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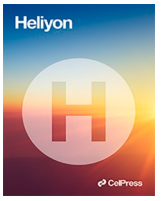

Review article

Pathophysiology and management of testicular ischemia/reperfusion injury: Lessons from animal models

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ABSTRACT

Testicular torsion is a urological emergency that involves the twisting of the spermatic cord along its course. Compelling pieces of evidence have implicated oxidative stress-sensitive signaling in pathogenesis of testicular I/R injury. Although, surgical detorsion is the mainstay management; blockade of the pathways involved in the pathogenesis may improve the surgical outcome. Experimental studies using various testicular I/R models have been reported in a bid to explore the mechanisms associated with testicular I/R and evaluate the benefits of potential therapeutic measures; however, most are limited by their shortcomings. Thus, this review was intended to describe the details of the available testicular I/R models as well as their merits and drawbacks, the pathophysiological basis and consequences of testicular I/R, and the pharmacological agents that have being proposed to confer testicular benefits against testicular I/R. This provides an understanding of the pathophysiological events and available models used in studying testicular I/R. In addition, this research provides evidence-based molecules with therapeutic potentials as well as their mechanisms of action in testicular I/R.

1. Introduction

Ischemia/reperfusion (I/R) is a common emergency that is usually associated with various pathological conditions like cerebrovascular [1]. Although almost all organs are susceptible to I/R injury [2–5], testicular torsion poses a threat to male fertility [6,7]. Testicular torsion is a urological emergency that involves the twist of the spermatic cord along its axis. The spermatic cord and testis may twist within the tunica vaginalis (intravaginal torsion), but sometimes the twist involves the twisting of the tunica vaginalis (extravaginal torsion) [8]. The former usually occurs among pubertal males, especially with a "bell-clapper" deformity, while the latter occurs in the perinatal period during testicular descent into the scrotum [9]. It has impact on all age range, though with a greater occurrence in neonates, children, and juveniles [10,11]. The annual prevalence is about 4.5 in 100, 000 males; however, this varies across the globe [12].

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The mainstay of treatment remains surgical detorsion of the spermatic cord; nonetheless, clinical and experimental studies revealed atrophy of the ipsilateral testis even after detorsion and orchiopexy [6,13]. This is accompanied by distortion of testicular histoarchitecture [14–16], impaired spermatogenesis and gem cell loss [6,17], and reduced testosterone [6,18]. The contralateral testis has also been shown to be affected [6,8]. Convincing shreds of evidence have implicated oxidative stress-sensitive signaling in testicular I/R injury. It is possible that blockade of these pathways will improve the surgical outcome of detorsion and ochiopexy. Thus, it remains pertinent to assess the impact of therapeutic molecules on testicular I/R using animal models of testicular torsion/detorsion. Several animal models have been reported, each having its own merits and drawbacks.

Therefore, this review was designed to describe the details of the available testicular I/R models as well as their advantages and challenges, the pathophysiological basis and consequences of testicular I/R, and the pharmacological agents that have being proposed to confer testicular benefits during testicular I/R. This aims to provide an understanding of the pathological events and available models used in the study of testicular I/R. The current study also provides evidence-based molecules with therapeutic potentials as well as their mechanisms of action in testicular I/R.

2. Animal models of testicular I/R injury

Based on the available literature, there are basically two types of models for testicular I/R. These include the application of clamp on the spermatic cord or the artery and the twisting of the spermatic cord [19]. In both methods, asepsis is ensured and adequate anesthesia is maintained. The animal is anaesthetized with ketamine and xylazine [5,20], urethane [21] or thiopental sodium [22] *ip*. Since the left testis is the commonly affected one due to the associated long spermatic cord, it is preferred that the left testis is torsed.

Under anesthesia, the fur over the skin in the left ilio-inguinal region is removed and cleansed with an antiseptic solution such as chlorhexidine solution, and an oblique incision is made and bluntly delivered into the pelvis [6]. The testis and spermatic cord are gently milked out of the scrotal sac and exteriorized, then twisted at 720° clockwise about its course. The torsed testis is retained in this position by stationing it in position with a non-absorbable suture like silk suture, and then placed back into the scrotum. The skin is apposed with nylon suture and covered with a sterile gauze pad till the end of torsion (prior to detorsion) [7,20]. In some cases, a scrotal approach is preferred. Instead of assessing the testes through the ilio-inguinal region, a perpendicular incision is made on the scrotum, one of the testis is exteriorized gently and torsed at 720°, then immobilized by stitching the tunica albuginea to the scrotal cavity [23]. The scrotum is then apposed. Skondras et al. [24] reported inducing ischemia by twisting at 1080°, rather than 720° that is commonly reported, because they observed that rotation at 720° did not adequately induce testicular ischemia. Although both ilio-inguinal and scrotal approaches are similar, some disparities exist. In the ilio-inguinal approach, an oblique incision is made on the skin over the ilio-inguinal region and developed into the pelvis until the spermatic cord is identified. The testis is then gently milked out of the scrotal sac through the incision made on the ilio-inguinal region. On the other hand, in the scrotal approach, a longitudinal incision is made on the scrotum, preferably the scrotal raphe and developed into the scrotal bag until the scrotal contents are identified, and the testis can be exteriorized. Another common approach is the low midline laparotomy [25–27] which is similar to the ilio-inguinal approach; however, in the low midline laparotomy, a longitudinal incision is made on the skin in the lower part of the ventral region along the midline and developed into the pelvis, and then the testis is exteriorize through this incision. A major drawback of maintaining ischemia by anchoring the testis to the scrotum is the likely histopathological and biochemical changes that may occur in the testicular tissue as the anchoring stitch may induce testicular injury. Before the introduction of suture application following spermatic cord torsion, Oettle and Harrison [28] employed testicular artery ligation and application of clamp to induce ischemia. This method is still being used [29]. Although ligation and clamp application is quite easy with little or no technical skills needed, it does not accurately mimic the clinical appearance of testicular torsion [19]. While spermatic cord twisting and suture application more closely resembles clinical testicular torsion [19], it requires a level of skill.

After the period of ischemia, the suture over the incision site is gently removed, the torsed testis and spermatic cord are assessed, and then detorsed by untwisting at 720° counter-clockwise [7]. A colour change (paleness) confirms ischemia. The incision site is then apposed with a suture, preferably vicryl, and 10 % Povidone-iodine is applied to the incision site. Although several studies have reported different time frame for the induction of ischemia, it is important to minimize the torsion period to avoid testicular infarction and necrosis [30]. Usually, a maximum of 2–3 h have been reported to sufficiently induce ischemia and avoid infarction and necrosis [6,7,20]. Nevertheless, some studies reported ischemia induction for 4 h [31–33]. Studies have reported a minimum of 1 h for rats [34] and pigs [35], and 2 h for mice [36]. In clinical practice, detorsion within 6 h, 6–12 h, and 12–24 h of torsion (presenting with pain) will salvage 90%–100 %, 20–50 %, and 0–10 % of the testis [37,38], depending on the degree of torsion [6]. Hence, it is recommended that detorsion should be established between 4 and 6 h of torsion [6]. Invariably, the interval between torsion and detorsion, and the degree of torsion are primary determinants of the severity of testicular injury in I/R.

It is essential to note that reperfusion is a vital phase in the pathophysiology of I/R injury, a phase where superlative damage occurs; hence, the timeframe for reperfusion is essential. The original stage of reperfusion commences after the first minutes of ischemia and spans for up to 6 h [39]. Although reperfusion injury is said to peak at about 48–72 h, till date, varying timeframes are used in experimental model because no consensus has been reached.

To reduce mortality secondary to infection, it may be beneficial to administer a broad spectrum antibiotic like ciprofloxacin [6,7,20] in addition to the application of aseptic solution to the incision site. This is administered to all animals to avoid confounding.

3. Mechanisms of testicular I/R injury

The pathophysiology of testicular I/R injury is multifaceted and is yet to be fully grasped. Testicular injury occurs in two phases

during torsion/detorsion; the first is the ischemic phase and the second is the reperfusion phase (Fig. 1). Testicular torsion damages testicular blood flow, resulting in venous overload, arterial blockage, ischemia, and necrosis if surgical intervention is delayed [6,7]. Impairment of testicular blood flow leads to hypoxia, which is associated with an oxygen concentration insufficient to maintain testicular homeostasis [40,41]. The testis is highly susceptible to hypoxia because it is a highly metabolic organ [41]. Hypoxia impairs oxygen and nutrient supplies to the testicular tissue. This leads to anaerobic glycolysis that hinders ATP generation and produces lactic acid, resulting in acidosis of the tissue, failure of cellular ATP-dependent pumps and efflux of cellular potassium [42]. Several pro-inflammatory genes and transcription factors are up-regulated during ischemia. Hypoxia-driven reduction in ATP and glycogen content as well as increase in testicular calcium ions (Ca^{2+}) are key players in testicular injury. Dysfunction of ATP-dependent pumps results in efflux of potassium and intracellular accumulation of calcium ions [43], which impairs testicular metabolic functions, cell lysis, and altered cell volume. Testicular hypoxia also results in enhanced prostaglandin E1 (PGE1) production that in turn overpowers tissue growth factor β1 (TGF β1), resulting in collagen deposition, and vascular dysfunction. Additionally, hypoxia upregulates vascular endothelial growth factor (VEGF), which triggers inhibition of germ cell proliferation and spermatogenic arrest [41].

It has also been confirmed that hypoxia induces reactive oxygen species (ROS) generation via several pathways. Hypoxia down-regulates NRF-1 and initiates excessive generation of ROS, which in turn activates testicular and sperm cell lipid peroxidation, DNA damage and apoptosis [41]. Hypoxia-induced ROS generation may also be mitochondrial-dependent. Hypoxia induces mitochondrial damage, and activates xanthine oxidase (XO) and inducible nitric oxide synthetase (iNOS) [44], which are known triggers of oxidative stress [45]. Mitochondrial damage is associated with reduced mitochondrial oxidative phosphorylation and increased electron leakage from the electron transport chain, leading to increased generation of ROS like superoxide radicals [46]. XO promotes the conversion of xanthine to uric acid (along with some ROS), a potent trigger of oxidative stress [47]. When tetrahydrobiopterin or L-arginine is deficient, iNOS is uncoupled, leading to increased ROS generation [46].

Usually, oedema is the first ultra-structural cell manifestation at the ischemic phase. Macroscopically, this is seen as paleness and increase turgor and weight of the testis. Microscopically, this is demonstrated as small clear cytoplasmic vacuoles characterized by vacuolar degeneration [48].

Testicular detorsion re-establishes testicular reperfusion. This is accompanied by enhanced ROS generation, accumulation of intracellular calcium, lipid peroxidation, and local inflammatory response [7,49]. The increased cytokine production and adhesion molecules expression in the ischemic phase by hypoxic parenchymal and endothelial cells set a background for the superlative reperfusion injury. Reperfusion causes mobilization of neutrophils through chemotaxis and endothelial adherence, circulating platelets and $CD4^{+}$ T-lymphocytes into the vascular space [50]. The accumulated neutrophils are usually demonstrated by increased myeloperoxidase activities [51]. The accumulated neutrophils trigger the production of ROS, tumor necrosis factor alpha (TNF-α), and local inflammatory mediators [50], thus aggravating testicular injury. $CD4^{+}$ T lymphocytes generate macrophage-stimulating factors, TNF-β, and interferon-gamma that exacerbate the induction of local macrophage cells and the release of cytokines [39]. In addition, reperfusion elevates the amount of ROS in the parenchymal, endothelial, and lymphocytic cells that infiltrate the lesion. The increased neutrophil accumulation and mitochondrial dysfunction leads to incomplete oxygen reduction and consequent production of superoxide anions and ROS generation [39,48,52]. This cascade of events amplifies ischemia-induced testicular injury during reperfusion.

Reperfusion further increases intracellular Ca2+ accumulation, stimulation of the inflammatory response and cellular adhesion receptors, and migration of neutrophils via the endothelial wall into the tissue parenchyma, thus releasing cytotoxic mediators like TNF-α, interleukins (ILs), and NOS with resultant ROS generation [53,54].

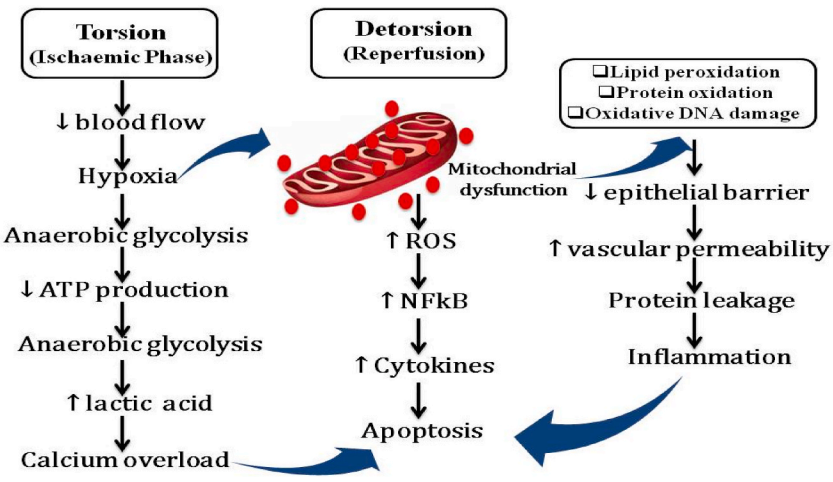

Fig. 1. Schematic illustration of the mechanism of ischemia/reperfusion injury following testicular torsion/detorsion.

Table 1
|Potential pharmacological measures in the management of IR injury.

Reference	Animal model	Ischemia method	Ischemia duration	Incision site	Reperfusion duration	Drug	Time of drug administration	Route of drug administration	Dose of drug	Findings
Analgesia										
[77]	Rat model	Suture	4 h	Scrotum or ilioinguinal	6 h	Dexmedetomidine	1 h post ischemia	Intraperitoneal	50 and 100 μg/kg	Dexmedetomidine at both doses reversed I/R-induced ↑oxidative stress but has no significant effect on histology
[26]	Rat model	Suture	1 h	Midline laparotomy	4 h	Dexmedetomidine	30 min post ischemia	Intraperitoneal	10 μg/kg	Dexmedetomidine reversed I/R-induced ↑oxidative stress and inflammatory markers. It significantly ameliorated I/R-induced distortion in the histology of the testis
[78]	Rat model		1 h	Transcrotal incision	24 h	etomidate	30 min post ischemia	Intraperitoneal	4 mg/kg	Etomidate prevented I/R-induced↑ in germ cell damage and Leydig cell loss, but did not alter the percentage of necrosis, histological score, and tubule rupture in the ipsilateral tissue.
[79]	Rat model		1 h	Transcrotal incision	24 h	Fentanyl	30 min post ischemia	Intraperitoneal	1 mg/kg	Fentanyl prevented I/R-induced↑ in oxidative stress markers and germ cell damage, but did not alter histological score, Leydig cell counts, tubule rupture, and percentage of necrosis.
[80]	Rat model	Suture	1 h	Transcrotal incision	24 h	Propofol	Throughout the ischemia period	Ventral tail vein	20–30 mg/kg/hr	Propofol reduced the NO level and APAF-1 expression by inhibiting I/R-induced testicular iNOS expression.
[81]	Rat model	Suture	1 h	Transcrotal incision	90 days	Propofol	15 min post ischemia	Intraperitoneal	20 mg/kg/h	Propofol ameliorated I/R-induced structural damage to seminiferous tubules.
[16]	Rat model	Suture	1 h	Scrotum	7 days	Sumatriptan	30 min post ischemia	Intraperitoneal	0.1, 0.3 and 1 mg/kg	Sumatriptan ameliorated I/R-induced testicular toxicity via 5-HT 1B/1D receptor dependent anti-inflammatory and antioxidant mechanism.
Anti-convaulsants										
[82]	Rat model	Scrotal fixation with suture	4hrs	Scrotal incision	1hr	pyrrolidine dithiocarbamate	15 min prior to reperfusion	Intraperitoneal	100 mg/kg	PDTC ↓MDA levels and apoptotic cells, ↑ SOD activity,
[83]	Rat model	?	1hr	Scrotal vertical midline incision	5hrs	Topiramate	30 min before detorsion)	Intraperitoneal	100 mg/kg,	TPM ↓MDA and ↑ antioxidants in sperm cells.
Anti-Depresssan										
[84]	Rat model	–	1 h	Scrotal	4 h	Nortriptyline	30 min pre-ischemia, 30 min post-reperfusion	Intraperitoneal	2, 10 and 20 mg	Nortriptyline ↓MDA, caspase 3 activity and ↑GSH, SOD, catalase
[85]	Rat model	Suture	1 h	Low midline incision	4 and 24 h	Rolipram	30 min before ischemia, during detorsion, and 30 min after detorsion	Intraperitoneal	1 mg/kg	Rolipram↓ necrosis and apoptosis
Antidiabetes										
[86]	Rat	Suture	2 h	ilioinguinal incision	4 h	Vildagliptin and sitagliptin	1 h post ischemia	Intraperitoneal	10 mg/kg and 5 mg/kg respectively	Vildagliptin and sitagliptin ameliorated I/R-induced testicular toxicity via their antioxidative stress, anti-inflammatory, and antiapoptotic actions mediated by nitric oxide-induced activation of HIF-1α
[87]	Rat model	Suture	2 h	Scrotum	4 h	Liraglutide	1hr 30 min post ischemia	Intraperitoneal	0.6 mg/kg	Liraglutide reversed I/R-induced ↑oxidative stress, apoptosis, and inflammatory markers.
[88]	Rat model	Suture	1 h	Low midline laparotomy	4 and 24 h and 30 days	Metformin	Immediately before ischemia and 30 min post ischemia	Intraperitoneal	300 mg/kg	Metformin significantly reversed I/R-induced increase in oxidative stress, apoptosis, histological changes and impaired sperm quality.

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Table 1 (*continued*)

[89]	Rat model	Suture	1 h	Low midline laparotomy	4 and 24 h	Metformin and rapamycin	30 min post ischemia	Intraperitoneal	100 and 0.25 mg/kg respectively	Although metformin and rapammycin significantly reversed I/R-induced increase in oxidative stress and apoptotic markers and germ cell apoptosis, their combination showed a better ameliorative effect against I/R-induced testicular toxicity.
[90]	Rat model	Suture	4 h	Abdominal midline incision	4 h	Metformin	3 h post ischemia	orogastric	300 mg/kg	Metformin reversed I/R-induced testicular damage via an apoptosis dependent mechanism
[91]	Rat	Suture	4 h	Scrotal incision	4 h	Pioglitazone	1 h 30 min post ischemia	Intraperitoneal	1 and 3 mg/kg	Pioglitazone reversed I/R-induced testicular toxicity via its antioxidant, anti-inflammatory and antiapoptotic properties.
[92]	Rat	Suture	5 h	Midline incision	5 h and 7 days	Rosiglitazone	4 h 20 min and 10 h post ischemia	gavage	4 mg/kg	Rosiglitazone reduces contralateral testicular damage formed after unilateral testicular torsion and alleviates the oxidative events.
Aniti-hyperlipidaemia										
[93]	Rat model	Suture	1 h	Scrotal incision	3 h	Fenofibrate	30 min before reperfusion	Oral	100, 300 mg/kg	Fenofibrate ↓ MDA, NO, TNFα, and NFkB, and ↑GSH and SOD
[94]	Rat model	Suture	2 h	Ilioinguinal incision	4 h	Probucol	At reperfusion	Intraperitoneal	300 mg/kg stat	Probucol ↓ MDA, MPO, and *E*-selectin, and ↑ testicular weight, EH, STD
[95]	Rat model	Scrotal fixation with suture	2 h	Inguinal incision	1 h	Rouvastatin	30 min before detorsion	Intraperitoneal	10 mg/kg	Rosuvastatin ↑ testicular blood flow
[96]	Rat model	*Trans-meso*-orchial suture	4 h	Scrotal incision	24 h and 1 week	Verapamil	2 weeks before ischemia till 24 h and 1 week post-reperfusion	–	0.1 mg/kg	Verapamil ↑ tubular diameter of the contralateral testis
[97]	Rat model	Scrotal fixation with suture	2 h	Scrotal incision	2 h	Verapamil and heparin	30 min before detorsion	Intraperitoneal	0.3 mg/kg of verapamil; 800 IU of heparin	Verapamil and heparin ↑ TAC, catalase and GPx activities, and sperm quality.
Antihypertensives										
[31]	Rat		4 h		24 h	Losartan and lisinopril	3 h post ischemia	Intraperitoneal	30 mg/kg and 50 mg/kg respectively	Losartan and lisinopril reduced I/R-induced testicular tubular damage and apoptosis in the contralateral testes.
[98]	Rat model		2 h	Scrotum	2 h	Amlodipine	1hr 30 min post ischemia	Oral gavage	5 and 10 mg/kg	Amlodipine reversed I/R-induced increase in oxidative stress markers, inflammatory cytokines, and testicular tissue damage
[99]	Rat model	suture	2 h	Scrotum incision	2 h	Carvedilol	30 min post ischemia	Intraperitoneal	2 mg/kg	Carvedilol ameliorated I/R-induced testicular damage via an antioxidant dependent mechanisms
[100]	Rat model	Suture	2 h	Scrotal incision	4 h	Carvedilol	1 h 30 min post ischemia	Intraperitoneal	73 mg/kg	carvedilol blunted I/R-induced testicular tissue and spermatogonial cells damage via its antioxidant and antiapoptotic activities accompanied by the opening of the potassium ATP channel.
[101]	Rat model		2 h	Scrotal incision	2 h	Aliskiren	90 min post ischemia	Oral	100 and 200 mg/kg	Aliskiren reversed I/R-induced testicular damage by decreasing RAAS activities, inflammation, and oxidative stress.
[102]	Rat	Suture	4 h	Scrotal incision	7 days	Ranolazine	1 h and every 24 h post ischemia for 6 days	Intraperitoneally	30 mg/kg/day	Ranolazine prevented I/R-induced testicular damage and alleviated the oxidative events.
[103]	Rat	Suture	2 h	Scrotum	4 h	Trimetazidine	Every 24 h for 7 days prior to ischemia	Orally	5 mg/kg/day	Trimetazidine reversed I/R-induced testicular damage via its antioxidant activities.
[97]	Rat	Suture	2 h	Scrotum	2 h	Verahexal and heparin	30 min post ischemia	intraperitoneally	0.3 mg/kg and 800 IU/kg respectively	Co-admistration of Verahexal with heparin and single administration of heparin have better ameliorative effects on I/R-induced testicular damage and impaired spermatogenesis mediated by an oxidative stress mechanism.
[104]	Rat	Suture	2 h	Scrotum	4 h	Zofenopril	30 min post ischemia and once daily for 5 days	Orally	15 mg/kg/day	Zofenopril reversed I/R-induced testicular damage mediated by oxidative stress and inflammation

Anti-inflammatory and immunomodulators

[105]	Rat model	Suture	4 h	Scrotum	4 h	Anakinra	1 h prior ischeamia	Intraperitoneal	50 mg/kg and 100 mg/kg	Anakinra reversed I/R-induced ↓MPO, MDA, (MDA), IL-1β
[106]	Rat model	Suture	3 h	Scrotum	3 h	Colchicine	30 min prior to detorsion		1 mg/kg	Colchicine reversed I/R-induced ↓ MDA, caspase 3
[107]	Rat model	Suture	2 h	Scrotum	2 h	Cordycepin	15 min prior to detorsion	Intraperitoneal	10 mg/kg	Cordycepin Cordycepin reversed I/R-induced ↓ MDA, TNF-α, IL-6, and IL-1β l
[108]	Rat model	Suture	1 h	Scrotum	1 h	Cyclosporine	30 and 90 min after torsion	Intravenous	1, 5, and 10 mg/kg	Cyclosporine reversed I/R-induced ↓ MDA and caspase-3
[109]	Rat model	Suture	5 h	Scrotum	24 h	Dexketoprofen	40 min prior and 12 h after detorsion.	Intraperitoneal	25 mg/kg	Dexketoprofen reversed I/R-induced ↓ MDA
[110]	Rat model	Suture	1 h	Scrotum	2 h	Diacerein	30 min prior to detorsion	Intramuscular	50 mg/kg	Diacerein reversed I/R-induced ↓MDA and NOx, n IL-1β
[111]	Rat model	Suture	5 h	Scrotum	5 h	Ibuprofen	40 min prior to detorsion		70 mg/kg	Ibuprofen reversed I/R-induced ↓MDA, eNOS
[112]	Rat model	Suture	3 h	Inguinoscrotal	3 h	Pirfenidone	Immediately post detorsion	Oral	325 mg/kg	Pirfenidone reversed I/R-induced ↓MDA
[113]	Rat model	Suture	4 h	Scrotum	4 h	Rapamycin	30 min before detorsion and 24 and 48 h after detorsion.			Rapamycin reversed I/R-induced ↓MDA
[114]	Rat model	Suture	1 h	Scrotum	1 h	Rapamycin	30 min after torsion	Intraperitoneal	0.5, 1, and 1.5 mg/kg	Rapamycin reversed I/R-induced ↓MDA, caspase 3, bax

Antimicrobial

Reference	Animal model	Ischemia method	Ischemia duration	Incision site	Reperfusion duration	Drug	Time of drug administration	Route of drug administration	Dose of drug	Findings
[15]	Rat model	suture	1 h	Scrotum	1 h	Dapsone	30 min before reperfusion	Intraperitoneal	12.5 mg/kg	Dapsone reversed I/R-induced ↓Tnf-α
[18]	Rat model	suture	4 h	Scrotum	4 h	Minocycline	30 min before reperfusion	oral	160 mg/kg	Minocycline reversed I/R-induced ↓ Caspase-3, Bax, IL-1β and TNF-α
[115]	Rat model	suture	1 h	Scrotum	1 h	Minocycline and Nx -nitro-L-arginine, aminoguanidine	4 h before reperfusion	Intraperitoneal	40, 80, 160 mg/kg and 10 mg/kg, 50 mg/kg	Minocycline reversed I/R-induced ↓ Cas
[64]	Rat model	suture	120 min	Scrotum	4 h	Oltipraz	30 min before reperfusion	Intraperitoneal	50 mg/kg and 150 mg/kg	Oltipraz reversed I/R-induced ↓ TGF-β1, GSH and MDA
[116]	Rat model	suture	4 h	Scrotum	4 h	Resveratrol	30 min before reperfusion	Intraperitoneal	30 mg/kg	ReversedI/R- induced ↓mean apoptotic score
[117]	Rat model	suture	4 h	Scrotum	4 h	Resveratrol	30 min before reperfusion	Intraperitoneal	30 mg/kg	ReversedI/R- induced ↓mean apoptotic score

Antioxidants

[118]	Rat		4 h	Laparotomy	2 h	N-acetylcysteine	210 min post ischemia	Intraperitoneal	20 mg/kg	N-acetylcysteine ameliorated I/R-induced ER stress, oxidative stress, and cellular apoptosis.
[119]	Rat model	Suture	5 h	Scrotum incision	5 h	L-carnitine	5hrs 30 min after ischemia	Intraperitoneal	500 mg/kg	L-carnitine protected the testis against I/R-induced oxidative stress and histological testicular damage.
[120]	Rat model	suture	6 h	Scrotum	12 h	L-carnitine and betamethasone	Immediately after ischemia	Intraperitoneal	500 and 0.10 mg/kg respectively	L-carnitine and betamethasone ameliorated I/R-induced testicular tissue damage and impaired sperm quality.
[121]	Rat model		6 h		7 days	Carnitine	1 h before detorsion	Intraperitoneal	100 mg/kg	Carnitine ameliorated I/R-induced testicular tissue damage.

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Table 1 (*continued*)

[122]	Rat model		90 min		10 days	Diamond nanoparticles and Co enzyme Q 10 (CoQ10)		Intraperitoneal	0.02 mg/kg each	Co-administration of diamond nanoparticles with CoQ10 synergistically improved sperm parameters.
[123]	Rat model	Clamp	2 h	Scrotum	4, 22, and 70 h	Co enzyme Q 10	Once per day after ischemia	Gastric gavage	10 mg/kg/day	Coenzyme Q10 reversed I/R-induced oxidative damage, inflammatory response, remodeling of extracellular matrix, and apoptosis.
[124]	Rat model	Suture	2 h	Scrotal incision	2 h	Ebselen	1 h post ischemia	Intraperitoneal	10 mg/kg	Ebselen prevented I/R testicular injury by reducing oxidative biochemical and histopathological damage.
	Rat model	Suture	4 h	Ilioinguinal incisions	3 h	Tationil Gluthatione	Just before detorsion	Intravenous	25 mg	Tationil Glutathione prevented I/R-induced ROS generation and histopathological damage. .
[125]	Rat model	suture	1 h	Scrotal incision	4 days	Hesperetin	30 post ischemia	Intraperitoneal	50 and 100 mg/kg	Hesperetin ameliorated I/R-induced oxidative stress and histopathological damage
[126]	Rat model	Suture	2 h	Illioinguinal incision	4 h	Idebenone	1hr before ischemia	Intraperitoneal	100 mg/kg	Idebenone ameliorated I/R-induced oxidative stress, infllamtion, and apoptosis via Sirt1/Nrf2/TNF-pathway
[127]	Rat model	Suture	2 h	Scrotal incision	4 h	N-acetylcysteine	1 h post ischemia and after detorsion	Intraperitoneal	150 mg/kg	N-acetylcysteine prevented I/R-induced oxidative stress, distortion in the structure of seminiferous tubules, and damage to germinative cells I/R injury.
[128]	Rat model	Suture	2 h	Scrotum	2 h	N-acetylcysteine	60 and 115 min post ischemia	Intraperitoneal	20 mg/kg	N-acetylcysteine ameliorated I/R-induced oxidative stress and histological damage.
[129]	Rat model	Suture	4 h	Scrotal incision	2 h	N-acetylcysteine and ethyl pyruvate	3 h and 30 min post ischemia	Intraperitoneal	20 and 50 mg/kg respectively	N-acetylcysteine and ethyl pyruvate attenuated I/R-induced oxidative stress and histological damage. However, N-acetylcysteine administration was more effective since it decreased serum ischemia-modified albumin
[130]	Rat model	Suture	5 h	ilioinguinal incisions	2 h	N-acetylcysteine	4 h 55 min post ischemia	Intravenously	20 mg/kg	N-acetylcysteine ameliorated I/R-induced lipid peroxidation and histopathological damage.
[131]	Rat model	Suture	3 h	Scrotal incision	30 days	N-acetylcysteine	After detorsion	Intrascrotal	10 and 100 mg/kg	N-acetylcysteine at higher dose reduced I/R-induced loss of testis volume and height, and also yields Sertoli cell numbers.
[132]	Rat model	Suture	90 min	Scrotal incision	24 h	Quercetin and resveratrol	60 min of torsion	Intraperitoneal	20 mg/kg each	Although quercetin and resveratrol attenuated I/R-induced oxidative stress and histological damage, quercetin is more effective.
[133]	Rat model	Suture	5 h	Scrotual incisions	5 h	Quercetin	4 h 20 min post ischemia	Intraperitoneal	15 mg/kg	Quercetin improved I/R- induced histopathological damage, increased immunoexpression of testicular eNOS and germ cell apoptosis.
Anti-thrombotic										
	Rat model	Scrotal fixation with suture	3 h and 6 h	Scrotal incision	7 day	Enoxaparin and alteplase	At reperfusion	Enoxaparin: subcutaneous; Alteplase: intravenous	200 IU/kg of enoxaparin and 0.9 mg/kg alteplase	Enoxaparin and alteplase↑ testicular weight, inhibin level, redox balance and testicular histoarchitecture
Anti-Ulcer										
[134]	Rat model	Scrotal fixation with suture	3 h	Scrotal incision	2 h	Famotidine	I hr pre-ischemia	Oral	20 mg/kg	Famotidine ↓ testicular DNA damage, ↑ spermatogenesis and antioxidant activities
[135]	Rat model	Scrotal fixation with suture	2 h	Scrotal incision	3 days	Omeprazole	At reperfusion, then once per day for another 2 days	Oral	0.02 mg/kg	Omeprazole ↓ MDA, MPO, 8OHdG, HSP40, HSP70, HSP90
Cysteine Protease										
[136]	Rat model	Scrotal fixation	?	Scrotal incision	1, 3, 5, 7, 14, 35, and 70 days	calpain inhibitor	7 days post ischemia	i.p	2 mg/kg/day	Calpain inhibitor↓ sperm formation disorder
Growth Factor										

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Table 1 (*continued*)

[137]	Rat model	Scrotal fixation	2hrs	Ilioinguinal incision	60 days	VEGF	Immediately before detorsion	Intratesticular	4 μg	VEGF ↑ MSTD, GECT, MTBS, and ↓ caspase 3	
[138]	Rat model	?	4 h	?	24 h	IGF-1	Just before torsion	SC	20 mg/kg	IGF-1 ↓ apoptosis of germ cells	
[139]	Rat model	Scrotal fixation	4 h	Longitudinal scrotalincision	48 h	EGF	Immediately after detorsion, once daily	SC	100 μg/kg	EGF↑ testicular weight and volume, histoarchitecture and spermatogenesis	
Hormones and Receptors											
[140]	Rat	Clamp	2 h	Scrotal incision	30 and 60 days	Testosterone	3–7 days post ischemia	Intratesticular	25 mg	Intratesticular testosterone led to testicular atrophy while the rats that did not received testosterone recovered after 60 days.	
[141]	Rat model	Suture	2 h	Scrotum	3 days	propyl pyrazole-triol (ERα agonist), diarylpropionitrile (ERβ agonist) and estradiol	Every 24 h immediately after ischemia for 2 days	Subcutaneous and oral	1 mg/kg/kg	Estradiol and ERβ agonist ameliorated impaired testicular blood flow, androgen receptor expression, oxidant injury, apoptosis and tubular damage. In addition, ERβ improved sperm quality	
[142]	Rat model	Suture	12 and 24 h	midline vertical skin	72 h	N-acetyl cysteine	Every 24 h	Intraperitoneal	100 mg/kg/d	N-acetyl cysteine abrogated I/R-induced testicular toxicity by preventing oxidative stress increasing octanoylated ghrelin.	
[143]	Rat model	Suture	1 h	Scrotal incision	7 and 30 days	Ghrelin	45 min post ischemia	Intraperitoneal	40 nmol	Ghrelin prevent I/R testicular tissue distortion by improving oxidant and antioxidant status.	
[144]	Rat model	Suture		inguinoscrotal incision	3 weeks	Human chorionic gonadotropin (HCG)	Twice weekly for 3 weeks		100 IU/kg	HCG prevented contralateral histomorphometric alterations and serum testosterone in unilateral torsion	
Hydrogen Sulfite											
[145]	Rat	Suture	2 h	Scrotal incision	4 and 24 h	Sodium hydrogen sulphide	1 h 30 min post ischemia	Intratesticular	75 μmol/kg	Sodium hydrogen sulpjide protected against I/R-induced testicular toxicity via its anti-inflammatory, antioxidant and antiapoptotic properties.	
[146]	Rat model	Suture	1 h	Scrotum	4 h	GYY4137	Immediately after ischemia	Intraperitoneal and intratesticular	100 μmol/kg	Intratesticular administration of GYY4137 was more effective than intraperitoneal administration in ameliorating I/R-induced oxidative stress and spermatogenic cell apoptosis.	
[147]	Rat model	Suture	4 and 8 h	Scrotum	48 h	thiol/disulphide measurement	thiol/disulphide was evaluated 4 and 8 h post ischemia			A decrease in the total thiol value was proportional to I/R-induced histopathologic injury.	
Hydroxylcynamic acid											
[148]	Rat	Suture	2 h		4 days	Caffeic acid phenethyl ester (CAPE)	2 h after torsion and 30 min before detorsion and every day for 3 days	Intraperitoneal	10 μml/kg	CAPE prevented I/R-induced testicular damage via PI3K/AKT/mTOR signaling.	
[149]	Rat model	Suture	2 h	Scrotum	4 h	Sinapic acid	30 min post ischemia	Intraperitoneal	10 and 20 mg/kg	Sinapic acid protected the testes against I/R injury via its anti-inflammatory, antioxidant and antiapoptotic activities.	
Nitric oxide and vasodilators											
[56]	Rat		1 h	Scrotum	0, 0.5, 1,6, 24 h and 60 days	L-NAME	5 min before torsion	Left femoral vein	20 mg = kg	NO produced from eNOS regulates the vasomotor function in the contralateral testis, possibly through a testis-specific reflex arc	
[150]	Rat model	Suture	3 h	inguinoscrotal incision	3 h	Milrinone	Immediately after torsion	Intraperitoneal	0.5 mg/kg	Milrinone reversed I/R-induced testicular damage and increase in oxidative stress and inflammatory markers	

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Table 1 (*continued*)

[151]	Rat model	suture	1 h	Scrotum incision	0, 1, 6, 24, 48, 96, or 192 h and 60 days	Aminoguanidine (AMG)	24–96 h of reperfusion every 12 h	Intraperitoneal	200 mg/kg	NO ameliorated I/R-induced testicular damage via an antioxidant dependent mechanisms
[100]	Rat model	Suture	2 h	Scrotal incision	4 h	Aminoguanidine (AMG)	1 h 30 min post ischemia	Intraperitoneal	73 mg/kg	I/R of the testis induces iNOS, which promotes germ cell injury, possibly through necrotic cell death
[152]	Rat model		4 h	Scrotal incision	24 h	Sodium nitrite, sodium nitrate, and 2-(4-carboxyphenyl)-4,4,5,5-tetramethyli midazoline-1-oxyl-3-oxide potassium (C-PTIO)	5 min before ischemia and 1 min before reperfusion	Intravenous	0.12, 1.2, and 12 nmol g	NO protected the testis against I/R-induced testicular toxicity via its anti-oxidant and anti-apoptotic properties. .
[153]	Rat model	Suture	4 h	Scrotal incision	14 days	Papaverine and alprostadil	During detorsion	Spermatic cord	20 mg/kg and 20 μg/kg respectively	Papaverine and alprostadil protected against I/R testicular injury.
[154]	Rat model	Suture	2 h	Scrotal incision	4 h	Trapidil	1 h post ischemia	Intraperitoneal	40 mg/kg	Trapidil attenuated I/R-induced oxidative stress and histological damage in the ipsilateral twisted testis. .
[155]	Rat model	Suture	2 h	ilioinguinal incisions	60 days	Trapidil	1hr 30 min post ischemia	Intraperitoneal	40 mg/kg	Trapidil attenuated I/R-induced histologic damage.
PDE5i										
[156]	Rat model	Suture	60 min		240 min	Sildenafl	10 min prior to reperfusion	Intravenous	0.7 mg/kg	Sildenafl reversed I/R-induced ↓RBCV ↓ infammatory cascade
[157]	Rat model		2 h	Scrotum	2 h	Sildenafl	1 h prior to detorsion	Intraperitoneal	1.4 mg	Sildenafl reversed I/R-induced ↓ NO and MDA
[158]	Rat model	Suture	2 h	Scrotum	2 h	Sildenafl	1 h prior to detorsion	Intraperitoneal	0.7 mg/kg, 1.4 mg	Sildenafl reversed I/R-induced ↓NO, MDA
[159]	Rat model	Suture	2 h	Scrotum	2 h	Sildenafl	1 h prior to detorsion	Intraperitoneal	0.7 mg/kg, 1.4 mg	Sildenafl reversed I/R-induced ↓ NO, MDA
[160]	Rat model	Suture	90 min	Scrotum	90 min	Erythropoietin and sildenafil	60 min after torsion	Intraperitoneal	1000 IU/kg, 0.7 mg/kg	Erythropoietin and sildenafl reversed I/R-induced ↓ coagulative necrosis of the germinal cells
[161]	Rat model	Suture	90 min	Scrotum	120 min	Darbepoetin and tadalafil	90 min after torsion	Intraperitoneal	1 mcg/kg, 0.25 mg/kg	Darbepoetin and tadalafil reversed I/R-induced ↓ fibrosis ↓caspase 3
[162]	Rat model	Suture	4 h	Scrotum	24 h	Verapamil and tadalafil	30 min before detorsion		0/1 mg/kg, 0/4 mg/kg	Verapamil and tadalafil reversed I/R-induced ↓MDA
[163]	Rat model	Suture	2 h	Scrotum	4 h	Udenafil	1 h before detorsion	Intraperitoneal	2 mg/kg	Udenafil reversed I/R-induced ↓ IL1-β, TNF-α
[164]	Rat model	Suture	4 h	Scrotum	4 h	Udenafil citrate, dexmedetomidine and piracetam	60 min before detorsion	Intraperitoneal	1.4 mg/kg and 2.8 mg/kg, 25 μg/kg, 200 mg/kg	Udenafi citrate, Dexmedtomid-ne and piracetam reversed I/R-induced ↓TOS MDA, germ cell apoptotic indicators, and eNOS and iNOS
[165]	Rat model	Suture	1 h	Scrotum	1 h	Vardenafil	30 min after torsion	Intraperitoneal	1 mg/kg	Vardenafil reversed I/R-induced ↓MDA, germ cell apoptotic indicators, and eNOS and iNOS
Stem Cells										
[166]	Rat model	Suture	3 h	Scrotal incision	1 and 4 weeks	Human Adipose-Derived Stem Cell (hADSC)	90 min post ischemia	Intratesticular	1×10^6 cells	hADSC protected the testis against I/R-induced oxidative stress
[167]	Rat model	Suture	3 h	Scrotal incision	3 days	Mesenchymal stem cells (MSC)	150 min post ischemia	Intratesticulr	3×104 cells in 20 μl phosphate-buffered saline	MSC restored sperm quality and glycogenesis/glycolysis imbalance following I/R testicular

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Table 1 (*continued*)

										injury. .
[168]	Rat model	Suture	3 h	Scrotal incision	7 days	Bone marrow-derived mesenchymal stem cells (BM-MSCs)	Immediately after detorsion	Intratesticular	5×10^4 cells	BM-MSCs protected the testis against I/R-induced oxidative stress and impaired spermatogenesis
Stimulants										
[169]	Rat model		1hr		7 days	modafinil	7 days post ischemia	Intraperitoneal	10 mg/kg	Modafinil reversed I/R-induced ↓ testicular injury, ↓
Vitamins and Minerals										
[170]	Rat	Suture	2 h	Scrotum	60 days	Dexpanthenol	90 min post ischemia	Intraperitoneal	500 mg = kg	Dexpanthenol prevented testicular atrophy following I/R injury.
[171]	Rat model	Suture	2 h	Pelvic midline incision	4 h	Dexpanthenol	Immediately after torsion	Intratesticular	500 mg/kg	Dexpanthenol protected the testis against I/R-induced histological and functional injury.
[21]	Rat model	suture	2 h	Ilioinguinal	2 days	Erdosteine	Immediately after detorsion	Intraperitoneal	50 mg/kg/day	Erdosteine ameliorated the histological testicular damage via its antioxidant activities.
[172]	Rat model	Suture	2 h	Scrotal incision	0, 1,3, and 6 h	α-lipoic acid	21, 9, and 1 h before ischemia	Intraperitoneal	12 mg/kg per dose	α-lipoic acid protected the testis from I/R injury by decreasing lipid peroxidation and increasing GSH and total antioxidant power
[173]	Rat model	Suture	2 h	Scrotal incision	3 and 10 days	Lycopene	30 min after detersion	Intraperitoneal	20 mg/kg/day	Lycopene prevented I/R- induced testicular injury in the early period but not on the long term.
[174]	Rat model	Clamp	1 h	Abdominal incision	3 and 24 h and 30 days	Lycopene	65 min post ischemia	Gavage	4 mg/kg/day	Lycopene blunted IR-induced impaired sperm quality and oxidative stress.
[175]	Rat model	Suture	4 h	Scrotal incision	4 h	Sodium selenite (selenium)	3hrs 40 min s post ischemia	Intraperitoneal	0.2 mg/kg	Selenium attenuated I/R-induced lipid peroxidation and histological damage in the ipsilateral and contralateral testes …
[176]	Rat model	Suture	3 h	Scrotal incisions	7 days	selenium (sodium selenite)	2hr 50 min post ischemia	Intraperitoneal	0.5 mg/kg/day	Selenium ameliorated I/R testicular injury by preventing increase oxidative stress and apoptosis markers …
[177]	Rat model	suture	3 h	Scrotal incision	1 days	Vitamin E	30 days before torsion	Oral	100 mg/kg/day	Vitamin E reversed I/R-induced testicular damage
[178]	Rat model	Suture	3 h	Scrotal incision	6 h	Vitamin E	1hr post ischeamia and immediately after detorsion	Intraperitoneal	30 IU/kg	I/R- induced ipsilateral and contralateral testicular damage is not associated with lipid peroxidation and vitamin does not have any beneficial effect.
[179]	Rat model		4 h		4 h	Vitamin E and coenzyme Q10	30 min after detersion	Intraperitoneal	100 and 10 mg/kg	Coenzyme Q10 prevented I/R testicular injury by reducing oxidative stress and histopathological damages, while Vitamin E increased the observed I/R injury.
[180]	Rat model	Suture	5 and 9 h	Scrotum	30 days	Vitamin C	30 min before detorsion	Intraperitoneal	100 mg/kg	Vitamin c and tunica vaginalis flap improved testosterone and histological parameters following 5 h of ischemia.
[22]	Rat model	Suture	2 h	Scrotal incision	1,2, and 3 months	Zinc	1, 2, and 3 months after ischemia	Oral	0.016 ml/rat	Zinc attenuated I/R-induced oxidative stress and histological damage in the ipsilateral and contralateral testes …
[181]	Rat model	Suture	4 h	Scrotal incisions	4 days	Zinc Aspartate	210 min post ischemia	Intraperitoneal	50 mg/kg	Zinc aspartate ameliorated I/R testicular injury by preventing increase oxidative stress …
[70]	Rat model	Suture	1 h	Scrotal incision	1 h	Zinc sulfate and melatonin	21 days before ischemia	Intraperitoneal	5 and 3 mg/kg respectively	Zinc sulfate and melatonin ameliorated I/R testicular injury when used singly and combined. This is associated with an improved spermatogenic activities and antioxidant status
Others										

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Table 1 (*continued*)

[182]	Rat model	Suture	3 h	Scrotum	4 h	Acupuncture/eletroacupuncture	5 min post ischemia	Bilaterally	2 Hz or 10 Hz	Acupuncture/eletroacupun-ctureversed reversed I/R-induced ↓MDA, MPO
[183]	Rat model	Suture	5 min	Scrotum	5 min	Acupuncture/electrical nerve stimulation	5 min post ischemia	Unilateral, Percutaneous	10 Hz	Acupuncture/eletroacupun-ctureversed reversed I/R-induced ↓MDA
[184]	Rat model	Suture	4 h	Scrotum	4 h	Albumin (IMA)	48 h post ischemia	Intraperitoneal		Albumin (IMA) reversed I/R-induced ↓
[185]	Rat model	Suture	4 h	Scrotum	4 h	Amniomax	1 min post ischemia	Intraparenchymal		Amniomax reversed I/R-induced ↓
[186]	Rat model	Suture	5 min	Scrotum	15 min	Cryoablation (liquid nitrogen)	Immediately after ischemia	Stabbed to the testes	25 mgr/kg	Cryoablation reversed I/R-induced ↓
[187]	Rat model	Suture	2 h	Scrotum	4 h	Darbepoetin alfa (Aranesp, Amgen)	30 min post ischemia	Intraperitoneal		Darbepoetin alfa reversed I/R-induced ↓MDA, NO
[188]	Rat model	Suture	6 h/12 h	Scrotum	6 h/ 12 h	Decompressive fasciotomy		Tunica albuginea	50 mg/kg	Decompressive fasciotomy reversed I/R-induced ↓
[189]	Rat model		4 h		2 h	Ethyl pyruvate	30 min post ischemia	Intraperitoneally	8 mg/kg	Ethyl pyruvate reversed I/R-induced ↓TOS
[190]	Rat model	Suture	3 h	Scrotum	3 h	DNase1	24 & 48 h post ischemia	Intravenous/ Intraperitoneal	10 mg/kg & 3 mg/kg	DNase1 reversed I/R-induced ↓ MDA
[191]	Rat model			Scrotum						
[192]	Rat model		1 h		3 h	CysLT1 receptor antagonist montelukast & 5-LO inhibitor zileuton	3 h post ischemia		1 g/kg/day	CysLT1 receptor antagonist montelukast reversed I/R-induced ↓ MDA
[193]	Rat model	Suture	2 h	Ilioinguinal	2 h	Omega-3 polyunsaturated fatty acids (n-3 PUFAs)	4 h post ischemia		1.2 g/kg/day	Omega-3 n-3 PUFAs reversed I/R-induced ↓ MDA, T-AOC
[6]	Rat model	Suture	2 h:30min	Ilioinguinal	72 h	Omega-3 fatty acid	15 min post ischemia	Intraperitoneal	50 mg/kg	Omega-3 reversed I/R-induced ↓ MDA, MPO, NO, TNF- α, IL-1 β
[194]	Rat model	Suture	30 min	Laparotomy	30 min	Pentoxifylline	15 min before ischemia	Intraperitoneal	50 mg/kg	Pentoxifylline reversed I/R-induced ↓ MDA
[195]	Rat model	Suture	30 min	Scrotum	30 min	Pentoxifylline		Intraperitoneal		Pentoxifylline reversed I/R-induced ↓
[184]	Rat model	Suture	4 h	Scrotum		Platelet-rich plasma	15 min before ischemia			
[196]	Rat model	Suture	2.5 h	Scrotum		Platelet-rich plasma			1 mT; 15 Hz, 50 Hz, 1 Mt	Platelet-rich plasma reversed I/R-induced ↓ MDA, NO, TNF- α, IL-1 β, caspase 3
[197]	Rat model	Suture	2 h	Ilioinguinal	2 h	Pulsed Magnetic Field and Melatonin	2 h post ischemia		1 mg/kg	
[198]	Rat model	Suture	2 h		2 h	Endothelin type A receptor antagonist (BQ123)	30 min before ischemia	Intravenous		BQ123 reversed I/R-induced ↓

4. Consequences of testicular I/R injury

4.1. Vascular consequences

Testicular microvascular blood supply is controlled by vasomotion or cyclic contraction and relaxation of the vessel tightly regulated by complex mechanisms. Testicular I/R alters vasomotion for days even after surgical detorsion [55]. Reperfusion-induced upregulation of NO promotes vasodilatation and prevents vascular contractions, which is essential for vasomotion [56,57]. The increased NO also up-regulate cell adhesion molecule expression [58,59], which is important for leukocyte recruitment, a key player in I/R pathophysiology [59,60]. In addition, testicular I/R increases testicular vascular permeability [61] that may be involved in myeloperoxidase-mediated neutrophil diapedesis.

4.2. Morpho-histological consequences

Paleness and increase in testicular weight due to oedema are the first structural cell manifestations during ischemia [48], which is followed by a reduction in testicular weight. Although, the time interval between the transition from ischemia-induced increase in testicular weight and the decline in testicular weight is not certain; studies have revealed that I/R led to a reduction in testicular weight [7,62]. I/R-led decline in testicular weight may be attributed to the exacerbated ROS release from reperfusion [6,7] and associated decline in testicular metabolism [63]. Testicular planimetry revealed that I/R significantly reduced the diameter and area of the seminiferous tubules (shrunken seminiferous tubules), the diameter of the seminiferous lumen, and epithelial height [6,7]. This is accompanied by distortion of testicular histoarchitecture evidenced by an increase in Cosentino's score, accumulation of inflammatory cells, intratubular oedema, and sloughing of the testicular germ cells [6,7,15,64].

4.3. Endocrine consequences

The primary endocrine function of the testis is the synthesis of testosterone by the Sertoli cells under the influence of luteinizing hormone. Studies have shown that testicular I/R injury lowers both intratesticular and circulating testosterone levels [65–67]. Although, Turner et al. [68] reported that the decline in testosterone levels return to normal after some days; Sangodele et al. [67] demonstrated that the fall in testosterone persistent more than 7 days. Since the Leydig cell mass reduces significantly [6,7,67], it is plausible to ascribe the observed drop in testosterone levels to a disruption in Leydig cell function.

4.4. Cellular consequences

The testicular tissue is primarily made up of the Leydig cells, Sertoli cells, and the germ cells at varying maturation degree. The testis is highly susceptible to ROS attack as a result of its great level of polyunsaturated fatty acid [69]. Testicular I/R-driven ROS disrupts testicular membrane via oxidative injury [6], thus the cells become prone to ROS attack, leading to a decline in Leydig cell mass with resultant fall in testosterone levels [6,7,67]. Evidently, I/R causes sloughing of germ cells and reduction in epithelial cell height, and impaired spermatogenesis [6,7,70]. Since the secretion of proteins *in vivo* by Sertoli cells are not significantly altered, suggesting that Sertoli cells survived I/R injury, it is difficult to ascribe the observed disruption of germ cells to a decline in Sertoli cell function [71].

4. 5Consequences on the contralateral testis

Although, possible contralateral damage of the testis has been debated [8]; experimental studies provide compelling evidence that demonstrate that unilateral testicular torsion, as usually seen in real-time events, is associated with bilateral testicular injury. Koşar et al. [72] revealed that testicular I/R resulted in varying degrees of declination in the germinal epithelium and interstitial cells of the contralateral testis. It was also observed that I/R led to reductions in testicular volume and tubular diameter of the contralateral testis [72]. In addition, unilateral testicular torsion has been revealed to initiate oxidative stress [6,15,16], inflammation [6,15,16], and apoptosis in both testis via upregulation of p53/caspase 3 signaling and downregulation of Bcl-2 [6,73].

Although, it is possible that contralateral testicular function is impaired prior to testicular I/R due to a pre-exiting pathology in that testis [74]; it is also likely that unilateral torsion breaks down the blood-testis barrier, leading to a rise in anti-sperm antibodies and destruction of the germ cells via an immunological process [75]. More so, ipsilateral reperfusion results in contralateral reflectory sympathetic-mediated vasoconstriction, resulting in hypoxia and impaired function of the contralateral testis [8,76].

5. Pharmacological potentials in the management of I/R injury

The summary of the pharmacological agents with potentials in the management of testicular I/R injury is provided in Table 1.

5. 1Amino acids and amines

Afolabi et al. [199] found that rats with testicular torsion/detorsion-induced reperfusion injury had less damage to their testicular tissue when they were given cysteamine first. This is because cysteamine is an anti-inflammatory, antioxidant, and pathway-inhibiting

Table 2
Potential phytomolecules in the management of IR injury.

Phytomolecules										
Reference	Animal model	Ischemia method	Ischemia duration	Incision site	Reperfusion duration	Drug	Time of administration	Route of administration	Dose of drug	Findings
[24]	Rat model	Scrotal fixation with suture	3 h	Left inguino-scrotal	15 and 120 min	Apigenin	At reperfusion	Intravenously via the right femoral vein	10 mg/kg	Apigenin ↓ TNF-α, IL-10, and apoptotic cells.
[215]	Rat model	Scrotal fixation with suture	4 h	Scrotal midline incision	1 h	Apocynin	210th minute of ischemia	Intraperitoneal	20 mg/kg	Apocynin ↓ MDA, TOC, and OSI and ↑ SOD and catalase activities
[33]	Rat model	–	240 min	–	2 h	Berberine	210th minute of ischemia (30 min before detorsion)	Intraperitoneal	200 mg/kg	Berberine ↓ MDA, TOS and OSI, and ↑ TAS, tubular diameter, germinal thickness, and spermatogenesis
[216]	Rat model	Scrotal fixation with suture	30 min	Scrotal midline incision	24 and 72 h	Capsaicin	1 h after reperfusion	–	100, 500 and 1000 μg/ml	Capsaicin ↑ Bcl-2, but ↓ apoptotic index, FOXO1, and Bax
[217]	Rat model	Suture	2 h	Left ilio-inguinal	2 and 24 h	Chrysin	30 min before reperfusion	Intraperitoneal	50 mg/kg	Chrysin ↓MDA and TNF-α levels, and caspase-3 and caspase-8 actvities
[218]	Rat model	Scrotal fixation with suture	5 h	Scrotal midline incision	5 h	Curcumin	45 min before reperfusion	Gastric gavage	150 mg/kg	No protection
[219]	Rat model	Suture	2 h	Left ilio-inguinal incision	4 h and 3 months	Curcumin	At reperfusion	Intravenous via the tail vein	200 mg/kg	Curcumin ↓XO activity, MDA, and ↑ HO-1 and spermatogenesis
[220]	Rat model	Scrotal fixation with suture	2 h	right vertical paramedian incision	One week	*Plantago major* ethanolic leaf extracts	At reperfusion	Intraperitoneal	50 and 100 mg/kg	*Plantago major* ↑ catalase activities, and ↓ peroxidase activity, MDA level, and germ cell degeneration
[66]	Rat model	Scrotal fixation with suture	4 h	Scrotal incision	14 days	*Fumaria parviflora* hydroalcoholic flower extract	After reperfusion	Oral	250 mg/kg	*Fumaria parviflora* ↑ testosterone, spermatogenesis, sperm count, motility, normal morphology, SOD, GPx, Bcl-2, and ↓ Bax, Bax/Bcl-2, apoptotic index
[221]	Rat model	Scrotal fixation with suture	2.5 h	?	7 days	*Ganoderma lucidum*	After reperfusion	Gastric lavage	20 ml/kg	*Ganoderma lucidum* ↓ MDA and apoptosis, and ↑ GSH, SOD, catalase, VEGF and tubular diameter
[222]	Rat model	Scrotal fixation with suture	1 h	*Trans*-scrotal incision	2 h and one month	*Ginkgo biloba*	?	Oral	50 mg/kg	*Ginkgo biloba* ↓MDA, nitrate, and nitrite levels
[223]	Rat model	Scrotal fixation with suture	1 h	*Trans*-scrotal incision	2 h and one month	*Ginkgo biloba*	?	Oral	50 mg/kg	*Ginkgo biloba* ↓apoptotic cells, Apaf-1, eNOS, iNOS
[224]	Rat model	Scrotal fixation with suture	5 h	Scrotal midline incision	5 h	*Ginkgo biloba*	40 min before detorsion	Oral	50 mg/kg	*Ginkgo biloba* ↓apoptotic cells, eNOS, and ↑ tubular diameter and spermatogenesis
[65]	Rat model	Microvascular clamp	2 h	Scrotal paramidline incision	2 h	*Ginkgo biloba*	40 min before detorsion	Oral	50 mg/kg	*Ginkgo biloba* ↑testosterone, and ↓FSH, mitochondrial NAD^+, TNF-α, and IL-1β.
[225]	Rat model	Scrotal fixation with suture	2 h	Scrotal midline incicion	2 h	Grape seed proanthocyanidin extract (GSPE)	Daily for a week prior to torsion/detorsion	Oral	100 mg/kg	GSPE ↓MDA, AOPP, eNOS, apoptotic cells, and ↑ tubular diameter and spermatogenesis
[226]	Rat model	?	2 h	Left-sided inguinal incision	6 h, 24 h, 3 months	Honokiol	Immediately before detorsion	i.p	5 and 10 mg/kg	Honokiol↓ PARP, caspase 3, caspase 7, and ER stress-related molecules like Phospho eIF2α and CHOP

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Table 2 (*continued*)

Phytomolecules										
Reference	Animal model	Ischemia method	Ischemia duration	Incision site	Reperfusion duration	Drug	Time of administration	Route of administration	Dose of drug	Findings
[227]	Rat model	Suture	4 h	Scrotal midline incicion	1 h	Lumbrokinase	At reperfusion	Intragstric using a sonde tube	80 mg/kg	Lumbrokinase ↓ Bax
[228]	Rat model	Scrotal fixation with suture	4 h	Scrotal midline incision	24 h	*Matricaria chamomile* ethanolic plant extract	30 min before detorsion	i.p	300 mg/kg	*Matricaria chamomile* ethanolic plant extract
[229]	Rat model	Scrotal fixation with suture	3 h	Right scrotal incision	3 h	Osthole	30 min before and after detorsion	i.p	20 mg/kg	Osthole ↑ GSH, Nrf2, SOD, and ↓MDA, 8OHdG, IL-6, MPO, and caspases 3, 8, and 9.
[230]	Rat model	?	1 h	Vertical scrotal incision	3 h	Paeonol	3 consecutive days before torsion/detorsion	Intragastric tube	50 mg/kg and 200 mg/kg	Paeonol ↓ MDA, TNF-α, IL-1β, IL-6, HIF-1α, and HSP70 and ↑ testosterone, GSH, Nrf2, SOD, and spermatogenesis
[231]	Rat model	Scrotal fixation with suture	1, 2, 4 h	Scrotal midline incision	56 days	*Pausinystalia macroceras* aqueous bark extract	Daily for 56 days	?	0.1 g/kg	*Pausinystalia macroceras* aqueous bark extract ↑ sperm count, sperm motility, and testosterone
[232]	Rat model	?	90 min	?	60 days	*Punica granatum* (pomegranate) hydroalcoholic peel extract	Daily for 60 days	Oral	500 mg/kg	*Punica granatum* (pomegranate) hydroalcoholic peel extract ↑ sperm count, motility and testosterone
[67]	Rat model	?	1 h	Longitudinal scrotal incision	4 h and 7 days	Proxeed Plus	Before detorsion and daily for 7 days	Oral	1000 mg/kg and 5000 mg/kg	Proxeed Plus ↑ testosterone level, tubular diameter, leydig cell mass, spermatogenesis, GSH, catalase, SOD, GPx, GST and ↓ hydroxyl peroxide, MDA, iNOS, caspase 3 and 9
[233]	Rat model	Scrotal fixation with a suture	2hr	Midline scrotal incision	2 h	Rosamaric acid	30 min before reperfusion	*i.p*	50 mg/kg and 70 mg/kg	Rosamaric acid ↓ MDA and ↑ GPx, catalase, sperm concentration and motility
[234]	Rat model	Scrotal fixation with suture	2 h	Scrotal incision	4 h	*Rhodiola rosea*	15 min before detorsion	i.p	75 mg/kg	*Rhodiola rosea* ↓ MDA, apoptotic cells and ↑ GSH
[235]	Rat model	?	90 min	?	50 days	*Royal jelly*	After reperfusion	Oral	100 mg/kg	*Royal jelly* ↑ testosterone and spermatogenesis
[236]	Rat model	Scrotal fixation with suture	2 h	Vertical scrotal incision	2 h	*Salvia miltiorrhiza* hydroalcoholic leaf extract	30 min before detorsion	i.p	200 mg/kg	*Salvia miltiorrhiza* hydroalcoholic leaf extract ↑sperm motility, vitality, concentration, and morphology, TAC, catalase GPx, germinal cell thickness, tubular diameter, and ↓ MDA
[237]	Rat model	?	2 h	?	5 h	*Stevia rebaudiana* aqueous leaf extract	30 min before torsion	i.p	500 and 1000 mg/kg	*Stevia rebaudiana* aqueous leaf extract ↑ spermatogenesis, SOD, GPx, ↓ MDA
[238]	Rat model	?	?	?	?	Ternatin	?	i.p	10 ml/kg	Ternatin ↓ MDA
[239]	Rat model	Scrotal fixation with suture	2 h	Scrotal midline incision	10 days	Vinpocetine	After reperfusion and daily for 10 days	i.p	10 mg/kg	Vinpocetine ↓ HSP70 and apoptotic cell, ↑ tubular diameter and spermatogenesis
[240]	Rat model	?	1 h	?	7 days	*Vitex doniana* aqueous leaf extract	After reperfusion	Oral	50, 100, 200 mg/kg	*Vitex doniana* aqueous leaf extract ↑ germ cell height, tubular diameter and luminal diameter

protein. Noticeably increased sperm motility supported the findings. In a different study, Afolabi and his colleagues [7] showed for the first time that giving rats glutamine before detorsion kept testicular redox balance, testicular integrity, and testicular function, which decreased I/R damage in a rat model of T/D. The therapeutic effects of glutamine were associated with down-regulation of the caspase 3 pathway and NF-kB signaling. According to Leitão et al. [200], Alanyl-glutamine dipeptide (L-Ala-Gln) diminishes lipid peroxidation during ischemia and shields the testes from oxidative stress by upregulating GSH levels after reperfusion. This therapy is administered prior to spermatic cord torsion or detorsion. The shielding effects of melatonin on testicular torsion/detorsion-induced ischemia–reperfusion injury in rats were reported by Kanter [201]. The treatment with melatonin markedly improved the histopathological damages, elevated the immunoexpression of PCNA and testosterone, and reduced germ cell apoptosis in I/R testis. Advantageous impact of melatonin compared with allopurinol was reported in experimental testicular torsion study.

Abasiyanik and Dadönderen [202] showed that melatonin administration lessens I/R injury in an experimental testicular torsion model. Sekmenli et al. [203] reported the impact of melatonin and colchicine on ischemia–reperfusion injury in experimental rat testicular torsion model. Their study showed that colchicine decreased testicular ischemia–reperfusion injury in experimental rat testis torsion model. The histopathologic scores, total oxidant status (TOS), IL-6, total antioxidant status (TAS), TNF-α levels in control and torsion/detorsion/colchicine groups were significantly lower than torsion/detorsion and torsion/detorsion/melatonin groups. Also, Mirhoseini et al. [204] demonstrated that melatonin protected against T/D-induced testicular damage. Asghari et al. [205] established that testicular IR triggered a significant increase in testicular injury. There was no significant difference among individual and combined treatment of melatonin and metformin co-treatment on testicular ischemia/reperfusion. Semercioz et al. [70], showed that the amplified oxidative stress in testicular ischemia/reperfusion in rats was decreased by zinc supplementation, which was associated with optimal levels of inhibin-B aversion of impaired spermatogenic activity. In another study, Ekici et al. [206], demonstrated that ozone therapy had advantages in the management of testicular torsion. Both melatonin and ozone management expressively preserved spermatogenesis from IRI with similar effectiveness. Its effectiveness was comparable with melatonin. Melatonin and ozone treatment led to substantial enhancement of tissue GSH and reduced MDA levels.

Nesfatin-1 averted tubular degeneration caused by torsion-detorsion by maintaining the balance between pro-inflammatory and anti-inflammatory cytokines, modulating Akt/CREB signaling pathways, and improving the survival of spermatogenic cells [207]. In a different study, Aydos et al. [208] showed that ozone therapy and/or taurine before reperfusion ameliorated germ cell degeneration brought about by testicular torsion. Taurine injection mitigates the damage caused by testicular ischemia and reperfusion. Taurine caused a substantial decline in myeloperoxidase activity and malondialdehyde level and a marked increase in testicular spermatogenesis in the ipsilateral testes in comparison to the torsion-detorsion group [209]. Abbasoğlu et al. [210] demonstrated that taurine and carnosine reduced testicular prooxidant status without significant changes in antioxidant parameters in I/R-exposed rats.

5. 2Analgesic, anaesthetics, and sedatives

According to the study of Tuglu et al. [77], dexmedetomidine, at 50 and 100 μg/kg, significantly reversed IR-induced increase in oxidative stress but had no significant effect on IR-induced alterations in the testicular histology according to Johnsen's scoring system. Also, dexmedetomidine, at 10 μg/kg, significantly ameliorated the I/R-induced increase in oxidative stress and inflammatory response, and distortion in testicular histology. Further, Jafarova Demirkapu et al. [78] observed that Etomidate prevented I/R-induced increase in germ cell damage and Leydig cell loss but did not alter the percentage of necrosis, tubule rupture and histological score in the ipsilateral testis. The study of Mordeniz et al. [79] also reported that fentanyl prevented I/R-induced increase in oxidative stress markers and germ cell damage, but did not alter the histological score, Leydig cell counts, tubule rupture, and the percentage of necrosis.

In addition, propofol reduced nitric oxide (NO) level and protease-activating factor 1 (APAF-1) expression by inhibiting I/R-induced testicular inducible macrophage NOS (iNOS) expression [80]. Also, propofol ameliorated I/R-induced structural damage to seminiferous tubules [81]. The study of Dejban et al. [16] also revealed that Sumatriptan ameliorated I/R-induced testicular toxicity via 5-HT 1B/1D receptor-dependent anti-inflammatory and antioxidant mechanism.

5. 3Anticonvulsants

Jafari et al. [83] revealed that intraperitoneal pre-treatment with 100 mg/kg of topiramate, 30 min prior to testicular torsion/-detorsion, induced anti-ischaemic effects by diminishing MDA levels and elevating antioxidant enzymes activities (such SOD and GPx activities). Another study conducted by Kemahli et al. [82] demonstrated that pre-treatment with 100 mg/kg of pyrrolidine dithiocarbamate for about 15 min before detorsion had advantageous impact on both biochemical and histopathological levels against I/R injury. Pyrrolidine dithiocarbamate amplified the antioxidant system by dampening MDA levels and elevating SOD activity, as well as lessening apoptotic cells [82].

5. 4Antidepressant

Pre- and post-reperfusion treatment with nortriptyline, a second-generation antidepressant, was shown to restore testicular I/R-induced alteration in redox balance and inhibit the rise in caspase 3 activity [84]. Also, nortriptyline improved I/R-driven germ cell apoptosis, tubular diameter reduction, and impaired sperm cell functions. It is likely that the effect of nortriptyline was interceded by the prevention of increased mitochondrial permeability transition pore [84]. In another study, Abat et al. [85] demonstrated the beneficial role of rolipram, an antidepressant belonging to the class monoamine oxidase inhibitor, in testicular torsion/detorsion. It

was observed that pre-ischemic, intra-ischemic, and post-ischemic treatment with rolipram reduced the rate of apoptosis and necrosis of testicular tissue following testicular torsion/detorsion [85].

6. Anti-diabetics

The study of Abdelzaher et al. [86] revealed that Vildagliptin and sitagliptin (dipeptidyl peptidase-4 inhibitors) ameliorated I/R-induced testicular toxicity via their antioxidative stress, anti-inflammatory, and antiapoptotic actions mediated by nitric oxide-induced activation of HIF-1α. Degirmentepe et al. [87] reported that Liraglutide reversed I/R-induced decrease in SOD, GPx, catalase, and a rise in iNOS, NO, Apoptosis protease activating factor-1 and MDA. Furthermore, the study of Ghasemnejad-Berenji et al. [88] showed that metformin ameliorated I/R-induced increased oxidative stress, apoptosis, histological changes, and impaired sperm quality. Similarly, metformin and rapamycin synergistically reversed I/R-induced increases in oxidative stress, apoptosis, and histological changes [89]. In addition, the study of Sarıbal et al. [90] showed that metformin reversed I/R-induced testicular damage via a caspase 3-mediated pathway. Also, pioglitazone reversed I/R-induced testicular toxicity via its antioxidant, anti-inflammatory, and anti-apoptotic activities [91]. In addition, rosiglitazone reduced contralateral testicular damage following unilateral testicular torsion and ameliorated oxidative events [92].

6. 1Anti-hyperlipidaemia

Some anti-dyslipidaemic drugs have been shown to confer protection against testicular I/R injury. Refaie [93] revealed that oral administration of fenofibrate prevented I/R-induced rise in MDA, NO, and TNF-α concentrations, and decline in GSH and SOD activity in the testis. These findings were accompanied by improved testicular histoarchitecture and increased circulating testosterone by fenofibrate [93]. The activities of fenofibrate were demonstrated to be mediated by suppression of NFkB signaling and modulation of peroxisome proliferator activated receptor alpha (PPARα) [93]. Also, probucol, a lipid-lowering drug with antioxidant and anti-inflammatory activities, militated against I/R-induced distortion in testicular histoarchitecture and a rise in MDA and myeloperoxidase-mediated neutrophil accumulation via suppression of *E*-selectin protein expression [94]. Karakaya et al. [95] demonstrated the effect of rosuvastatin, a synthetic statin, on testicular blood flow measured with LASER Doppler flowmeter. Rouvastatin was observed to markedly enhance testicular blood flow, suggestive of improved testicular microvascular perfusion after I/R [95]. In addition, verapamil protects the contralateral testis from ipsilateral I/R injury evidenced by improved testicular histoarchitecture and increased tubular diameter [96]. In another study using a rat model of testicular I/R, Davoodi et al. [97] revealed that co-administration of heparin with verapamil ameliorated torsion/detorsion-induced rise in MDA level, and decline in catalase, GPx activities and total antioxidant capacity. These were associated with improved sperm quality and testicular histoarchitecture [97].

6.2. Anti-hypertensive and anti-angina

The study of Gokce et al. [31] revealed that angiotensin-converting enzyme inhibition (by lisinopril) and angiotensin II type 1 receptor blockade (by losartan) ameliorated I/R-induced testicular tubular damage and apoptosis in the contralateral testes. Furthermore, Dogan et al. [98] showed that amlodipine significantly reversed I/R-induced increase in inflammatory cytokines, oxidative stress, and testicular tissue damage. In addition, Parlaktas et al. [99] revealed that carvedilol ameliorated I/R-induced testicular damage via antioxidant-dependent mechanisms. In the same vein, Balci et al. [100] observed that carvedilol blunted I/R-induced testicular tissue and spermatogonial cells damage via its antioxidant and antiapoptotic activities accompanied by the opening of the potassium ATP channel. Also, Un et al. [101] revealed that aliskiren (an inhibitor of the renin-angiotensin-aldosterone system) reversed I/R-induced testicular damage by reducing the concentration of angiotensin II, oxidative stress markers, and inflammatory response.

Furthermore, Keseroglu et al. [102] reported that ranolazine prevented I/R-induced testicular damage and alleviated oxidative events. Also, Pekcetin et al. [103] observed that trimetazidine reversed I/R-induced testicular damage via its antioxidant activities. Additionally, co-administration of verahexal with heparin and administration of only heparin have a better ameliorative effect on I/R-induced testicular damage and impaired spermatogenesis via an oxidative stress-sensitive mechanism. Also, Altunoluk et al. [104] showed that zofenopril reversed I/R-induced testicular damage mediated by oxidative stress and inflammation.

6. 3Anti-inflammatory and immune-modulators

Biochemical, gene expression, and histological techniques were used to study the impact of anakinra on I/R damage generated in the testes of rats with torsion/detorsion. The biochemical findings showed that oxidant parameters such as MDA and MPO were raised while antioxidant parameters such as GPx, GST, and GSH were reduced in the testicular tissue of the testicular torsion/detorsion group compared to the sham-operated group [105]. Colchicine has been shown to have protective benefits against testicular torsion/detorsion-induced ischemia/reperfusion damage in rats [106]. The stimulation of inflammatory and apoptotic pathways caused the most substantial damage to testicular tissue, which was reversed by colchicine therapy. Histology and biochemistry evaluations showed that cordycepin protected the testicles from damage caused by IR [107]. According to biochemical tests, the cordycepin group had lower levels of IL-6, IL-1, and TNF- than the ischemia and I/R groups did. In the ipsilateral and contralateral testicles of the ischemia and I/R groups, the spermatozoa count fell, but it rose in the cordycepin group.

Yazdani et al. [108] revealed that treatment with Cyclosporine A (CsA), a strong agent for closing the mitochondrial permeability

transition pore (mPTP), could maintain the antioxidant enzymes, abate oxidative stress-induced cell apoptosis, improve sperm quality, demonstrating CsA as a potential pharmaceutical adjunct for treating and preventing I/R-induced testicular injury in post-conditioning men to enhance fertility. In another investigation, Yildirim et al. [109] investigated the impact of dexketoprofen on ischemia-reperfusion damage. It reduces pathologic alterations in spermatogenic cells and serum MDA levels in testicular torsion, suggesting that it attenuates oxidative stress [211]. Abdel-Gaber et al. [110] have identified the mechanism mediating diacerein (DIAprotective) action in ischemia-reperfusion-induced testicular damage in rats.

The use of Johnsen's scoring method demonstrated that testicular ischemia-reperfusion (TIR) significantly reduced spermatogenesis in the testis affected when compared to the sham control group. Still, the spermatogenesis of DIA-treated rats that were subjected to I/R was much better than that of untreated rats that were subjected to I/R. Ibuprofen may be able to prevent testicular damage due to I/R, according to Dokmeci et al. [111]. According to Kölükçü et al. [112], pirfenidone may be an option for treating testicular torsion-related ischemia-reperfusion damage. By considerably enhancing spermatogenesis and upregulating antioxidants in testicular ischemia-reperfusion, rapamycin administration prior to reperfusion may lessen the histologic damage that occurs after testicular torsion [113]. Ghasemnejad-Berenji et al. [114] reported the effect of rapamycin in the ipsilateral testis. Testicular T/D increased the levels of apoptosis, malondialdehyde (MDA), and caspase-3 and decreased the activities of glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase, which were ameliorated by rapamycin treatment.

6. 4Antimicrobial

According to Dejban et al. [15], dapsone had a protective effect on ipsilateral and contralateral testes against ischemia/reperfusion injury, which was presumably related to the anti-inflammatory and antioxidative properties of dapsone. In another study, the administration of minocycline was documented to downregulate the mRNA expression of pro-apoptosis and inflammatory-related genes in testicular tissue of rats subjected to torsion/detorsion via its anti-apoptotic and anti-inflammatory properties. Moreover, management with minocycline increased the serum level of testosterone, mRNA expression of some genes involved in the activity of antioxidant enzymes, steroidogenesis, and the histopathological integrity, including the thickness and diameter of seminiferous tubule epithelium [18]. Saravi et al. [115] also demonstrated for the first time that minocycline attenuated testicular T/D-induced reduction in serum testosterone concentration and an upsurge in serum nitrite level via modulation NO/cGMP pathway.

In another experimental study, it was shown that oltipraz treatment has an advantageous effect to testicular I/R injury. Oltipraz exerts cytoprotective, antioxidant and anti-apoptotic activities [64]. Uguralp and his colleagues [116] reported that resveratrol diminished apoptosis in the ipsilateral testes but did not reduce apoptosis in the contralateral testes. In a separate research, Uguralp et al. [117] demonstrated that intraperitoneal treatment of resveratrol efficiently shields the testes from injury connected with reperfusion in rats.

6. 5Antioxidant

The study of Kazaz et al. [118] showed that N-acetylcysteine ameliorated I/R-induced ER stress, oxidative stress, and cellular apoptosis. Also, Dokmeci et al. [119] revealed that L-carnitine protected the testis against I/R-induced oxidative stress and histological testicular damage. Furthermore, Kazemi-Darabadi et al. [120] established that L-carnitine and betamethasone ameliorated I/R-induced testicular tissue damage and impaired sperm quality. Similarly, Cankorkmaz et al. [121] observed that Carnitine ameliorated I/R-induced testicular tissue injury. Furthermore, Masoumi et al. [122] demonstrated that the co-administration of diamond nanoparticles with CoQ10 synergistically improved sperm parameters. Also, Ayengin et al. [123] observed that coenzyme Q10 reversed I/R-induced oxidative damage, inflammatory response, remodeling of extracellular matrix, and apoptosis. Also, Rifaioglu et al. [124] established that ebselen prevented I/R testicular injury by reducing oxidative biochemical and histopathological damage. In addition, Bilommi et al. [212] reported that tationil glutathione prevented I/R-induced ROS generation and histopathological damage. The study of Celik et al. [125] established that hesperedin ameliorated I/R-induced oxidative stress and histopathological damage. More so, Abdelzaher et al. [126] observed that Idebenone ameliorated I/R-induced inflammation, oxidative stress, and apoptosis via Sirt1/Nrf2/TNF-dependent pathway. Additionally, Tangül et al. [127] reported that N-acetylcysteine abrogated I/R-induced oxidative stress, distortion in the structure of seminiferous tubules, and damage to germinative cells in I/R injury. In the same vein, Aktaş et al. [128] revealed that N-acetylcysteine ameliorated I/R-induced oxidative stress and histological damage. Also, Turkmen et al. [129] showed that N-acetylcysteine and ethyl pyruvate attenuated I/R-induced oxidative stress and histological damage. However, N-acetylcysteine administration was more effective since it decreased serum ischemia-modified albumin. Furthermore, Cay et al. [130] established that N-acetylcysteine ameliorated I/R-induced lipid peroxidation and histopathological damage. Additionally, Acer-Demir et al. [131] observed that N-acetylcysteine at 100 mg/kg reduced I/R-induced reduction in testicular volume and height and Sertoli cell numbers. Also, Chi et al. [132] demonstrated the protective roles of quercetin and resveratrol in I/R-induced oxidative stress and histological damage in rats subjected to torsion/detorsion. In addition, Aktoz et al. [133] established that quercetin improved I/R-induced histopathological damage and elevated immunoexpression of testicular eNOS and germ cell apoptosis. Furthermore, Ayan et al. [213] concluded that thymoquinone markedly reduced the number of apoptotic cells, immune reactivity, and histopathological damage following I/R testicular injury.

6.6. Antithrombotic drugs

Although studies evaluating the effect of anti-thrombotic agents on testicular I/R injury are scarce, Boettcher et al. [214] revealed

that the modulation of thrombosis with co-administration of enoxaparin and alteplase significantly improved testicular redox balance, ameliorated testicular damage, and improved inhibin and testosterone levels in testicular torsion/detorsion rats.

6. 7Antiulcer

Interestingly, anti-ulcer medications, such as H_2-receptor blockers and proton pump inhibitors, have been reported to exert antioxidant activities and protect against testicular I/R injury. In a recent research by Tanriverdi et al. [134], famotidine, a H_2-receptor blocker, was demonstrated to prevent testicular torsion/detorsion-induced impaired spermatogenesis and reduction in antioxidant activities and DNA injury in testicular tissues of male Sprague Dawley rats. Famotidine also preserved testicular histo-morphology [134]. In another experimental study, Güney et al. [135] revealed that omeprazole, a proton pump inhibitor, significantly reduced lipid peroxidation (as depicted by reduced MDA), oxidative DNA injury (evidenced by reduced (8OHdG), neutrophil accumulation (evidenced by reduced myeloperoxidase activity), and HSP40, HSP70, and HSP90. Güney et al. [135] also showed that omeprazole attenuated torsion/detorsion-induced distortion of testicular histoarchitecture.

6. 8Cysteine protease

Umemoto et al. [136] reported that treatment with 2 mg/kg/day of calpain inhibitors, administered intraperitoneally for 7 days, inhibited testicular torsion/detorsion-induced increase in apoptotic expression in sperm cells the contralateral testis.

6. 9Growth factors

Experimental studies have demonstrated that treatment with certain growth factors, like insulin-like growth factor-1 (IGF-1), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF), may protect against testicular I/R injury. VEGF treatment enhanced testicular performance by increasing the mean seminiferous tubular diameter, germinal epithelial cell thickness, and mean testicular biopsy score of the testes and decreasing caspase-3-positive cells in rats induced with testicular I/R [137]. IGF-1 administration reduces apoptosis of germ cells and increases testicular tissue and germ cell survival [138]. Quintaes et al. [139] showed that combining EGF with decompressive testicular fasciotomy improved testicular histoarchitecture, weight, and volume, as well as spermatogenesis in rats subjected to torsion/detorsion.

6. 10Hormones and their receptor modulators

According to the study of Teodosio Da Ros et al. [140], intratesticular administration of testosterone led to testicular atrophy, while the rats that did not receive testosterone recovered after 60 days. In the same vein, the study of Arabacı Tamer et al. [141] showed that estradiol and estradiol receptor beta (ERβ) agonists ameliorated compromised testicular blood supply, androgen receptor expression, oxidant injury, apoptosis, as well as tubular damage. In addition, ERβ improved sperm quality [20]. Also, Sarac et al. [142] revealed that the ameliorative effect of N-acetyl cysteine on I/R-induced testicular toxicity is via its antioxidative activities mediated by an increase in octanoylated ghrelin. Additionally, Taati et al. [143] concluded that restoring testicular tissue structure following I/R by ghrelin can be associated with its antioxidant activities. Furthermore, Savas et al. [144] established that administering human chorionic gonadotropin prevented contralateral histomorphometric alterations and serum testosterone in unilateral torsion.

6. 11Hydrogen sulphite

Bozkurt et al. [145] study revealed that sodium hydrogen sulphide protected against I/R-induced testicular toxicity via its anti-inflammatory, antioxidant, and antiapoptotic properties. In addition, Chen et al. [146] established that intratesticular treatment with GYY4137 added to the blockage of oxidative stress as well as spermatogenic cell apoptosis more than intraperitoneal administration. Furthermore, Urkmez et al. [147] suggested that thiol/disulphide hemostasis might be a haematologic parameter for I/R prognosis since they observed that a decrease in total thiol value was correlated with the distortion in testicular histology.

6.12. Hydroxynnamic acids

Also, Dilber et al. [148] reported that caffeic acid phenethyl ester (CAPE) blunted I/R-induced seminiferous tubular damage by initiating PI3K/AKT/mTOR signaling, which then suppressed inflammatory cell infiltration and protected testicular cells. Furthermore, the study of Unsal et al. [149] showed that sinapic acid protected the testes from I/R injury via its anti-inflammatory, antioxidant, and anti-apoptotic activities.

6.13. Nitric oxide and other vasodilators

The study of Shiraishi et al. [151] revealed that NO generated from eNOS controls the vasomotor performance in the contralateral testis, perhaps via a testis-specific reflex arc. The study of Kölükçü et al. [150] established that milrinone reversed I/R-induced testicular injury and increased oxidative stress and inflammatory markers. The study of Shiraishi et al. [56] showed that I/R of the testis initiates iNOS, which stimulates germ cell injury, perhaps via necrotic cell death initiated by NO and cytokines in the stalled

phase of reperfusion. The study by Lee et al. [152] reported that NO protected the testis against I/R-induced testicular toxicity via its anti-oxidant and anti-apoptotic properties. Furthermore, Karagoz et al. [153] reported that apaverine and alprostadil protected against I/R testicular injury. In addition, Somuncu et al. [154] stated that trapidil attenuated I/R-induced oxidative stress and histological injury in the ipsilateral twisted testis. In the same vein, the study of Bozlu et al. [155] also agreed that trapidil ameliorated I/R-induced testicular histological damage.

6. 14PDE5 inhibitors

Oroszi et al. [156] reported that intravenous sildenafl administration improves microcirculation in the testicle, offering significantly reduced ischaemic load on testicular cells and progresses short- and long-term surgical results. Similarly, intraperitoneal administration of low dose sildenafil citrate, 1 h prior to detorsion, could protect against I/R injury in testis after unilateral testicular torsion as revealed by amplified GSH level and CAT activities and diminished MDA and NO levels [157]. They also showed that giving low-dose sildenafil citrate prior to detorsion averts ischemia/reperfusion cell destruction in testicular tissue. Yldz and colleagues [158], on the other hand, demonstrated that high dosages of sildenafil dramatically reduced plasma and serum MDA levels. Low-dose sildenafil citrate seems to be effective in decreasing the consequences of testicular torsion damage. High-dosage of sildenafil therapy, on the other hand, showed no impact on biochemical and histological indicators of IRI [159]. According to Zavras et al. [160], intraperitoneal injection of erythropoietin plus sildenafil shields the testis from ischemia/reperfusion damage following torsion and detorsion. With the levels employed in this investigation (erythropoietin 1000 IU/kg and sildenafil 0.7 mg/kg), sildenafil may have a greater effect than erythropoietin. Darbepoetin and tadalafil, administered in combination, provided protective benefits on both testes and offered superior outcomes in maintaining testicular histology. This effect was more obvious in the contralateral testis, especially when the torsioned testis could not be saved [161].

Ameli et al. [162] demonstrated the beneficial effects of tadalafil and verapamil on testicular function and oxidative stress in adult male rats following torsion/detorsion. In addition, the levels of testosterone, SOD, and GPx, were substantially lower in the TD group in comparison to the therapeutic groups. The MDA level rose during the course of ischemia. Management with tadalafil and verapamil decreased the level of MDA and resulted in a significant change in sperm parameters compared to the Sham group. Sertkaya et al. [163] found that udenafil therapy abated testicular I/R injury by upregulating testicular antioxidant capacity and downregulating inflammatory cytokines. The prevention of testicular torsion/detorsion-induced ischemia/reperfusion damage in rats was also established by Tuglu et al. [164] using the compounds udenafil citrate, piracetam, and dexmedetomidine. Together with piracetam and dexmedetomidine, udenafil at increasing dosages showed antioxidant effects on the testis tissue. Histopathological alterations were also diminished, particularly with higher udenafil dosages. Vardenafil had anti-ischemic effects on the rat model of testicular torsion as shown by higher levels of total antioxidant enzymes and lower levels of MDA, germ cell apoptotic indicators, and iNOS and eNOS [165].

6.15. Phytomolecules

A list of the phyto-molecules with potentials in the management of testicular I/R injury is provided in Table 2.

The use of botanicals in the management of ailments has been from time immemorial [32,241,242]. Although these botanicals may have their side effects, they are readily available, relatively cheap [241,242], and have now become a part of human existence [32]. Evaluation of the potentials of phytomolecules, either as crude extracts or isolated molecules, has continued to gain attention especially in the management of testicular I/R injury since oxidative stress-sensitive pathways have been associated in the pathogenesis of testicular I/R injury and most of these botanicals are rich in phytomolecules that exert antioxidant and anti-inflammatory activities [243].

Several studies have shown the beneficial roles of phytomolecules in the management of testicular I/R injury. Skondras et al. [24] reported that apigenin, a natural dietary plant-derived molecule that belongs to the group of flavones called aglycone, ameliorated testicular I/R-induced rise in TNF-α, IL-10, and apoptotic cells. Apigenin also improved testicular histoarchitecture [24].

Apocynin (4-hydroxy-3- methoxyacetophenone), a phytomolecule extracted from the roots of *Apocynum cannabinum* and exerts NADPH oxidase (NOX) and superoxide inhibitory effects, has also been demonstrated to improve testicular I/R injury [215]. Apocynin reduced MDA, total oxidative capacity (TOC), and oxidative stress index (OSI) levels and increased superoxide dismutase and catalase activities in the testicular tissues of testicular torsed/detorsed rats (Ozbek et al., 2014). Ozbek et al. [215] also revealed that apocynin prevented testicular I/R-led escalation in the number of giant, desquamated and degenerated cells in the testicular tissues.

Berberine, an isoquinone quaternary alkaloid that is isolated from several plants like *Phellodendron amurense, Hydrastis canadensis, Coptis japonica, Berberis aristata, Coptis rhizome, Coptis chinensis* [244] and has been recounted to have anti-inflammatory and antioxidant properties [245,246] also protects against testicular I/R injury. Pre-treatment with berberine markedly reversed I/R-induced reductions in seminiferous tubular diameter, germinal thickness, and spermatogenesis as depicted by Johnsen's score [33]. Berberine pre-treatment also attenuated I/R-induced rise in MDA, total oxidative status (TOS), and OSI, and improved I/R-induced decline in total antioxidant status [33] of the testis.

Capsaicin, a key ingredient of red peppers that is contained in genus *Capsicum* plants and exerts anti-inflammatory activities, has been revealed to confer testicular protection against I/R injury. Javdan et al. [216] established that capsaicin increased Bcl-2 expression but reduced apoptotic index and FOXO1 and Bax expression in testicular I/R. Capsaicin also significantly reduced testicular tissue damage [216]. The effects of capsaicin were observed to be dose-dependent. Chrysin, a flavonoid found in honey, pollen and propolis, and the main compound in *oroxylum indicum* was revealed to reduce MDA and TNF-α levels, and caspase-3 and caspase-8

activities in the testis of rats subjected to torsion/detorsion [217]. These findings are similar to those of Abadi et al. [247] that revealed that chrysin attenuated testicular I/R injury and improved sperm concentration and motility as well as male sex hormone levels by lowering the testicular levels of MDA, upregulating the activities of enzymatic antioxidants, and modulating Bax/Bcl-2 signaling.

Curcumin, the key component of turmeric powder that is gotten from *Curcuma longa* [218,219], has been reported to stimulate antioxidant and anti-inflammatory activities by suppressing the release of proinflammatory cytokines and activating of nitric oxide synthase (NOS) inhibitor, NFkB activator protein 1, cyclooxygenase-2, and lipooxygenase [248]. In an experimental study by Basaran et al. [218], it was revealed that curcumin did not protect the ipsilateral and contralateral testes from testicular I/R damage as spermatogenesis (as depicted by Johnsen's score), MDA levels and iNOS and eNOS expressions were comparable between the curcumin-treated group and I/R group. However, using a similar rat model, Wei et al. [219] demonstrated that curcumin expressively reduced xanthine oxidase (XO) activity and MDA level and increased heme oxygenase-1 (HO-1) protein expression level and testicular spermatogenesis in ipsilateral testes in comparison with the torsion–detorsion group, suggestive of the protective effects of curcumin against testicular I/R injury. The variance between the results of Basaran et al. [218] and Wei et al. [219] may be due to the ischemia duration and drug dosage used. Wei et al. [219] induced ischemia for 2 h against Basaran et al. [218], who induced ischemia for 5 h. This may buttress the fact that ischemia beyond 4 h may cause irreversible damage. It is also likely that curcumin at 150 mg/kg as used by Basaran et al. [218] may be sub-therapeutic and not sufficient enough to elicit effective testicular protection against I/R injury.

Shokoohi et al. [66] established that *Fumaria parviflora* hydroalcoholic flower extract at 250 mg/kg administered orally improved circulating testosterone, spermatogenesis (proven by amplified Johnsen's score and germ cell height), and sperm quality as depicted by increased sperm count, percentage and motility of sperm with normal morphology in rats that were subjected to torsion/detorsion [66]. These findings were accompanied by improved testicular redox state, evidenced by significant increase in SOD and glutathione peroxidase (GPx) activities and reduction in MDA production, and apoptosis as revealed by increased Bcl-2, and reduced Bax, Bax/Bcl-2, and apoptotic index [66].

Ganoderma lucidum, a mushroom fit in to the *Polyporaceae* family of Basidiomycota [249], which is rich in polysaccharides, triterpenoids and proteins [250] has been reported to display antioxidant and anti-inflammatory activities [251]. Dogan and Ipek [221] demonstrated that *Ganoderma lucidum* prevented I/R injury by reducing MDA levels and elevating GSH levels, SOD and catalase activities, and tubular diameter in the testicular tissues of rats exposed to torsion/detorsion. The beneficial effect of *Ganoderma lucidum* was shown to be via induction of angiogenesis (evidenced by increased VEGF expression) and suppression of apoptosis [221]. In addition, several studies have reported the positive impacts of *Ginkgo biloba* on testicular I/R injury. Akgü et al. [222] demonstrated that oral administration of *Ginkgo biloba* at 50 mg/kg for a month alleviated I/R-induced rise in MDA, nitrate, and nitrite levels in testicular tissues. Also *Ginkgo biloba* minimized testicular oedema, congestion, and hemorrhage in rats subjected to torsion/detorsion [222]. These findings on the protective impact of *Ginkgo biloba* were associated with reduced apoptotic cells, apoptosis protease activating factor (Apaf-1), endothelial nitric oxide synthase (eNOS), and inducible NOS (iNOS) [223]. Kanter [224] confirmed the findings of Akgü et al. [222,223] that oral administration of *Ginkgo biloba* at 50 mg/kg reduced germ cell apoptosis and eNOS in the testis subjected to I/R. Kanter [224] also noted that *Ginkgo biloba* significantly enhanced spermatogenesis (evidenced by improved Johnsen's score), mean tubular diameter, and testicular ultrastructure. Ahmad et al. [65] demonstrated that *Ginkgo biloba* attenuated torsion/detorsion-induced decline in circulating testosterone and rise in FSH, mitochondrial NAD^+, TNF-α, and IL-1β. Bayatli et al. [225] revealed that Grape seed proanthocyanidin extract attenuated testicular I/R-induced rise in MDA, advanced oxidation protein product (AOPP), eNOS, and apoptotic cells, and decline in tubular diameter and spermatogenesis.

Honokiol, a natural biphenolic complex obtained from the bark of magnolia trees and commonly used China and Japan as an antidepressant, anxiolytic, anti-thrombotic, antibacterial, and antiemetic [252,253], has been established to exhibit antioxidant and anti-inflammatory activities [254,255]. Huang et al. [226] revealed that honokiol attenuated I/R-induced rise in apoptosis-related molecules like caspase 3 and caspase 7, poly (ADP-ribose) polymerase (PARP), and the expression levels of endoplasmic reticulum stress-associated molecules like phosphorylated-eukaryotic translation initiation factor 2 subunit α (Phospho eIF2α) and CCAAT/enhancer binding protein homologous protein (CHOP). Proteolytic enzymes-rich lumbrokinase, derived from *Lumbricus rubellus* extracts [256] and demonstrated to exert anti-oxidative, anti-inflammatory, anti-microbial, and anti-fibrotic activities [257,258], has also been revealed to prevent I/R-induced apoptosis via the suppression of Bax [227]. *Matricaria chamomile* plant extract has been shown to improve spermatogenesis (using Johnsen's score), tubular diameter, epithelial height, testosterone level, and SOD and GPx activities and reduce MDA generation in rats subjected to torsion/detorsion [228].

Osthole (7-methoxy-8-isopentenoxy-coumarin), a natural coumarin derivative extracted from plants like *Angelica pubescens*, *Cnidium monnieri*, and *Peucedanum ostruthium* [259], has been revealed to increase testicular GSH and Nrf2 contents and SOD activity, and reduce MDA, 8OHdG and IL-6 levels, MPO activity, and caspases 3, 8, and 9 expressions [229].

Paeonol (2′-hydroxy-4′-methoxyacetophenone), a natural phenolic compound with antioxidant and anti-inflammatory effects [260,261], has been revealed to protect against testicular I/R injury by decreasing HSP70 TNF-α, HIF-1α, IL-1β, MDA, and IL-6, levels and increasing testosterone, GSH and Nrf2 levels, SOD activities, and spermatogenesis [230]. *Pausinystalia macroceras* aqueous bark extract significantly improved sperm count, sperm motility, and circulating testosterone concentrations in rats subjected to testicular torsion/detorsion [231].

Plantago major ethanolic leaf extract, a medicinal plant that is rich in Baicalein (a flavonoid) and aucubin (an iridoid glycoside) and exerts antioxidant and anti-inflammatory activities, has been stated to shield the testis from I/R injury [220]. *Plantago major* ethanolic leaf extract alleviated testicular I/R-induced upsurge in peroxidase activity and rise in MDA level [220]. *Plantago major* ethanolic leaf extract also improved catalase activity in the testicular tissues and I/R-induced necrosis and depletion of germ cells [220].

Punica granatum (pomegranate) hydroalcoholic peel extract increased sperm count and viability and testosterone levels in animals subjected to testicular torsion/detorsion [232]. Proxeed Plus, a dietary supplement that contains vitamin B12 L-carnitine, fructose,

zinc, fumarate, CoQ10, folic acid, vitamin C, and acetyl-L-carnitine [262], has been shown to increase testosterone level, tubular diameter, leydig cell mass, and spermatogenesis by upregulating serum and epididymal GSH, catalase, SOD, GPx, GST and down-regulating hydroxyl peroxide and MDA generation, iNOS, caspase 3 and 9 activities [67]. Raisi et al. [233] that revealed that rosmarinic acid, a natural polyphenol that is an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid, attenuated testicular I/R injury and improved sperm concentration and motility by lowering the testicular levels of MDA and upregulating the activities of enzymatic antioxidants.

Rhodiola rosea (*R. rosea*), also referred to as the golden root or arctic root and rich in flavonoids, rosarin, tyrosol, rosin, rosavin, and salidroside [263], has been demonstrated to improve testicular histoarchitecture by suppressing MDA level, apoptotic cells, and increasing GSH content of the testicular tissues of rats exposed to testicular I/R [234]. Royal jelly, a product of honey bee has also been shown to improve testicular histoarchitecture, testosterone level, and spermatogenesis of rats subjected to testicular torsion/detorsion [235].

Salvia miltiorrhiza hydroalcoholic leaf extract improved sperm motility, vitality, concentration, and morphology, testicular and plasma TAC, and catalase and GPx activities, and reduced MDA level [236]. *Salvia miltiorrhiza* hydroalcoholic leaf extract also increased tubular diameter and germinal epithelial thickness in rats subjected to testicular torsion/detorsion [236]. *Stevia rebaudiana* aqueous leaf extract improved testicular histoarchitecture and spermatogenesis by suppressing MDA release, and increasing SOD and GPx activities in rats subjected ti testicular I/R [237].

Ternatin, a tetramoxyflavone from *Egletes viscosa* L., was reported to reduce MDA levels in the testicular tissues of rat expoed to testicular I/R [238]. Vinpocetine (ethyl apovincamine-22-oate), a synthetic ethyl ester of apovincamine, which is extracted from the leaves of Vinca minor [264] and has been reported to exert antioxidant and anti-inflammatory effect especially on the neurons [265], was revealed to improve tubular diameter and spermatogenesis by suppressing apoptotic cells and HSP70 expression in the Leydig and germ cells [239]. *Vitex doniana* aqueous leaf extract prevented testicular I/R-induced reduction in testicular weight, tubular and luminal diameters, germ cell height [240].

6. 16Stem cells

The study of Siregar et al. [166] established that hADSC protected the testis against I/R-induced oxidative stress. Also, Hsiao et al. [167] revealed that Mesenchymal stem cells restored sperm quality and glycogenesis/glycolysis imbalance following I/R testicular injury via the modulation of Akt/GSK3 signaling. Furthermore, Ertürk reported that BM-MSCs shielded the testis from I/R-induced oxidative stress and impaired spermatogenesis.

6. 17Stimulants

Yousefi-Manesh et al. [169] demonstrated that *i.p* administration of modafinil for 7 days inhibited testicular torsion/detorsion-induced rise in MDA (a marker of lipid peroxidation) and TNF and IL-1 (inflammatory mediators). These findings were associated with the prevention of torsion/detorsion-induced degeneration of germ cells, oedema and hemorrhage by modafinil in the testicular tissue.

6. 18Vitamins and minerals

The study of Etensel et al. [170] revealed that dexpanthenol prevented testicular atrophy following I/R injury. Additionally, Aydın et al. [171] presented that dexpanthenol protected the testis from I/R-prompted histological and functional damage. Also, the study of Koc et al. {21] established that Erdosteine ameliorated histological testicular damage via its antioxidant activities. Guimarães et al. [172] also showed that α-lipoic acid shielded the testis from I/R injury by decreasing lipid peroxidation and increasing GSH and total antioxidant power. Furthermore, Güzel et al. [173] revealed that lycopene prevented I/R-induced testicular injury within 3 days of reperfusion but not after 10 days. Also, Hekimoglu et al. [174] established that lycopene blunted IR-induced impaired sperm quality and oxidative stress. Furthermore, selenium diminished lipid peroxidation and hindered histological damage in both ipsilateral and contralateral testes [175]. Also, the study of Kara et al. [176] established that selenium ameliorated I/R testicular injury by preventing increased oxidative stress and apoptosis markers. In addition, Ranade et al. [177] showed that 30 days of pretreatment with vitamin E reversed I/R-induced testicular damage. Surprisingly, Turan et al. [178] reported that I/R-induced ipsilateral and contralateral testicular damage is not associated with lipid peroxidation, and vitamin has no beneficial effect. Similarly, Arda et al. [179] reported that Vitamin E increased the observed I/R testicular injury, while coenzyme Q10 prevented I/R testicular injury by reducing oxidative stress and histopathological damages. Also, Moghimian et al. [180] observed that vitamin c and tunica vaginalis flap improved testosterone and histological parameters following 5 h of ischemia. Furthermore, Oral et al. [22] revealed that Zinc decreased I/R-induced oxidative stress and histological damage in the ipsilateral and contralateral testes. Additionally, Ozkan et al. [181] revealed that zinc aspartate ameliorated I/R testicular injury by preventing increased oxidative stress. Semerciozet al. [70] also observed that Zinc sulfate and melatonin ameliorated I/R testicular injury when used singly and combined. This is associated with improved spermatogenic activities and antioxidant status.

6. 19Others

Acioli et al. [266] found that electroacupuncture stimulation (2 and 10 Hz) reduces oxidative stress and inflammation in rats

subjected to testicular torsion/detorsion. In addition, electroacupuncture may enhance bilateral testicular blood flow in a rat model with 180-degree unilateral testicular torsion [183]. The use of preventive agents prior to conducting detorsion or progressive detorsion may be effective in avoiding ischemia/reperfusion damage since it may manifest after detorsion even in the early stages [184]. Amniomax (AMX) injection, according to Aydogdu et al. [185], lowers oxidative stress and promotes the antioxidant system, abrogating morphological damage in rat testes after ischemia/reperfusion. Whether the AMX injection has to be administered just before or after detorsion is unclear, however. Another study demonstrated that testicular cryoablation might be used to achieve histological orchiectomy. In the cryoablation group, 13 of the 18 testes had varying degrees of paratesticular inflammation and necrosis [186]. According to Akcora et al. [187], darbepoetin alfa therapy may have a shielding impact against testicular I/R damage. Darbepoetin is a long-acting erythropoietin (EPO) analog. They examined darbepoetin alfa's early antioxidant impact on I/R damage. When compared to a group of animals that underwent torsion for 12 h, followed by detorsion and fasciotomy, decompressive testicular fasciotomy resulted in testicular macroscopic changes (increased weight and testicular volume) as well as improved histopathological changes [188].

Demir et al. [189] discovered that ethyl pyruvate EP to rats 30 min before detorsion protected the testicles from I-R injury brought on by oxidative and endoplasmic reticulum (ER) stress. Ethyl pyruvate (EP) seems to have a protective impact due to of its anti-inflammatory and antioxidant qualities. Intriguingly, Boettcher et al. [190] reported that dissolving cell-free DNA (including NETs) expressively reduces testicular injury in rats and that thrombus development during testicular torsion (TT) is probably NET-associated. Also, an experiment showed that rats with who underwent torsion/detorsion had much higher levels of IMA and D-dimer in their blood than the rats in the control group. A possible relevance for the high serum D-dimer and IMA levels as a serum marker in the early diagnosis of torsion/detorsion [191]. Another study shows that montelukast, which is a CysLT1 receptor antagonist, and zileuton, which is a 5-LO inhibitor, reduce the damage to the testicles caused by T/D. Nonetheless, Isikdemir et al. [192] discovered that zileuton is more effective than montelukast at repairing the testicular damage caused by T/D. Qi et al. [193] found that omega-3 polyunsaturated fatty acids (n-3 PUFAs) helped repair damage to the testicles caused by testicular I/R injury via their anti-inflammatory and antioxidative activities, which involved the activation of Nrf2 and blockade of NF-kB.

In addition, Akhigbe et al. [6] investigated the preventive and therapeutic effects of omega -3 in testicular and sperm damage caused by T/D-driven I/R. Through a deterioration in testicular lactate metabolism and passage and an upsurge in XO/uric acid signaling in both the torsed (ipsilateral) testis and the contralateral testis, they established that I/R-induced injury to the testis and sperm cell succeeding T/D is accompanied by oxidative stress, an inflammatory response, and apoptosis. Additionally, by improving lactate transport and suppressing XO/uric acid signaling, omega-3 protects the testes and sperm cells against T/D-induced oxido-inflammatory injury and death. According to Savas et al. [194,195], pentoxifylline therapy may lessen the effects of reperfusion damage on T/D by affecting neutrophils and blood flow. The MDA levels of both testes increased during unilateral testicular torsion and detorsion. The ipsilateral side had interstitial bleeding, according to histopathological analysis. Pentoxifylline reduced MDA levels on both sides and lessened ipsilateral interstitial damage Kutluhan et al. [184]. Against T/D, platelet-rich plasma (PRP) has excellent cytoprotective benefits by decreasing TNF-α, NO, caspase-3, IL-1β, and increasing Bcl-2, catalase, GSH, and GST with histological enhancements in all rats' testes subjeceted to torsion/detorsion [196]. Another study found that pulsed magnetic field (PMF) treatment was just as effective as melatonin delivery in protecting against testicular I/R injury. Also, it was shown that testicular scintigraphy using 99 mTc pertechnetate and PET/CT using 18 F-FDG may be utilized to diagnose and assess the effectiveness of treatment for testis torsion [197]. In the I/R-damaged rat testis, BQ123 (an endothelin type A receptor antagonist) not only reduces the production of apoptotic proteins but also lessens DNA damage [198]. BQ123, an essential drug for preserving the testis after I/R injury, is an antagonist of the endothelin type A receptor that decreases DNA damage and apoptosis when administered.

7. Non-pharmacological potentials in the management of I/R injury

The summary of the non-pharmacological agents with potentials in the management of testicular I/R injury is provided in Table 3.

7.1. Hyperbaric oxygen

Although Senkul et al. [267] reported that hyperbaric oxygen therapy (HBO) ameliorated I/R-initiated testicular injury, they did not detect any significant difference between the single and multiple HBO sessions. In addition, the study of Karli et al. [268] revealed that HBO is more effective than medical ozone (MO) in preventing I/R testicular toxicity by improving testicular antioxidant status. Also, Zhang et al. [27] established that HBO heightened I/R-induced testicular toxicity by preventing oxidative stress, inflammatory response, and reducing NO formation. Additionally, Kolski et al. [269] observed that HBO prevented I/R-induced testicular injury by preserving the germinal epithelium.

7.2. Hypothermia

Erdem et al. [270] found that both hypothermia and intermittent reperfusion shield tissue from harm caused by IR. Nevertheless, there was no biochemical or histological advantage for hypothermia, intermittent reperfusion, or combination treatments. In another study, Elmimehr et al. [271] reported the impacts of hypothermia and pentoxifylline on the adnexal torsion/detorsion injuries in a rat testis model. Pentoxifylline as an antioxidant component, raised the activities of antioxidant enzymes, decreased the expression of the BAX gene (*Bcl-2 Associated X-protein*) and dropped the rate of apoptosis in testicular tissues of rats after torsion detorsion, while hypothermia, and hypothermia plus pentoxifylline, did not manifest this. Vitamin E and hypothermia have been shown to repair

testicular damage in rats and lower the rate at which spermatogenic cells die off [272]. Moreover, it was shown to raise LH and FSH levels and drastically lower the apoptosis rate in spermatogenic cells. SOD activity was decreased, and MDA increased significantly as a result.

7.3. Leech therapy (Hirudo medicinalis)

Leech therapy is a complementary and alternative therapy. Although there are several species of leech, *Hirudo medicinalis* seems to be the commonest, especially in folklore medicine. The therapy is associated with site biting, blood sucking, and injection of its saliva into the saliva [277]. The analgesic, anti-thrombotic, anti-inflammatory, and anti-microbial activities of leech therapy [278] have been attributed to the contents of the saliva such as Hirudin, Calin, Destabilase-lysozyme, Hyaluronidase, Bdellastasin (bdellin A), Tryptase inhibitor, Saratin, and γ-Glutamy transpeptidase [279]. Davoodi et al. [273] demonstrated that leech therapy following testicular ischemia and 30 min before reperfusion for 7 min improved testicular histology and sperm quality by reducing MDA generation and Bax expression, and increasing TAC, GPx and catalase activities, and Bcl-2 expression. This abrogated testicular I/R-induced inflammation, oxidative stress, and apoptosis.

7.4. Ozone therapy

The study of Tusat et al. [274] established that MO ameliorated I/R-induced testicular injury via an oxidative stress mechanism. Furthermore, Shahi et al. [275] also reported that Ozone/oxygen therapy prevented I/R-induced testicular injury via oxidative stress-dependent mechanism. The study also concluded that mitochondrial dysfunction and the disconnection of oxidative phosphorylation may play vital parts in I/R injury. Furthermore, Ekici et al. [206] revealed that MO ameliorated I/R-induced testicular injury with respect to biochemical and histopathological findings, and its effects were comparable with that of melatonin. In addition, Aydos et al. [208] established that MO and taurine ameliorated I/R-induced testicular injury by preventing apoptosis and germ cell degeneration. Also, Mete et al. [276] revealed that although intratesticular and intraperitoneal administration of MO ameliorated I/R-induced histopathological distortion and apoptosis, intratesticular administration was found to be more effective.

8. Preconditioning and post-conditioning

Ischaemic pre-conditioning and post-conditioning have been established to confer shield against I/R injury. This involves subjecting the organism to a series of short ischaemic bouts and reperfusion just before the secondary ischemia and reperfusion. These conditionings may induce endogenous protective substances to aid tolerance and adaptation to I/R injury [266]. Shimizu et al. [266] revealed that ischaemic pre-conditioning, consisting of 3 series of 5 min of ischemia and 5 min of reperfusion before 60 min of secondary ischemia, and then 120 min of reperfusion, attenuated I/R-induced pathological alterations of the testicular tissue via a decrease in MDA, 8-OHdG, MPO, and mRNA expression of HSP70. Gozen et al. [280] demonstrated that ischaemic pre-conditioning, characterized by 3 episodes of 5 min of ischemia alternated by 5 min of reperfusion before a 180-min ischemia and 60-min reperfusion significantly suppressed lipid peroxidation, MPO activity, total oxidative status (TOS), and the oxidative stress index (OSI) of the testicular tissue. Zhang et al. [281] reported that ischaemic pre-conditioning and/or ischaemic post-conditioning shielded the testes from testicular I/R injury by reducing the OSI and cell apoptosis and restoring Bcl-2/Bax.

However, Sahinkanat et al. [282] revealed the varying effects of different ischaemic pre-conditionings. Using a rat model, Sahinkanat et al. [282] subjected animals to different ischaemic pre-conditionings (20 min of ischemia with 10 min of reperfusion; 30 min of ischemia with 10 min of reperfusion; 3 cycles of 10 min of early phase transient ischemia with 10 min of reperfusion; 5, 10, and 15 min of early phase transient ischemia with 10 min of reperfusion; and 10, 20, and 30 min of early phase transient ischemia with 10 min of reperfusion 0 and observed that all forms of preconditioning minimized testicular tissue damage but only the groups that were subjected to one and 3 cycles of 10 min of early phase transient ischemia with 10 min of reperfusion showed significant decrease in MDA. Also, only the group subjected to 3 cycles of 10 min of early phase transient ischemia with 10 min of reperfusion showed significant decrease in NO levels [282]. Also, Ozkisacik et al. [283] reported that ischaemic post-conditioning for 5 and 10 s, but not 20 s, significantly reduced testicular I/R-induced rise in MDA level; however, only the ischaemic post-conditioning for 5 s showed significant reduction in the histopathological grading after 1 h [283] and after 60 days [284]. In addition, Ceylan et al. [285] demonstrated that ischaemic, consisting of a 5- or 10-min preconditioning and 3 cycles of 10 min preconditioning, did not confer any form of protection on both the ipsilateral and contralateral testes. It could be inferred from the findings of Sahinkanat et al. [282], Ozkisacik et al. [283,284], and Ceylan et al. [285] that the protect effects of preconditioning and post-conditioning may be dependent on the approached utilized. It is likely that about 3 cycles of alternate ischemia and reperfusion of same duration may be protective.

9. Conclusions and future perspectives

This review clearly describes the various testicular I/R models available in the literature. Common approaches to assessing the testis are ilio-inguinal, low midline laparotomy, and scrotal incisions. Although, no shoe fits all; the use of suture on twisted spermatic cord mimics the event observed in humans than other available models. The duration of torsion before intervention may also affect the outcome of intervention. Nonetheless, oxidative stress-mediated pathways, which are initiated at the ischaemic phase and worsened at reperfusion, plays a central part in testicular I/R damage. In addition, known pharmacological agents and nutraceuticals with anti-inflammatory and antioxidant activities have been demonstrated to be beneficial in mitigating testicular I/R injury. More so,

Table 3
Potential non-pharmacological measures in the management of IR injury.

Hyperbaric Therapy										
Reference	Animal model	Ischemia method	Ischemia duration	Incision site	Reperfusion duration	Drug	Time of administration	Route of administration	Dose of drug	Findings
[267]	Rat model	Suture	4 h	Bilateral vertical incision.	7 days	Hyperbaric oxygen therapy (HBO)	Immediately after detorsion		1 or 7 sessions	Although was found to significantly ameliorate I/R-induced testicular injury, there was no significant difference between the single and multiple HBO sessions.
[268]	Rat model	Suture	1 h	Scrotual incisions	7 days	HBO and Medical Ozone (MO)	Immediately after detorsion for 7 days	Intraperitoneal	98 % oxygen at 2.4 ATM pressure in a total of 21 sessions of 60 min for HBO and 1 mg/kg for MO. The generator supplied 6 % oxygen and 4 % ozone	HBO is more effective than MO in preventing I/R testicular toxicity by improving testicular antioxidant status.
[27]	Rat model	Suture	2 h	Low midline laparotomy	30 days	HBO	1 and 12 h post-ischeamia and once daily for 30 days		100 % oxygen for 1 h at the pressure of 2.4 atm for 30 days	HBO ameliorated I/R-induced testicular toxicity by preventing oxidative stress, inflammatory response, and reducing NO formation
[269]	Rat model	Clamp	4 h	Inguinal incisions.	2 weeks	HBO	150 min post-ischeamia and immediately after ischeamia		90 min treatment at 2.5 atm with 100 % oxygen	HBO prevented I/R-induced testicular injury by preserving the germinal epithelium
Hypothermia										
[270]	Rat model	Clamp	4 h	Scrotum	1 h	Hypothermia	5s, 10s intermittent reperfusion		4^0c	Hypothermia reversed I/R-induced ↓MDA, MPO
[271]	Rat model	Suture	4 h	Scrotum	4 h	Pentoxifylline, Hypothermia	30 min pre detorsion		40 mg/kg	Hypothermia reversed I/R-induced ↓aperm count and testosterone↓MDA↓Bcl 2, caspase 3 and Bax
[272]	Rat model	Suture	2 h	Scrotum	2 h	Hypothermia And vit E	30 min, 90min and 30 min before reduction	Intravenous	72 °C 200 mg/kg	Hypothermia reversed I/R-induced ↓LH, FSH and testosterone ↓MDA, IL-1β and hs-CRP
Leech therapy										
[273]	Rat model	Scrotal fixation	2 h	Scrotal midline incision	2 h	Leech therapy (*Hirudo medicinalis*)	30 min before reperfusion for 7 min	Local (on the incision site)	7 min of leech exposure	Leech therapy ↓MDA, Bax, and caspase 3, and ↑TAC, GPx catalase, Bcl-2, and sperm quality

Ozone therapy										
[274]	Rat model	Suture	2 h	Scrotal incision.	24 h	MO	Immediately after torsion	Intraperitoneal	1 mg/kg	MO ameliorated I/R-induced testicular injury via an oxidative stress mechanism.
[275]	Rat model	Suture	2 h	ilioinguinal	30 days	MO (Ozone/ Oxygen ratio: 99.95 %/0.05 %)		Intravenous	30 μg/ml	Ozone/oxygen therapy prevented I/R-induced testicular injury via oxidative stress dependent mechanism. The study also concluded that mitochondrial dysfunction and the uncoupling of oxidative phosphorylation may play key roles in I/R injury.
[206]	Rat model	Suture	6 h	Inguinoscrotal incision.	7 days	MO and melatonin	5 h 45 min post-ischeamia and once daily for 7 days	Intraperitoneal	50 μg/mL and 1 mL respectively	MO ameliorated I/R-induced testicular injury.
[208]	Rat model	Suture	2 h	Scrotum	4 h	MO and taurine	105 min post-ischeamia	Intraperitoneal	1 mg/kg and 7.5 mL/ kg in 10 % water solution respectively	MO and taurine ameliorated I/R-induced testicular injury by preventing apoptosis and germ cell degeneration.
[276]	Rat model	Suture	1 h	Scrotum	4 h	MO	90 before reperfusion	Intraperitoneal and intratesticular	4 mg/kg	Although intratesticular and intraperitoneal administration of MO ameliorated I/R-induced histopathological distortion and apoptosis, intratesticular administration was found to be more effective.

alternative therapies like hyperbaric therapy, hypothermia, leech therapy, ozone therapy, and ischemic pre-conditioning and post-conditioning strategies are useful measures in attenuating testicular I/R injury. Despite studies that stated the benefits of several pharmacological and non-pharmacological therapeutic measures when instituted with surgical detorsion, there is a paucity of clinical/human randomized controlled trials validating the data from animal studies. More studies exploring the associated pathogenesis of testicular I/R injury and the mechanisms of action of therapeutic strategies would provide alternative regimen in the management of testicular I/R injury. Also, clinical studies and/or randomized controlled trials evaluating the reports from animal models would be useful in validating these therapeutic strategies.

Ethical approval

The research was approved by the institution's Ethics Review Committee, Ethical Review Committee, Oasis of Grace Hospital, Nigeria (Approval number: OGH/2023/133).

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Data availability

Data will be made available on request.

CRediT authorship contribution statement

R.E. Akhigbe: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **A.F. Odetayo:** Writing – review & editing, Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Data curation. **T.M. Akhigbe:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **M.A. Hamed:** Writing – review & editing, Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Data curation. **P.J. Ashonibare:** Writing – review & editing, Writing – original draft, Resources, Project administration, Investigation, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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