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REVIEW ARTICLE

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Antioxidant effects of N-acetylcysteine on the male reproductive system: A systematic review

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Abstract

This study aimed to evaluate the effect of N-acetyl cysteine on the male reproductive system and consensus and classification of data found from previous studies. It is undeniable that N-acetyl cysteine as a powerful antioxidant compound can medicate many diseases such as cardiovascular, kidney, liver and reproductive system disorders. With the increasing environmental pollution that has a direct adverse effect on male fertility, the use of this compound is able to positively function on human fertility health. In this study, we have been collected the main data of scientific articles (1994–2020) about N-acetyl cysteine effects. By searching in the scientific databases of PubMed, Google Scholar, Science Direct, Wiley and Web of Science, related articles were extracted. As a result, all observations have confirmed that N-acetyl cysteine can improve and normalise the spermatogenesis in the male reproduction system.

KEYWORDS

fertility, N-acetylcysteine, oxidative stress, spermatogenesis, testicular tissue

1 | INTRODUCTION

NAC is a cysteine-derived amino acid compound developed in the 1950s that acts as an antioxidant by increasing glutathione (Malmir, Soleimani Mehranjani, et al., 2018). It is a powerful antioxidant compound that, due to its properties, can be effective in male and female infertility, cardiovascular diseases, human immunodeficiency virus infections, liver poisoning and metal poisoning (Malmir, Soleimani Mehranjani, et al., 2018; Millea et al., 2009). In the research studies, one of the key issues is dose founding. In infertility theme, due to a large number of studies on a particular topic, finding out how different doses of an antioxidant or toxin affect laboratory animals or humans requires a lot of time-consuming. Therefore, three complete tables to express the effects of NAC on spermatogenesis, testicular tissue and blood biochemistry were designed by two purposes: first, easy access to important results of past study for future research and second, explaining the effect of NAC on the treatment of male infertility.

2 | METHODOLOGY

The inclusion criteria of articles in the present review included evaluation of spermatogenesis, testicular tissue and blood biochemistry in NAC users, which have been done from 1998 to 2020. Electronic search was performed in PubMed, Science Direct, Scopus and Springer databases. Finally, the Google Scholar database was used to ensure that the content was complete. Present study was performed using the MeSH words including N-acetylcysteine, spermatozoa, testicular tissue, antioxidant, antioxidant defence system, apoptosis, mechanism of action, sex hormones and male infertility. The search result in the databases was a total of 281 articles. The number of these articles was reduced to 84 after passing the Identification, Screening and Eligibility stages. Exclusion criteria included unreliable journals and scholarly comments, duplication, and lack of access to the full text (Figure 1). The steps related to articles searching and results and data extracting

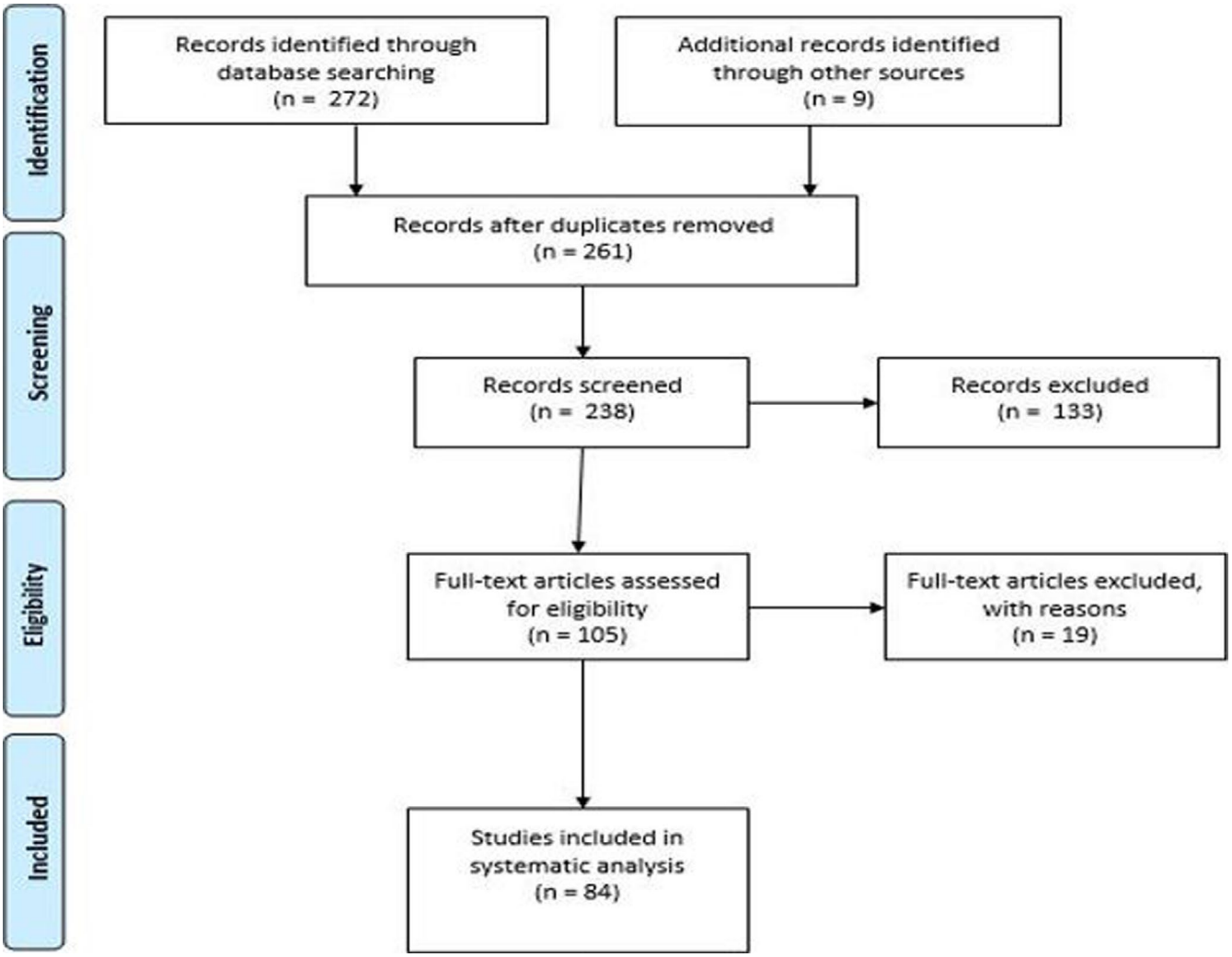

FIGURE 1 PRISMA diagram

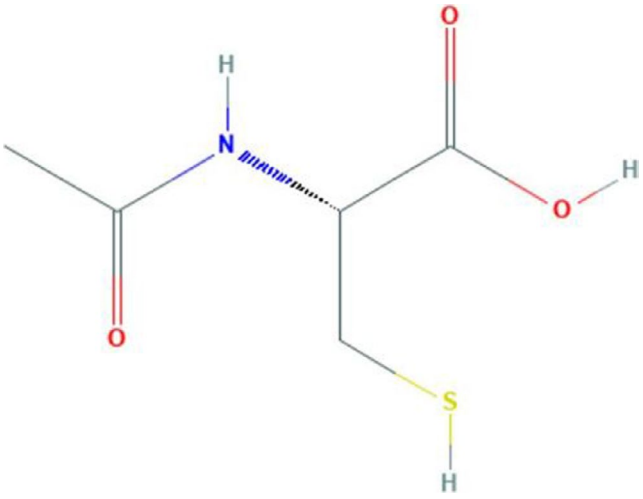

FIGURE 2 Chemical structure depiction of N-acetylcysteine

were performed independently by two researchers, and in case of differences in each of the steps, they were reviewed by a third researcher.

3 | CHEMICAL STRUCTURE DEPICTION NAC

N-acetylcysteine (thiol-containing compound) is separated from the L-cysteine amino acid that is soluble in alcohol and water (Moldeus & Cotgreave, 1994; Samuni et al., 2013). NAC has been introduced by synonyms such as acetylcysteine, N-acetyl-L-cysteine and mercapturic acid in various articles. This vital compound was developed in the 1950s, which has C5H9NO3S chemical structure (Figure 2) with a molecular weight of 163.195 (Gillissen & Nowak, 1998, Juch et al., 1995).

4 | CLINICAL EFFECT OF NAC

From a pharmacological point of view, NAC injection causes the production of disulphides in plasma, the effect of which lasts from a few minutes to 6 hr (Radomska & Skopinski, 2012). According to previous studies, NAC may play an essential and specific function in: glutathione synthesising (Shackebaei et al., 2005), preventing

and down-regulation the adverse effects of toxins on the kidneys and liver (Mokhtari et al., 2017), improving the addictive behaviour and psychiatric disorders (Dean et al., 2011; Samuni et al., 2013), decreasing of respiratory state symptoms (Tirouvanziam et al., 2006), providing brain health with refilling glutathione and regularisation glutamate (Costa et al., 2016; Mokhtari et al., 2017), decreasing inflammation in fat cells and fixate sugar of the blood (Jain et al., 2009; Ma et al., 2016), decreasing heart disease risk by preventing the damage of oxidative stress (Anfossi et al., 2001), improving immune system function by boosting glutathione levels (Monroy et al., 2016) and also increasing fertility in men (Barekat et al., 2016) and women (Badawy et al., 2007). Furthermore, NAC is a cysteine metabolite (Dodd et al., 2008) that prescribed to acetaminophen poisoning and also commonly used to treat pulmonary fibrosis (Dodd et al., 2008). Moreover, NAC is traditionally used as an expectorant (mucolytic) and has been shown to have antimicrobial effects (Millea, 2009). Also, NAC in photography with contrast agents (substances to increase contrast in radiography), as adjuvant therapy in the root Kenny Helicobacter pylori, prevention of hearing impairment gentamicin and in dialysis patients as a dietary supplement (Millea, 2009), is used. In this paragraph, some of the benefits of NAC for the treatment of some diseases in humans were mentioned.

5 | OXIDATIVE STRESS & ANTIOXIDANT

Oxidative stress is accompanied by an imbalance between oxidants and antioxidants (Crespy & Williamson, 2004). Reactive oxygen species (ROS) is a general term that refers to molecules derived from molecular oxygen which are active species or can easily become active species (Crespy & Williamson, 2004). Some ROS include peroxides, superoxide, hydroxyl radical, singlet oxygen and alpha-oxygen (Hayyan et al., 2016). The reduction of molecular oxygen produces superoxide which is the precursor of most other reactive oxygen species (Turrens, 2003). The dismutation of superoxide produces hydrogen peroxide. Hydrogen peroxide in turn may be partially reduced, thus forming hydroxide ion and hydroxyl radical, or fully reduced to water (Hayyan et al., 2016; Turrens, 2003). Simply put, ROS are active chemical mediators that result from incomplete oxygen regeneration (Cotter et al., 2007). ROS are short-lived molecules that able to cause oxidative damage to DNA and also these oxidants are the most critical oxidative stress marker in the human body (Cotter et al., 2007). Antioxidants via their specific chemical structure can prevent oxidation, which is chemically divided into two categories: water-soluble (glutathione, e.g.) and fat-soluble (vitamin E, e.g.; Sies, 1997). Water-soluble antioxidants in blood plasma and cell cytosol react with oxidants, and vice versa, fat-soluble antioxidants protect phospholipid membranes from lipid peroxidation (Vertuani et al., 2004). The cysteine group in glutathione, which is a reducing agent, can be reversibly reduced and oxidised, and this action gives glutathione antioxidant properties (Meister, 1994; Newton et al., 2009). Free radicals damage most macromolecules, including lipids, proteins and nucleic acids (Agarwal, 2005; Fanaei et al., 2014). Due to the high levels of fatty acids in germ cell and sperm membranes, these cells are highly susceptible to lipid peroxidation (Aitken et al., 1993). ROS also stimulates apoptosis in germ cells and Sertoli (Malmir, Soleimani Mehranjani, et al., 2018), decreases testosterone production (Agarwal & Said, 2005; Malmir, Faraji, et al., 2018) and causes DNA fragmentation (Malmir, Soleimani Mehranjani, et al., 2018; Marchetti et al., 2002), thereby disrupting germ epithelium.

6 | MECHANISM OF ACTION OF NAC

In the first, the connection between NAC and glutamine synthesis must be addressed. NAC does not require active transmission to move from cell membrane and simply passes (inactive transfer) through the membrane (Van Schooten et al., 2002). It is rapidly hydrolysed by γ-GCS (c-glutamylcysteine synthetase) and glutathione synthetase enzymes to form glutathione (Marmolino & Manto, 2010; Van Schooten et al., 2002). Intracellular glutathione is converted to thiol by the enzyme glutathione reductase, which reacts nonenzymatically with ROS to neutralise them (Marmolino & Manto, 2010). NAC is converted to cysteine in the body, which is the anti-porter glutamate-cysteine substrate and causes glutamate to be reversed into extracellular space and ultimately reduces the release of glutamate from synapses (McFarland et al., 2003). Glutathione is one of the critical antioxidants in the cells that be disposed of detoxifying toxins including xenobiotic (Pena-Llopis et al., 2014). During oxidative stress, the concentration of glutathione decreases, prescribing NAC by upregulation glutathione compensate for this deficiency (Atkuri et al., 2007). On the other side, NAC via a sulphur group in chemical composition directly confronts free radicals, especially ROS, and stabilises them by donating an electron from its capacity layer (Dickinson et al., 2003; Radomska-Leoeniewska & Skopi-ski, 2012). Moreover, this powerful antioxidant facilitates the production of nitric oxide by dilating the arteries, which also has many therapeutic applications with this function (Ardissino et al., 1997). Also, NAC acts as an inhibitor of neutrophil penetration and with balancing the oxidant–antioxidant state and regulating inflammatory mediators as protecting tissues (Alturfan et al., 2012). In the last, NAC uses the following mechanisms to prevent endoplasmic reticulum (ER) stress: 1—It reduces the activation of the unfolded protein response signal, which triggers ER dysfunction and induces apoptosis in somatic cells (Ji et al., 2013). 2—NAC reduces the expression of the glucose-regulating protein (GRP78), which GRP78 is an important chaperone at the level of ER and can activate caspase 12 that induce apoptosis (Chen et al., 2011; Ji et al., 2013). 3—It prevents phosphorylation of the translational initiating factor in eukaryotic testes (eIF2a), which is one of the factors inducing unfolded protein response (UPR) signals (Ji et al., 2013; Oh & Lim, 2006). 4—NAC can also inhibit the proliferation of two main causes of ER stress called C/EBP homologous protein (CHOP) and c-Jun N-terminal kinase (JNK). These factors are transcription factors that reduce the expression of Bcl-2 (anti-apoptotic agent in the cell) and induce apoptosis (Ji et al., 2013).

TABLE 1 Evaluation of the effect of NAC on men and different species of animals (spermatogenesis)

Species	Type of response: Dose of NAC & duration of treatment	Mot	Abn	Cou	DSP	Via	Other Parameters	T & D	Reference
Human	600 mg/day _ 3 month	↑		↑			↑ Volume, ↓ Viscosity, ↓ Liquefaction time	Varicocele	Ciftci et al. (2009)
Human	600 mg/days – 26 weeks	↑	↓	↑			↑ Sperm concentration, ↑ Ejaculate volume	AT	Safarinejad and Safarinejad (2009)
Swiss albino mice	75 mg/kg – 35 days	↑		↑		↑	↑ Tail coiled spermatozoa, ↑ Sperm quality, ↑ Spermatogenesis	Arsenic	Reddy et al. (2011)
Human	50 mg – 2–12 months in vitro	↑		↑			↑ Semen quality, has remarkable benefit for IVF patients having restricted sperm parameters	OAT	Wirleitner et al. (2012)
Wistar rat	800 ppm – 35 days			↑			↑ (nonsignificant) motility and viability	Lead	Asadpour et al. (2013)
Wistar rat	300 mg/kg – 3 months			↑			↑ Spermatogenesis	Lead & Cadmium	Kumar et al. (2013)
Wistar rat	1 hr/day, 6 days/week for consecutive 8 weeks	↑	↓	↑			↑ Spermatogenesis, ↑ Spermatogenic cells	IFS	Jana et al. (2014)
Albino rat	100 mg/ kg 3 months						↑ Spermatogenesis, ↑ Rat of cytokines and spermatogenesis genes	Titanium Dioxide	Male (2014)
SD rat	150 mg/kg –7 weeks	↑	↓	↑			↑ Spermatogenesis	Sodium fluoride	Feng et al. (2015)
Human	200 mg/days–3 month	↑	↓	↑			↑ P, ↓ ROS, ↑Volume, ↓ SDF, ↓ +T	Varicocele	Barekat et al. (2016)
Rat	20 mg/kg 30 min + 4 H 2 months						↑ Spermatogenesis, ↑ Spermatozoa and spermatid	I/R	Bodur et al. (2016)
Human	5 mM	↑				↑	↓ SDF, ↓ +T	Post-thaw recovery	Kobori et al. (2017)
Lidia bovine	1 mM and 2.5 mM – 24, 48, 72 or 96 hr prior cryopreservation						Did not significantly affect total and progressive motility, sperm velocity and kinematic parameters	Frozen-thawed	De & Prolongado (2017)
Wistar rat	*160* mg/kg 8 weeks	↑	↓	↑		↑	↑ Spermatogenesis, ↓ SDF	*Glyphosate*	Avdatek et al. (2018)
NIMRI mice	150 mg/kg – 35 days	↑	↓	↑	↑	↑	↑Sperm tail length, ↑ Spermatogenic index	Para-nonylphenol	Malmir, et al. 2018)
Wistar albino rat	150 mg/kg – 2 weeks	↑	↓	↑		↑	↑ Spermatogenesis	Paracetamol	El-Maddawy & El-Sayed (2018)
Albino rat	100 mg/kg 12 weeks						↑ Spermatogenesis	Titanium Dioxide	Elnagar et al. (2018)
NIMRI mice	200 mg/kg – (twice/week) –40 days	↑		↑			↑ Spermatogenesis, ↑ Germinal cells	Mancozeb	Mohammadi-Sardoo et al. (2018)
SD rat	300 mg/kg – 5 days						↑ Spermatogenesis, ↑ Germinal cells	X-radiation	Topcu et al. (2019)
Mice	35 mg/kg – 4 week	↑	↓	↑			↑ Spermatogenesis	Chlorpyrifos	Kheradmandi et al. (2019)
G. rarus Fish	100 mg/kg – 7 days						Inhibition of DNA methylation, Not effect on sperm motility and DNA integrity	bisphenol A	Yuan et al. (2019)
Human	50 μg - 2 hr in vitro	↓					↓ Sperm DNA fragmentation, ↓ Immature chromatin, ↓ Sperm hypoosmotic swelling		Baetas et al. (2019)

(Continues)

TABLE 1 (Continued)

Species	Type of response						T & D	Reference
	Dose of NAC & duration of treatment	Mot	Abn	Cou	DSP	Via	Other Parameters		
Human	600 mg/days - 3 month	↑	↓	↑			↓ SDF, ↓ +T, ↓ MDA, ↑ TAC, ↓ ROS, ↑ Volume, ↓ Chromomycin A3	AT	Jannatifar et al. (2019)
Wistar rat	100 mg/days - 21 days						↓ Sperm Cun (nonsignificant), ↓ Interstitial space distance, ↓SDF, ↓ Degenerated Leydig cells, ↑ Sperm maturation	Cyclophosphamide	Shittu et al. (2019)
SD rat	20 mg/kg – 30 min + 6 hr						↑ Spermatogenesis, ↑ Germinal epithelium and Sperm maturation	I/R	Kazaz et al. (2019)
Balb/C mice	100 mg/kg – 14 days						↑ Spermatogenesis	MK–801 in Schizophrenic	Turkmen et al. (2019)
Wistar rat	10, 20 and 40 mg/kg – 28 days						↑ Spermatogenesis, ↑ Spermatogenic and sertoli cells	Acrylamide	Shahrzad et al. (2020)

Note: +T, Positive-TUNEL; ↑, Increase or Improve; ↓, Decrease (comparison in the toxin/disease group with NAC + toxin/disease group); Abn, Abnormality; AT, Astheno-teratospermia; Balb/c, Bagg albino, laboratory-bred; Cou, Count; CPF, Chlorpyrifos; DSP, Daily sperm production; G, Gobiocypris; I/R, Testicular ischaemia–reperfusion; IFS, Intensive forced swimming; Mot, Motility; NAC, N-acetylcysteine; *NIMRI, Naval Medical Research Institute*; OAT, Oligo-astheno-teratozoospermic; P, Protamine deficiency; ROS, Reactive oxygen species; *SD, Sprague-Dawley*; SDF, Sperm DNA fragmentation; T & D, Against Toxin & Diseases; TAC, Total antioxidant capacity; Via, Viability.

NAC inhibits the activity of c-Jun N-terminal kinase, mitogen-activated protein kinase (MAP) kinase p38, SAPK/INK (stress-activated protein kinase), c-fos pathway and NF-κB (nuclear factor κB), which able to regulate many anti-apoptotic genes and pre-inflammatories (Marmolino & Manto, 2010; Van Schooten et al., 2002).

7 | IMPROVING SPERMATOGENESIS BY NAC

Spermatogenesis is the process in which spermatogonia cells evolve under meiosis to form spermatozoa (Junqueira & Carneiro, 2005). Germ cells in the germinal epithelium are highly vulnerable to oxidative stress, and the presence of antioxidants such as NAC can defend the spermatogenesis process against oxidative stress (Malmir, Faraji, et al., 2018; Malmir, Soleimani Mehranjani, et al., 2018). The quality and quantity of spermatogenesis can be assessed by evaluation parameters such as count, motility, velocity, viability, DNA fragmentation and integrity, the morphology of spermatozoa and population of Sertoli and spermatogenic cells (Malmir, Soleimani Mehranjani, et al., 2018; Rabaca et al., 2020; Shahrzad et al., 2020). Plentiful papers have elucidated that NAC can enhance sperm quality and quantity that accompanied by boosting spermatogenesis (Malmir, Soleimani Mehranjani, et al., 2018; Shahrzad et al., 2020; Verdi et al., 2019). According to the information obtained, there is a strong possibility that NAC improves the count (Verdi et al., 2019), motility (Kheradmandi et al., 2019), velocity (Ciftci et al., 2009), viability (Malmir, Soleimani Mehranjani, et al., 2018), normal DNA (Baetas et al., 2019), normal morphology of spermatozoa (Kheradmandi et al., 2019) and also a population of Sertoli (Shahrzad et al., 2020) and spermatogenic cells (Topcu et al., 2019) with its antioxidant effect and boosting the antioxidant enzyme system (Table 1). NAC improves spermatogenesis in several ways, including by reducing ROS lead to maintain membrane integrity and prevent lipid peroxidation, which plays an important role in sperm morphology (Malmir, Soleimani Mehranjani, et al., 2018). On the other hand, it increases testosterone levels, which promotes sperm health and protects cell division (Nashwa et al., 2011). Also, NAC can inhibit the activity of c-Jun N-terminal kinase, MAP kinase p38, SAPK/INK, c-fos pathway and NF-κB, which decrease apoptosis induction (Marmolino & Manto, 2010). Besides, preventing DNA fragmentation, boost sperm viability (Malmir, Soleimani Mehranjani, et al., 2018). The environmental pollutants and toxins mentioned in the tables mainly affect the male reproductive system by causing oxidative stress. Hence, the antioxidant role of NAC neutralises these toxins (Malmir, Soleimani Mehranjani, et al., 2018; Marmolino & Manto, 2010; Nashwa et al., 2011).

8 | IMPROVING TESTICULAR TISSUE BY NAC

Since the process of spermatogenesis turns up in testicular tissue (Junqueira & Carneiro, 2005) the safety of Sertoli,

TABLE 2 Evaluation of the effect of NAC on men and different species of animals (testicular tissue)

		Type of response			
Species	Dose of NAC & duration of treatment	T & D	Oxidative stress & Apoptosis	Histology, Testicular biochemistry & PCR	Reference
Human	25, 50 and 100 mmol/L - 4, 24, and 48 hr, in vitro	Oli	↓ Ap, ↓ OS	↓ DNA fragmentation in human germ cells, ↓ +T seminiferous tubules cultured	Erkkilä et al. (1998)
Wistar albino rat	500 mg/kg - 5 hr			↑ Most tubules showing maturation up to the level of spermatozoa, ↑ preservation of tubular morphology, ↑ mean seminiferous tubule diameter and ↑ Johnsen's mean testicular biopsy score	Dokmeci et al. (2007)
Wistar albino rat	20 mg/kg - 2 hr and 5 min – 2 hr and 60 min, in vitro	I/R		↓ TBARS, ↑ Mean seminiferous tubular diameter, ↑ Mean germinal epithelial cell thickness and ↑ Mean testicular biopsy scores.	Aktaş et al. (2010)
Wistar rat	50 mg/kg – 2 months	Varicocele		NAC did not significantly affect spermatogenesis and degree of testicular germ cell apoptosis	
Swiss albino mice	75 mg/kg – 35 days	Arsenic	↓ OS	↑ Weights of reproductive organs, ↑ CAT and SOD, ↓ MDA, ↑ Activity of 17ß and 3 ß- HSD	Duarte et al. (2010)
Wistar rat	20 mg/kg – 2 hr and 30 min, in vitro	I/R	↓ OS	↑ Protective effect against I/R testicular injury, ↓ (nonsignificant) MDA, ↑ (nonsignificant) Histopathological score Median	Reddy et al. (2011)
Wistar albino rat	150 mg/kg – 4 Weeks	Diazinon	↓ OS	↑ Spermatogenesis and ↓ testicular oxidative injury, ↓ MDA, ↑ Glutathione, ↑ C and E Vitamin, ↑ ß-carotene	Turkmen et al. (2012)
CD–1 mice	100 mg/kg – 8 hr and 24 hr, in vitro	Cadmium	↓ Ap, ↓ OS	↓ Testis weight, ↓ Oedema, ↓ Necrosis, ↓ Haemorrhage in interstitium, ↓ ER stress in the testes, ↓ GRP78 protein, ↓ Grp78 mRNA levels, ↓ Levels of testicular uXbp–1 and sXbp–1 mRNA, ↓ Level of testicular peIF2a and p-JNK, ↓ Levels of testicular HO–1 and 3-NT and ↑ GSH, ↓ +T	Oksay et al. (2013)
Wistar rat	800 ppm – 35 days	Lead	↓ OS	↑ (nonsignificant) Total protein, ↑ SOD and GSH-$_{Px}$,↓ (nonsignificant) MDA	Ji et al. (2013)
Wistar rat	300 mg/kg – 3 months	Lead & Cadmium	↓ OS	↑ Protective effect in histopathological injury, ↓ Pc, ↓ GST, ↑ TBARS, ↓ LDH, ↑ GSH-$_{Px}$	Asadpour et al. (2013)
Wistar rat	1 hr/day, 6 days/week for consecutive 8 weeks	IFS	↓ Ap, ↓ OS	↑ Activity of 17ß and 3 ß- HSD, ↑ Intratesticular testosterone concentrations, ↓ Pc, ↓ MDA, ↑ GSH, ↑ SDH, ↓ ROS, ↑ GST, ↑ GSH/GSSG, ↓ Gene Casp3, ↓ DAN testicular damage	Kumar et al. (2013)
Albino rat	100 mg/kg 3 months	Titanium Dioxide	↓ Ap, ↓ OS	↓ mRNA expression of IL–6 and TNF-a, Expression of gene, ↑ GST, ↓ BcL$_2$, ↑ ABR, ↑ 17ß-HSD, ↑ CYP17α and ↑ Aromatase, ↓ Degeneration in seminiferous tubules, ↓Congestion and oedema, ↓ Apoptosis in spermatogenic and sertoli cells, ↓ Testicular dysfunction	Jana et al. (2014)
Wistar rat	100 μM – 3 hr, in vitro (Leydig cell)	Cadmium	↓ Ap, ↓ OS	↓ ROS, ↑ Viability, ↑ GSH	Male (2014)
Human (not adult)	30 mg – 2 days 150 mg/kg – 5 days	ITT		No clear impact of graft supplementation was found	Khanna et al. (2016)
Wistar albino rat	100 mg/kg – 70 days	UT	↓ Ap, ↓ OS	↓ SOD (nonsignificant), ↑ GSH-$_{Px}$, ↓ MDA, ↓ +T, ↓ Oedema and hyaline deposition, ↑ regular seminiferous tubule structures	Poels et al. (2014)

(Continues)

(Continues)

TABLE 2 (Continued)

Species	Dose of NAC & duration of treatment	Type of response: T & D	Type of response: Oxidative stress & Apoptosis	Histology, Testicular biochemistry & PCR	Reference
SD rat	150 mg/kg – 7 weeks	Sodium fluoride	↓ OS	↑ Body weight, Testis weight and Epididymis weight, ↓ 8-OHdG, Protective effect in testicular tissue damage	Uyeturk et al. (2014)
Human	25, 50 and 100 mmol/L - 4, 24, and 48 hr, in vitro	Oli	↓ Ap, ↓ OS	↓ DNA fragmentation in human germ cells, ↓ +T seminiferous tubules cultured	Feng et al. (2015)
Wistar albino rat	150 mg/kg – 2 weeks	Paracetamol	↓ Ap, ↓ OS	↓ Testicular degeneration, ↓ Interstitial oedema, ↓ Congestion of interstitial capillaries, ↓ MDA, ↑ GSH, ↓ CAT	El-Maddawy & El-Sayed (2018)
Rat	20 mg/kg 30 min + 4 H 2 months	I/R		↓ MDA, ↑ GSH, ↑ (nonsignificant) $GSH\text{-}_{Px}$ and SOD, ↑ Seminiferous tubule diameter thickness, ↓ Degeneration of germ cell layer, ↓ Oedema, ↓ Vasocongestion, ↓ Germinal epithelium cells shedding in the lumen	Bodur et al. (2016)
Wistar rat	160 mg/kg 8 weeks	Glyphosate	↓ OS	↑ Sperm concentration in lumen, ↓ Degeneration of Sertoli cells	Avdatek et al. (2018)
NIMRI mice	150 mg/kg – 35 days	Para-nonylphenol	↓ Ap, ↓ OS	↓ +T in population of spermatogenes, Sertoli and Leydig cells, ↓ MDA, ↓ Vacuole, ↓ Oedema, ↓ Interstitial tissue volume and Seminiferous tubules volume, ↑ in Length of seminiferous Tubules, Diameter of seminiferous Tubules, Thickness of basement Membrane and Height of germinal epithelium, ↑ Population of Spermatogonia, Spermatocyte, Long Spermatid, Round Spermatid, Sertoli cells and Leydig	Malmir, et al. (2018) and B
Zebrafish	500 nM – 2 hr & 24 hr	MCLR	↓ Ap, ↓ OS	↓ ER stress in germ cells, ↓ Germ cell apoptosis, ↓ Caspase dependent apoptotic proteins, ↑ Total antioxidant capacity level and activity of antioxidant enzymes, ↓ GRP78, eIF2s1 and MAPK8 activation	Zhao et al. (2018)
NIMRI mice	200 mg/kg, (twice/week) - 40 days	Mancozeb	↓ Ap, ↓ OS	↓ LPO, ↑ TAC, ↓ CAT, ↑ SOD, ↓ Expression of iNOS and NOX4, ↑ Expression of GpxI, ↓ Expression of caspase−3, ↓ T+, ↓ Vacuolar degeneration of cells, ↓ Disintegration of the germinal layer, ↓ Tissue destruction and widening of the interstitial spaces	Mohammadi-Sardoo et al. (2018)
Albino rat	100 mg/kg 12 weeks	Titanium Dioxide	↓ OS	↓ in Disorganisation, spermatogenic cells with dark pyknotic nuclei, interstitial cells, extensive area between seminiferous tubules, and extravasation of blood in the interstitial, ↑ Vesicles, ↓ Positive TNF-α and ↓ Number of abnormal tailed nuclei and damaged cells	Elnagar et al. (2018)
Mice	35 mg/kg – 4 week	CPF		↑Spermatogonia, ↑Spermatocytes, ↑Spermatid, ↑Seminiferous tubules area, ↑Diameter of seminiferous tubules	Kheradmandi et al. (2019)
G. rarus Fish	100 mg/kg – 7 days	Bisphenol A	↓ OS	↓ GSH, ↓ GCS, ↓ H_2O_2, ↑ SOD, ↑ $GSH\text{-}_{Px}$, ↓ CAT, ↓ DNA methylation	Yuan et al. (2019)

(Continues)

TABLE 2 (Continued)

Species	Dose of NAC & duration of treatment	Type of response: T & D	Type of response: Oxidative stress & Apoptosis	Histology, Testicular biochemistry & PCR	Reference
SD rat	150 mg/kg – 7 weeks	Fluoride	↓ Ap, ↓ OS	↑ TT, ↓ +T, ↓ GRP78, ↓ p-JNK, ↓ p-JNK/JNK XBP1s/XBP1u ratio and IRE1, XBP1 and JNK transcript levels, ↓ Activating Nrf2-mediated antioxidant damage and Ire1α-JNK-mediated apoptosis, blocked cleavage of caspase−3	Hu et al. (2019)
Balb/C mice	100 mg/kg – 14 days	MK−801 in Schizophrenic	↓ OS	↑ Mean testis weight, Ineffective in germinal epithelium height and seminiferous tubule diameter, ↓ H_2O_2, ↑ Disorganisation in the basement membrane of the seminiferous tubules, ↓ Degenerative changes in the epithelial, ↑ Vacuole formation	Turkmen et al. (2019)
Wistar albino rat	100 mg/kg	I/R		Protective effect in testicular tissue damage	Acer-Demir et al. (2019)
SD rat	20 mg/kg – 30 min + 6 hr	I/R	↓ Ap, ↓ OS	↓ +T, ↓ GRP78, ↓ ATF6, ↓ 4-HNE, ↑ Histopathological scores	Kazaz et al. (2019)
SD rat	300 mg/kg – 5 days	X-radiation	↓ Ap, ↓ OS	↓ MDA, ↑ GSH (nonsignificant), ↓ Germinal epithelium vacuoles and oedematous, ↓ seminiferous tubular damage, ↓ Caspase−3 in Spermatogonium and Spermatocytes, ↑ Germinal epithelium thickness and seminiferous area	Topcu et al. (2019)
Wistar rat	10, 20 and 40 mg/kg – 28 days	Acrylamide		↑ Population of Spermatogonia, Spermatocyte, Spermatid, Sertoli (nonsignificant) cells and Leydig, ↓ vacuole	Shahrzad et al. (2020)

Note: +T, Positive-TUNEL; ↑, Increase or Improve; ↓, Decrease (comparison in the toxin/disease group with NAC + toxin/disease group); 4-HNE, 4-hydroxynonenal; 8-OHdG, 8-Hydroxy-2-deoxyguanosine; ABR, Androgen-binding protein; Ap, Apoptosis; ATF6: Activating transcription factor 6; BcL_2, B-cell lymphoma 2; CAT, Catalase; CC, Caspase cascade; CYP17α, 17α cytochrome P450 17A; G, Gobiocypris; GCS, γ-glutamylcysteine synthetase; Gpx1, Glutathione peroxidase; GRP78, 78-kDa glucose-regulated protein; GSH/GSSG, Reduced/oxidised glutathione, MDA, Malondialdehyde; GSH-$_{Px}$, Glutathione peroxidase; GST, Glutathione S transferase; H_2O_2, Hydrogen peroxide; HSD, Hydroxysteroid dehydrogenase; I/R, Testicular ischaemia–reperfusion; IFS, Intensive forced swimming; iNOS, Inducible nitric oxide synthase; ITT, Immature testicular tissue; LDH, Lactate dehydrogenase; LPO, Lipid peroxidation; MCLR, Microcystin-LR; NAC, N-acetylcysteine; *NIMRI*, *Naval Medical Research Institute*; NOX4, NADPH oxidase 4; Oli, Oligospermia; OS, Oxidative stress; Pc, Protein carbonyls; ROS, Reactive oxygen species; *SD*, *Sprague-Dawley*; SDH, Sorbitol dehydrogenase; SOD, Superoxide dismutase; T & D, Against Toxin & Diseases; TAC, Total antioxidant capacity; TBARS, Thiobarbituric acid reactive substances; TNF-α: Tumour necrosis factor; TT, Testicular testosterone; UT, Undescended testes.

spermatogenesis cells (spermatogonia, spermatocytes, primary and secondary spermatids) and Leydig cells, as well as the normal function of germinal epithelium, are so critical (Malmir, Faraji, et al., 2018; Rabaca et al., 2020; Shahrzad et al., 2020). Apoptosis induction as a result of oxidative stress in Sertoli cells can reduce the population of spermatogenic and Leydig cells (Malmir, Soleimani Mehranjani, et al., 2018; Shahrzad et al., 2020) and subsequently reduce testosterone levels (Shahrzad et al., 2020). On the other hand, the decrease in spermatogenic cells directly plays an adverse role in reducing count and daily production of spermatozoa (Malmir, Faraji, et al., 2018; Malmir, Soleimani Mehranjani, et al., 2018). Sertoli cells have a support act for spermatogenesis cells (Martinčič et al., 2001), motive coherence in the germinal epithelium and also prevent the disposing of germinal epithelium in the lumen (Hikim & Swerdloff, 1999; Martinčič et al., 2001; Malmir, Faraji, et al., 2018). In other words, the induction of oxidative stress in Sertoli cells can severely damage the spermatogenesis process (Shahrzad et al., 2020). Oxidative stress induction during spermatogenesis can damage DNA and spermatids phospholipid membrane (Barekat et al., 2016; Verdi et al., 2019; Yuan et al., 2019), then can cause various sperm malformation types and also a disorder in sperm motility and velocity. As a consequence, turn up a disorder in sperm penetration (into the oocyte) and fertilisation (Agarwal, 2005; Agarwal et al., 2005; Majzoub and Agarwal, 2018). Numerous studies have shown that NAC can protect against tissue damage caused by oxidative stress including oedema (Topcu et al., 2019), vacuole formation (Malmir, Soleimani Mehranjani, et al., 2018; Topcu et al., 2019), reproductive epithelial shedding in the lumen (Topcu et al., 2019), apoptosis induction in Sertoli cells (Malmir, Soleimani Mehranjani, et al., 2018; Shahrzad et al., 2020), spermatogenesis cells (Zhao et al., 2018), and wrinkling and irregularity in the seminiferous tube cells (Hu et al., 2019; Kheradmandi et al., 2019; Table 2). According to the mentioned, NAC can be considered as an antioxidant that improves testicular tissue function and the spermatogenesis process.

TABLE 3 Evaluation of the effect of NAC on men and different species of animals (Endocrinology and Blood biochemistry)

	Type of Response				
Species	Dose of NAC & Duration of treatment	Endocrinology	Blood biochemistry	T & D	Reference
Human	600 mg/day _ 3 month		↑ TAC, ↓ TP, ↓ OSI	Varicocele	Ciftci et al. (2009)
Swiss albino mice	75 mg/kg – 35 days	↑ T		Arsenic	Reddy et al. (2011)
Wistar rat	20 mg/kg - 2 hr and 30 min, in vitro		↓ IMA	I/R	Turkmen et al. (2012)
Wistar rat	800 ppm – 35 days	↑ T (nonsignificant), ↑ LH		Lead	Asadpour et al. (2013)
Wistar rat	1 hr/day, 6 days/week for consecutive 8 weeks	↑ T		IFS	Jana et al. (2014)
SD rat	150 mg/kg – 7 weeks	↑ T (nonsignificant)	↓ MDA, ↑ SOD, ↑ CAT	Sodium fluoride	Feng et al. (2015)
Wistar albino rat	150 mg/kg – 2 weeks	↑ T (nonsignificant)	↓ ALP ↓ AST, ↓ ALT	Paracetamol	El-Maddawy & El-Sayed (2018)
NIMRI mice	150 mg/kg – 35 days	↑ T	↓ IMA	Para-nonylphenol	Malmir, et al. (2018)
Wistar rat	160 mg/kg 8 weeks		↓ MDA, ↑ GSH-$_{Px}$, ↑ SOD (nonsignificant)	Glyphosate	Avdatek et al. (2018)
Albino rat	100 mg/kg 12 weeks	↑ T	↓ MDA, ↑ GSH	Titanium Dioxide	Elnagar et al. (2018)
SD rat	150 mg/kg – 7 weeks	↓ FSH, ↓ LH, ↑ T (nonsignificant)		Fluoride	Hu et al. (2019)
Human	600 mg/day –26 weeks	↓ FSH, ↑ LH, ↑ T	↑ IB, ↑ P	AT	Safarinejad and Safarinejad (2009)
Human	600 mg/day - 3 month	↓ FSH, ↓ LH ↑ T		AT	Jannatifar et al. (2019)
Wistar rat	10, 20 and 40 mg/kg – 28 days	↑ FSH, ↑ LH ↑ T		Acrylamide	Shahrzad et al. (2020)

Note: ↑, Increase or Improve; ↓, Decrease; ALP, Alkaline phosphatase; ALT, Alanine aminotransferase activity; AST, Plasma aminotransferase activity; CAT, Catalase; FSH, Follicle-stimulating hormone; GSH-$_{Px}$, Glutathione peroxidase; I/R, Testicular ischaemia–reperfusion; IB, Inhibin B; IFS, Intensive forced swimming; IMA, Ischaemia-modified albumin; LH, Luteinising hormone; MDA, Malondialdehyde; NAC, N-acetylcysteine; *NIMRI*, *Naval Medical Research Institute*; OSI, Oxidative stress index; P, Prolactin; *SD*, *Sprague-Dawley*; SOD, Superoxide dismutase; T & D, Against Toxin & Diseases (comparison in the toxin/disease group with NAC + toxin/disease group); T, Testosterone; TAC, Total antioxidant capacity; TP, Total peroxide.

9 | IMPROVING BIOCHEMICAL PARAMETERS BY NAC

Frequent studies have elucidated that NAC can regulate concentrations of luteinising hormone (LH), follicle-stimulating hormone (FSH) and testosterone against various toxins (Farombi et al., 2008; Nashwa et al., 2011; Shahrzad et al., 2020; Verdi et al., 2019). Oxidative stress in Leydig cells can directly affect testosterone depletion, and NAC can prevent this reduction (Malmir, Faraji, et al., 2018; Shahrzad et al., 2020). Testosterone is a critical hormone in the spermatogenesis process (Malmir, Soleimani Mehranjani, et al., 2018), and upregulate the production of this hormone can boost spermatogenesis (Verdi et al., 2019). Furthermore, NAC can prevent the increase of malondialdehyde (Topcu et al., 2019), hydrogen peroxide (Yuan et al., 2019) and lactate dehydrogenase (Uyeturk et al., 2014) in cells and also boost the antioxidant defence system (Yuan et al., 2019, Table 3).

10 | COMPENSATING ADVERSE EFFECT OF VARIOUS TOXINS AND CONDITIONS BY NAC

NAC can prevent the adverse effects of several toxins such as arsenic (Reddy et al., 2011), lead (Asadpour et al., 2013), lead & cadmium (Kumar et al., 2013), titanium dioxide (Male, 2014), sodium fluoride (Feng et al., 2015), glyphosate (Avdatek et al., 2018), para-nonylphenol (Malmir, Soleimani Mehranjani, et al., 2018), paracetamol (El-Maddawy & El-Sayed, 2018), mancozeb (Mohammadi-Sardoo et al., 2018), bisphenol A (Yuan et al., 2019), chlorpyrifos (Kheradmandi et al., 2019), cyclophosphamide (Shittu et al., 2019), MK-801 in schizophrenic (Turkmen et al., 2019), acrylamide (Shahrzad et al., 2020), diazinon (Oksay et al., 2013), cadmium (Ji et al., 2013) and microcystin-LR (Zhao et al., 2018). All of the toxins listed above cause serious dysfunction and damage to the male reproductive system that accompanied by a disorder in spermatogenesis. NAC similarly appears the same positive changes in disorders treatments such as varicocele (Ciftci et al., 2009), astheno-teratospermia (Safarinejad and Safarinejad, 2009), oligo-astheno-teratozoospermia (Wirleitner et al., 2012), intensive forced swimming (Jana et al., 2014), testicular ischaemia–reperfusion (Bodur et al., 2016), oligospermia (Erkkilä et al., 1998) and undescended testes (Uyeturk et al., 2014); furthermore, NAC had an ameliorative role in quality of frozen spermatozoa post-thaw (Kobori et al., 2017), X-radiation-induced (Topcu et al., 2019) and immature testicular tissue (Poels et al., 2014).

11 | CONCLUSION

The results of the present study indicate that NAC is a capable antioxidant and humans have used its pharmacological properties to treat a variety of diseases over the past 30 years. Antioxidant administration to improve male fertility has been shown to boost the function of the reproductive system against various environmental pollutants that cause oxidative stress. In light of recent scientific evidence, the positive effects of NAC on spermatogenesis and improved testicular function are undeniable. Therefore, it is recommended to prescribe this drug to the therapy of diseases caused by the effects of oxidative stress induction on the male reproductive system.

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DATA AVAILABLE ON REQUEST DUE TO PRIVACY/ETHICAL RESTRICTIONS

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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