linking oxidative stress, inflammation, and lactate production via the cAMP/AK signaling pathway. Neuroscience and Behavioral Physiology. 2025 Jan;55(1):43-60.
15. Peng H, Huang Y, Wei G, Pang Y, Yuan H, Zou X, et al. Testicular toxicity in rats exposed to AlCl3: a proteomics study. Biol Trace Elem Res. 2024;202(3):1084–1102.
16. Lokman M, Ashraf E, Kassab RB, Abdel Moneim AE, El-Yamany NA. Aluminum chloride–induced reproductive toxicity in rats: the protective role of zinc oxide nanoparticles. Biol Trace Elem Res. 2022;200(9):4035–4044.
17. Shahabuddin F, Naseem S, Alam T, Khan AA, Khan F. Chronic aluminum chloride exposure induces redox imbalance, metabolic distress, DNA damage, and histopathologic alterations in Wistar rat liver. Toxicol Ind Health. 2024;40(11):581–595.
18. Naseem S, Shahabuddin F, Alam T, Khan AA, Khan F. Oral Administration of Aluminum Chloride Inhibits Enzymes of Brush Border Membrane and Induces Metabolic Distress, Redox Imbalance, DNA Damage, and Histopathologic Alterations in Rat Intestine. Journal of Applied Toxicology. 2026 Feb;46(2):622-38.
19. Rai R, Jat D, Mishra SK. Naringenin ameliorates aluminum toxicity-induced testicular dysfunctions in mice by suppressing oxidative stress and histopathological alterations. Syst Biol Reprod Med. 2023;69(5):347–353. doi:10.1080/19396368.2023.2203794.
20. Ibrahim RM, Elaal FE, Zaki S. Effect of curcumin and nano-curcumin on reduce aluminum toxicity in rats. Int. J. Food Sci. Bioechnol. 2019; 4:64.
21. Talwar P, Hayatnagarkar S. Sperm function test. J Hum Reprod Sci. 2015;8(2):61–69.
22. Allameh A, Niayesh-Mehr R, Aliarab A, Sebastiani G, Pantopoulos K. Oxidative stress in liver pathophysiology and disease. Antioxidants (Basel). 2023;12(9):1653.

23. Nuhair R. Effects of aluminum chloride on some hormones level and reproductive organs of male rats (Rattus norvegicus). Univ Thi-Qar J Sci. 2015;5(2):3–9.

24. Khattab FKI, Khattab I. Histological and ultrastructural studies on the testis of rat after treatment with aluminum chloride. Aust J Basic Appl Sci. 2007;1(1):63–72.

25. Moselhy WA, Helmy NA, Abdel-Halim BR, Nabil TM, Abdel-Hamid MI. Role of ginger against the reproductive toxicity of aluminum chloride in albino male rats. Reprod Domest Anim. 2012;47(2):335–343.

26. Khalaf HA, Elsamanoudy AZ, Abo-Elkhair SM, Hassan FE, Mohie PM, Ghoneim FM. Endoplasmic reticulum stress and mitochondrial injury are critical molecular drivers of AlCl3-induced testicular and epididymal distortion and dysfunction: protective role of taurine. Histochem Cell Biol. 2022;158(1):97–121.

27. Arumugam K, Venugoapal R. Effect of Zingiber officinale on aluminum induced epididymal sperm abnormalities in albino rats. World J Pharm Sci. 2016;5(6):1664–1680.

28. Dare BJ, Oyeniyi F, Olaniyan OT. Role of antioxidant in testicular integrity. Ann Res Rev Biol. 2014;4(7):998.

29. Fan Y, Jiang X, Xiao Y, Li H, Chen J, Bai W. Natural antioxidants mitigate heavy metal induced reproductive toxicity: prospective mechanisms and biomarkers. Crit Rev Food Sci Nutr. 2024;64(31):11530–11542. doi:10.1080/10408398.2023.2240399.

30. Hajiyeva R, Durmuş S, Tunçdemir M, Gelişgen R, Sözer V, Mirzataş EB, et al. The role of quercetin in alleviating the testicular oxidative stress and apoptosis in streptozotocin-induced diabetes. Cerrahpasa Med J. 2021;45(3):159–166.

31. Qin W, Ren B, Wang S, Liang S, He B, Shi X, et al. Apigenin and naringenin ameliorate PKCβII-associated endothelial dysfunction via regulating ROS/caspase-3 and NO pathway in endothelial cells exposed to high glucose. Vasc Pharmacol. 2016; 85:39–49.

32. Jamalan M, Ghaffari MA, Hoseinzadeh P, Hashemitabar M, Zeinali M. Human sperm quality and metal toxicants: protective effects of some flavonoids on male reproductive function. Int J Fertil Steril. 2016;10(2):215–223. doi:10.22074/ijfs.2016.4912.

33. Behl T, Kaur G, Sehgal A, Zengin G, Singh S, Ahmadi A, Bungau S. Flavonoids, the family of plant-derived antioxidants making inroads into novel therapeutic design against ionizing radiation-induced oxidative stress in Parkinson's disease. Curr Neuropharmacol. 2022;20(2):324-43.

34. Falade AO, Adewole KE, Adekola AR, Ikokoh HA, Okaiyeto K, Oguntibeju OO. Aqueous extract of bay leaf (Laurus nobilis) ameliorates testicular toxicity induced by aluminum chloride in rats. Vet World. 2022;15(11):2525.