IJPSR (2023), Volume 14, Issue 9 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 06 November 2022; received in revised form, 30 July 2023; accepted, 04 August 2023; published 01 September 2023

ENDOCRINE DISRUPTING CHEMICALSAND MALE REPRODUCTION: A SPECIAL FOCUS ON ANTITHYROID DRUGS AND RECUPERATIVE EFFECTS OF A-LIPOIC ACID

R. Pavani, P. Prathima, K. Venkaiah and S. B. Sainath *

Department of Biotechnology, Vikrama Simhapuri University, Nellore - 524324, Andhra Pradesh, India.

Keywords:

Endocrine disruption, Fertility, Lipoic acid, Sperm, Thyroid hormones, Testosterone and testis

Correspondence to Author:
Dr. S. B. Sainath

Assistant Professor,
Department of Biotechnology,
Vikrama Simhapuri University,
Nellore - 524 324, Andhra Pradesh,
India.

E-mail: drsainathvsu@gmail.com

ABSTRACT: Male reproduction is controlled and coordinated by endocrine factors and therefore, even minute changes can able to interfere with the male fertility. Accumulation of data have shown that the humans are exposed to chemicals that can able to interfere with endocrine factors. Interestingly, published reports have shown that the continuous exposure to such chemicals occurs mainly due to their wide usage in a variety of personal care and daily products such as plastics, food, water, fertilizers, textiles, shampoos, toys and pharma drugs *etc*. In view of ongoing interest in exposure of humans to such agents and compromised male fertility, there is a major concern and attention towards the endocrine disrupting chemicals among the public, endocrinologists, andrologists and scientific community. These chemicals interfere with the endocrine functions *via* mimicking their structure, blocking the hormone receptor and/or function of genes and proteins that facilitate normal spermatogenesis and testosterone biosynthesis. The present review provides an overview of endocrine disrupting chemicals on male reproductive health with a special focus on thyroid hormone disrupting chemicals. The present review was categorized into three broad aspects. The first aspect deals with the endocrine disruption of spermatogenesis and steroidogenesis. The second aspect deals with the effect of thyroid hormone disrupting chemicals on testicular functions and the final aspect deals with the role of α-lipoic acid induced amelioration of male fertility efficacy against the thyroid hormone disrupting chemicals. Finally the challenges and gaps were highlighted.

INTRODUCTION: Male infertility is one of the serious ongoing problems all over the world. During the past five decades an increase in the congenital male reproductive disorders such as cryptorchidism, hypospadiasis, testicular cancer and testicular dysgenesis has been reported [1-5]. Reproductive disorders are increasing at an alarming rate which attracted the attention of public and scientific communities all over the world [5, 6].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(9).4209-24

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(9).4209-24

Many reproductive problems such as hypospadiasis, cryptorchidism, testicular germ cell tumors (TGCT) and even all these congenital effects could lead to low sperm numbers followed by male infertility [7]. Testicular dysgenesis syndrome is a common term given to the congenital defects and this syndrome is thought to be due to interference of a range of exogenous chemicals during embryonic programming and male reproductive tract development during fetal life [8-11].

Twenty-eight years back i.e. in the year 1992, increase in the incidences of deteriorated sperm density has been reported through meta-analysis studies wherein it was reported that the mean sperm concentration had fallen from 113 to 66 million/ml over a period of 50 years (1940 to 1990).

Since, then, many studies were carried out on male reproductive health worldwide and confirmed the deterioration of sperm quality and quantity [2-6, 13, 14]. In Danish men, a downtrend of sperm count with increase in sperm abnormalities has been reported [15]. In European men, the data over a period of 50 years indicated that almost 33% decrease in mean sperm concentration was observed [16]. The mean concentration of spermatozoa was reduced from 88 million per ml to 61 million per ml, almost 30% reduction was observed in Italian men [17]. Studies of Ravanos *et al.*[18] have shown that there was a significant deterioration of sperm quantity in French sperm donors. Similar trend in sperm concentration has been reported from Austria [15] and Finland [19]. Studies from India also revealed a decline in the sperm density [20, 21] and similar trend has been reported from China [22].

The ultimate effect of these congenital male reproductive abnormalities is deterioration of sperm quality and quantity associated with male infertility. The exact route causes remain obscure [7]. However, many studies claimed that a group of chemicals including pharmaceutical compounds and environmental toxicants can able to interfere and disrupt male reproductive tract and its functions thereby male fertility. These chemicals may exert their actions at the level of endocrine controlled male reproduction. Such chemicals with hormone disrupting activities are known as endocrine disruptors (EDs). They exert their actions at multiple levels: synthesis, secretion, transport, binding, action and elimination of endogenous hormones in the body thereby disrupt homeostasis of several biological processes including reproduction and development [5, 23].

EDs can able to 1) mimic endogenous hormones, 2) bind receptors of endogenous hormones thereby blocking the action of natural hormones, 3) modify the production and function of receptors and 4) inhibit the synthesis and secretion of endogenous hormones. Thus, based on these mechanisms, EDs can able to target the male reproductive tract development and its functions [7, 24]. It well known that proper development of male reproductive tract development and their functions sustain fertility efficacy later in life. EDs attack male reproductive system at all stages of development. If disturbances occur during developmental stages, it may lead to adverse effects on male reproductive health later in life. The findings of a registry-based TGCT case-control study in countries like Denmark, Finland, Sweeden and Norway (NORD-TEST) suggested a possible link between prenatal exposure to EDs and TGCT [25, 26]. A possible correlation has also been established between embryonic exposure to EDs and cryptorchidism and hypospadiasis [10, 11]. Interestingly, apart from endocrine disruption, the EDs can able to disrupt the homeostasis between the antioxidants and pro-oxidants thereby provoke oxidative stress. Thus, EDs-induced deterioration of male reproduction not only mediated by endocrine disruption but also *via* oxidative stress. Several while going through this review. On the flip side, in the current scenario, the therapeutic efficacy of antioxidants in the management of oxidative stress-induced testicular damage is an emerging area of reproductive toxicology.

Many studies indicated that antioxidant therapy could ameliorate deteriorated testicular functions against wide range chemicals including pharmaceutical chemicals and/or environmental toxicants with endocrine disrupting activities [33]. Interestingly, the putative role of antioxidants in the hormonal regulation is also well acknowledged [34]. One of the cogent examples of this trend includes α-lipoic acid (LA; 1, 2, dithiolane-3-pentanoic acid). LA is an essential cofactor for several enzymes that mediate energy production (acetyl-CoA synthesis from pyruvic acid), fatty acid metabolism (acyl CoA synthesis), TCA cycle (α-ketoglutaric acid to succinyl-CoA) and nucleotide synthesis (glycine synthesis) [35]and also exhibits extraordinary antioxidant properties [36].

The antioxidant and hormonal regulatory roles of LA have been demonstrated [34, 37]. Moreover, because of its lipophilic nature it can easily cross cell membranes and along with its redox couple, dihyrolipoic acid (DHLA) quenches free radicals more efficiently in both lipid and aqueous compartments [38]. Several studies also highlighted that the supplementation of α-Lipoic acid (LA) or 1,2-dithiolane-3-pentanoic acid in reducing testicular oxidative stress and amelioration of testosterone biosynthesis is well appreciated [34, 39, 40-45]. Based on the above literature, the current study was broadly classified into three aspects: the first aspect deals with the endocrine disruption of

spermatogenesis and steroidogenesis, the second aspect deals with the effect of thyroid disrupting chemicals on testicular functions and the final aspect deals with the role of LA induced amelioration of male fertility efficacy against the thyroid hormone disrupting chemicals. Finally, the challenges and gaps were highlighted.

Endocrine Disruption of Spermatogenesis and Steroidogenesis: Male reproduction is controlled and coordinated by the hormones synthesized and secreted from the hypothalamic-pituitary-testicular (HPT) axis.

Hypothalamus: It is the major gland associated with the stimulation of pituitary gland, thereby gonadotropins. It is located just below the thalamus region and comprises of diencephalon. It synthesizes and secretes, gonadotropin releasing hormone (GnRH), a decapeptide which stimulates anterior pituitary gland to secrete goandotropins. Therefore, hypothalamus is classically known as master controlling gland of HPT-axis.

Pituitary Gland: Pituitary gland is known as master of all endocrine glands as the secretions of pituitary gland regulate all most all the biological activities in the body. Upon stimulation from GnRH, the anterior pituitary gland secretes two important hormones: follicle stimulating hormone (FSH) and leutinizing hormone (LH) into the circulation to reach their target tissues, gonads. There are two spermatogoniogenesis, spermatocyte formation, spermiogenesis and spermiation [48].

These events are associated with two cell divisions: mitosis and meiosis, wherein mitotic division occurs at the level of spermatogonia and meiosis occurs at the level of spermatocytes and postmeiotic differentiation occurs at the level of spermatids. These events lead to spermiogenesis and spermiation process, eventually release of mature spermatozoa (haploid) into the tubular structure from the germinal epithelium. Spermatogenesis starts at puberty. Spermatogonia, the immature cells (diploid cells) undergo mitosis and develop into primary spermatocyte. The primary spermatocyte undergoes meiotic division to form secondary spermtocyte which in turn undergo meiotic division to form spermatids. Each secondary spermatocyte generates two haploid spermatids resulting into four haploid spermatids. Spemiogenesis is the final stage of spermatogenesis where mature sprermatozoa are developed from spermatids. In humans, the average length required for spermatogenesis is around 65 to 75 days, whereas in rats the average length required for spermatogenesis is around 54 to 60 days. For even production and availability of mature sperm, spermatogenesis takes place simultaneously at different times in different regions of testis. The events of spermatogenesis occur in a step-by-step manner and are regulated by the secretions of Sertoli cells and Leydig cells and also endocrine factors from the pitutary gland promote spermatogenesis.

FSH: Spermatogenesis is controlled and regulated by FSH via its membrane-bound receptors on the Sertoli cells. FSH is key player in the feedback mechanisms thereby regulation of testicular functions *via* HPT-axis [49]. The maturation of spermatogonia into mature spermatozoa is regulated by FSH *via* Sertoli cell functions. The number of Sertoli cells and their ability to support developing germ cells, thereby spermatogenesis is under the regulation of FSH [50].

With respect to the Sertoli cells, proliferation and differentiation of Sertoli cells is controlled by FSH, thereby their number in the testis. In addition, at molecular level, FSH mediated regulation at the level of structural genes of cell-cell junctions and gene that control regulatory and nutrient factors from Sertoli to germ cells are well appreciated [47, 51]. In humans, fertility phenotypes in carriers of inactivating *fshr* mutations leads to reduction of spermatogenesis.

LH: LH is plays a key role in the regulation of Leydig cell steroidogenesis, *via* its cognate receptor [52]. Upon ligand binding, adenylate cyclise activity stimulation occurs which in turn increases the rate of cholesterol transfer into the mitochondria of Leydig cells. This step is a rate limiting step in the testosterone biosynthesis. After translocation of cholesterol, cholesterol is metabolized into testosterone through a cascade of enzymes. Sertoli cell sustained spermatogenesis and Leydig cell steroidogenesis are controlled by several factors including hormones of hypothalamus (gonadotropin releasing hormone and pituitary

gland (gonadotropin: FSH and LH). Further, testosterone also controls spermatogenesis *via* Sertoli cells. Therefore, an intact HPT axis is critical for testicular functions [47]. Any disturbances at any of these critical levels of male reproduction may lead to infertility. Leydig cells are the steroidogenic cells of testis. They are present in the interstitium compartment of testis [53, 54]. They are primarily involved in the synthesis of male hormone, testosterone **Fig. 1.** The process of testosterone production occurs via a cascade of enzymes and proteins **Fig. 1**.

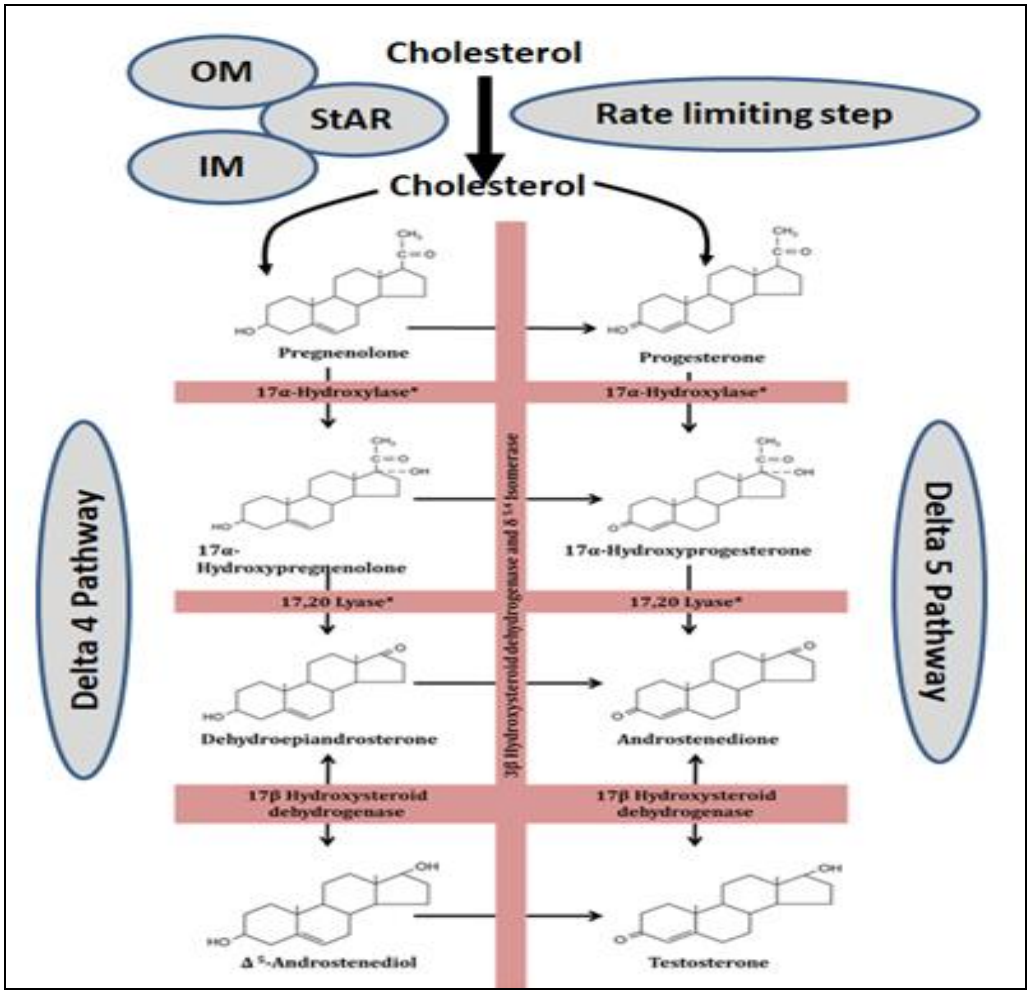

FIG. 1: TESTICULAR STEROIDOGENESIS, A PROCESS OF TESTOSTERONE BIOSYNTHESIS. STEROIDOGENIC ACUTE REGULATORY PROTEIN (STAR), A CHANNELLING PROTEIN FOR THE TRANSFER OF CHOLESTEROL WHICH IS A PRECURSOR FOR THE TESTOSTERONE SYNTHESIS. THIS CHANNELLING MECHANISM MEDIATED BY STAR IS ONE OF THE RATE LIMITING STEPS DURING TESTOSTERONE SYNTHESIS. THE PATHWAY OF TESTOSTERONE SYNTHESIS OCCURS VIA DELTA 4 PATHWAY OR PREGNENOLONE PATHWAY AND DELTA 5 PATHWAY OR PROGESTERONE PATHWAY. DETAILS OF COMPLETE PATHWAY OF TESTOSTERONE BIOSYNTHESIS WAS GIVEN IN THE TEXT. OM: OUTER MITOCHONDRIAL MEMBRANE; IM: INNER MITOCHONDRIAL MEMBRANE

The male hormone is an important regulator of a range of physiological processes, including spermato-genesis. Therefore, inadequate levels of testosterone are associated with various pathological conditions including male fertility related issues. During development period, two distinct populations of Leydig cells are present: fetal and adult Leydig cells. The fetal Leydig cells are important regulators of masculanization of male urogenital tract. The secretions of fetal Leydig cells also play important role in inducing testis descent. After birth, atrophy of these cells occurs and hence, they do not contribute to the adult Leydig cell population. On the other hand, undifferentiated precursors present after birth develop into adult Leydig cells and attain steroidogenic ability at puberty. The differentiation of fetal and adult Leydig cell populations is regulated by paracrine

and endocrine factors. Cholesterol is the precursor of steroid hormones [55, 56]. The transport or channelling of cholesterol from the outer mitochondrial membrane to the inner membrane is a rate limiting step. This is because, the space between the internal and external membranes are filled with aqueous environment and hence, allow only water-soluble molecules [57], updated by [58].

Therefore, proteins that can bind and able to transport cholesterol are required to full-fill this step. This problem is solved by proteins known as steroidogenic acute regulatory protein (StAR), which can able to bind and translocate cholesterol from the outer mitochondrial membrane to the inner mitochondrial membrane [59-61].

Many transcription factors including Sf1 are considered critical for the regulation of enzymes that mediate cholesterol synthesis and also StAR [58, 62]. After translocation, cholesterol conversion to testosterone includes two major pathways: delta-4 pathway Δ4 pathway and delta-5 pathway or Δ5 pathway. Δ4 pathway is also known as progesterone pathway, whereas Δ5 pathway is known as dihydroepiandrosterone pathway. The later pathway route appears to be most used in human testis. The cytochrome p450 enzymes include CYP11a1 and CYP17a1 and use nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor to catalyze the hydroxylation and cleavage of the steroid cholesterol. The enzyme activities of 17α-hydroxylase and 17, 20-lyase resideS in a single protein p450CYP17. The HSD enzymes include 3β-HSD and 17β-HSD and catalyze steroid hormone oxidation and reduction, including NAD / NADP as electron acceptors [63].

The first of the enzymatic reactions in steroidogenesis occurs at the inner mitochondrial membrane where CYP11a1 cleaves a six-cholesterol carbon chain to generate steroid pregnenolone [57]. Pregnenolone then diffuses into the smooth endoplasmic reticulum where it is metabolized into 3-hydroxysteroid dehydrogenases (3β-HSD) progesterone. Further, progesterone is metabolized to 17α-hydroxyprogetsrone by 17α-hydrolase and on the other hand, 17α-hydroxyprogetsrone is converted to androstenedione by 17, 20-lyase [58]. Eventually, androstenedione is converted to testosterone by 17β-HSD into testosterone [64]. In Δ5 pathway, pregnenolone is converted to 17α-hydroxypregnenolone by 17α-hydrolase and on the other hand, 17α-hydroxypregnenolone is converted to Δ5 androstenediol by 17β-HSD. Finally, Δ5 androstenediol is converted to testosterone by 3β-HSD [65].

Thyroid Hormone Disrupting Chemicals on Spermatogenesis and Steroidogenesis: It is appropriate to understand the thyroid hormone synthesis before addressing the thyroid hormone disrupting (THDCS).

Thyroid Hormone Synthesis: Thyroid gland is the major source of thyroid hormone synthesis. In vertebrates including mammals, the synthesis and secretion of thyroid hormones are tightly regulated by a negative feedback mechanism that involves endocrines of hypothalamo-pituitary-thyroid axis [66].

Thyrotropin releasing hormone (TRH), a tripeptide from hypothalamus is transported via axons and binds with TRH receptors in pituitary thyrotropes. This leads to the stimulation of thyrotropes to secrete a 28-kDa glycoprotein known as thyroid stimulating hormone (TSH) which upon binding to TSH receptor on thyroid follicular cells acts as a driving force to activate thyroid genes like Na^+/I^- symporter (SIS), thyroglobulin (Tg) and thyroid peroxidase (TPO) and promotes synthesis of thryroid hormones (THs). The first step in the TH synthesis is trapping of iodine through transport channels [67] in thyroid follicular cells is important step for synthesis of THs.

This step is followed by the action of thyroid peroxidise which couples tyrosine residues to iodine ions to form thyroglobulin iodination. Secondly, the converted form of iodine is incorporated into tyrosine residues of noniodinated 660-kDa glycoprotein Tg at either position 3 or 5 on phenolic ring forming 3-monoiodotyrosine (MIT) or 5-diiodotyrosine (DIT), respectively. Thus, for thyroglobulin iodination, tyrosine and iodine act as building blocks. Moreover, the action of TPO favors coupling of the iodinated phenol of one iodotyrosine residue to the phenol hydroxyl group of another residue leading to two possible

conjugations; MIT + DIT and DIT + DIT which forms T3 and T4, respectively. After synthesis, the iodinated components are stored in the form of colloids within the lumen of thyroid follicular cells, which are later released into the circulation by a process known as endocytosis. The majority of released THs consist of T4 as total serum concentration of T4 is 40-fold higher than that of serum T3. These hormones are transported by carrier proteins to target tissues.

THs and Male Reproductive Health: Male reproductive tract is one of the target tissues of THs. The role of thyroid hormones in the regulation of physiological processes is well acknowledged. They play a vital role in the regulation of metabolism, bone remodelling, cardiac function and mental status and reproduction and development [27].

Therefore, the homeostasis of normal thyroid function is considered for the organism's wellbeing to sustain normal physiological functions. During fetal development, thyroid hormones are key regulators of brain development and any disturbances at this level could lead to improper development and differentiation of nervous system [68].

It is worth to mention that the developmental aspects of fetus during first half of pregnancy at least in part depend on maternal thyroid hormones. Therefore, any disturbances at this stage might have serious consequences on developing fetus and the symptoms may persist later in life [69]. The major thyroid hormones are 3,5,3',5'-tetraiodothyronine (thyroxine; T4) and 3,5,3'-triiodothyronine (T3). The biological active form of thyroid hormones is T3 which are key regulators of metabolism and development and are known to have pleiotropic effects in different organs including male reproductive tract [70]. The role of T3 in the regulation of male reproductive tract functions is well documented [70-72]. T3 through its cognate receptors control the regulation of maturation and growth of testis, Sertoli cell and Leydig cell functions [27]. Studies of Sarkar *et al.* [73] indicated that thyroid hormone levels are critical for the normal development of testis during early life stages. In rat models, congenital hypothyroidism has been linked to improper Sertoli cell proliferation and differentiation [74]. Further, it has been shown that disturbances in THs causes several male reproductive abnormalities such as reduced weights of testis and accessory sex organs which are androgen dependent, reduced testosterone biosynthetic pathway thereby reduced circulatory levels of testosterone (at the level of Leydig cells), improper spermatogenesis due to disorganization of seminiferous tubule thereby reduced sperm count (at the level of germ cells and Sertoli cells), disrupted epididymal functions thereby improper sperm maturation events including sperm motility, reduces androgen expression levels, enhances testicular and epididymal oxidative stress through disruption of pro- and anti-oxidant homeostasis and induces apoptosis at the level of testis and epididymis and alter thyroid receptors, which perform genomic actions of thyroid hormones [16, 70, 75-78].

THDCs and Male Reproduction: THDCs are one of the endocrine disrupting chemicals that can able to interfere with thyroid hormone production or block their receptors by mimicking like thyroid hormones and/or both.

THDCS exhibit three properties to cause thyroid hormone disruption: a) mimicking or antagonizing the thyroid hormones, b) targeting the thyroid glands thereby synthesis and/or metabolism of hormones and c) altering thyroid hormone-thyroid receptor interactions and modulate regulation of gene expression in target cells. Thus, THDCS affects all most all aspects of TH synthesis, transport, metabolism and/or its actions including male reproduction [68] **Fig. 2.**

Antithyroid drugs (ATDs) are widely used in the management of thyroid disorders or to control thyroid hormone levels before surgery. There are three commonly used antithyroid drugs: methimazole (MMI) and carbimazole (CBZ) or derivatives of thiourea-propylthiouracyl preparation (PTU). All these ATDs acts at the level of the thyroid gland thereby inhibit thyroid hormone synthesis. PTU is one of the ATD that blocks the synthesis of new thyroid hormone synthesis through the inhibition of thyroid peroxidase thereby inhibits formation of DIT and MIT. Further, PTU also inhibits the peripheral conversion of T4 to T3, which is performed by

deiodenases and also effects thyroid hormone reserves in the existing thyroid gland or in the circulation [79]. MMI and CBZ acts at the level of thyroid peroxidase thereby inhibits coupling of iodination of tyrosine residues in tyroglobulin. This step leads to inhibition of T4 and T3 synthesis. Further, MMI also interfere with the oxidation of iodide ions which is required for the iodotyrosyl formation [80].

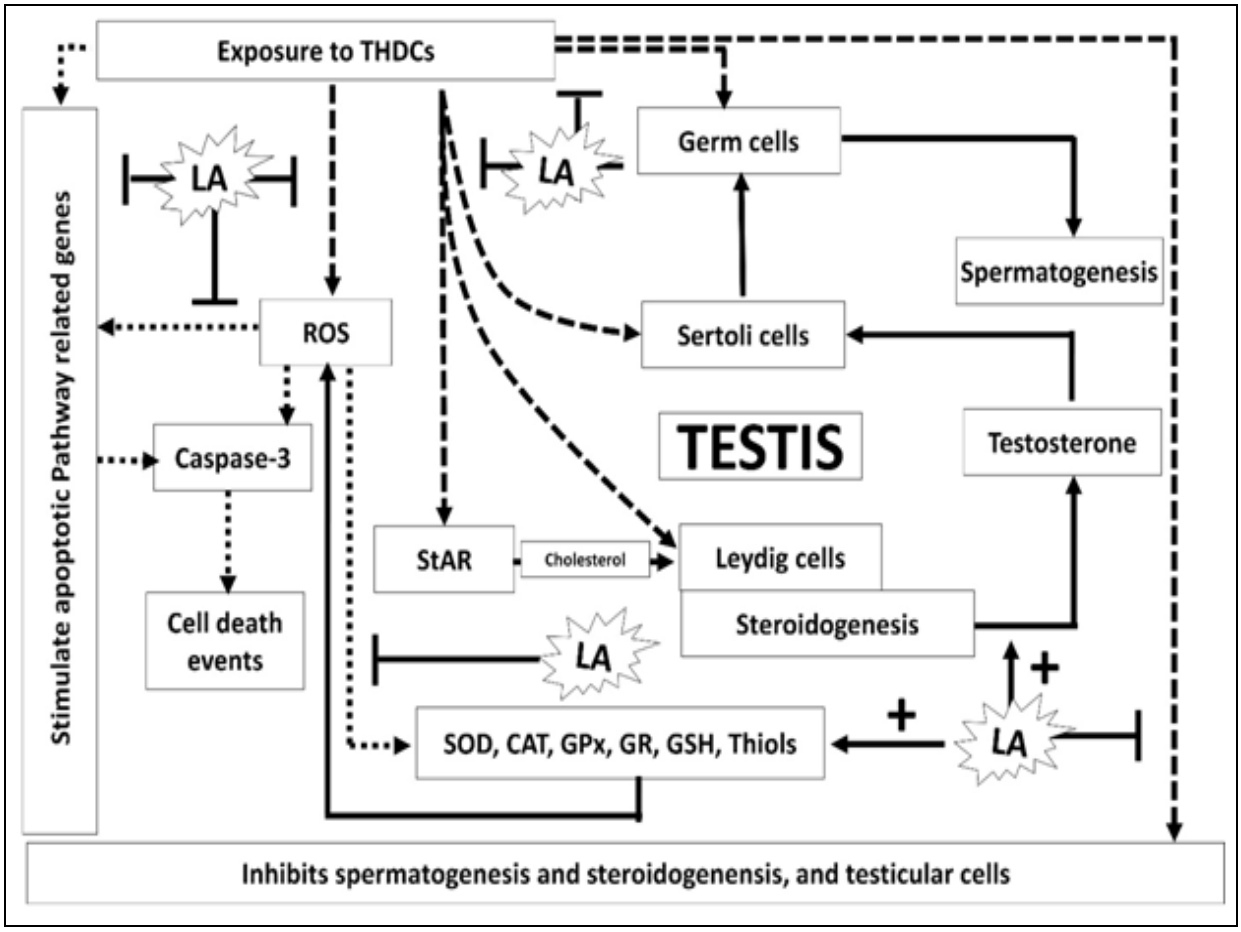

FIG. 2: ILLUSTRATES THE EFFECT OF LIPOIC ACID ON MALE REPRODUCTIVE HEALTH IN RATS EXPOSED TO THYROID HORMONE DISRUPTING CHEMICALS (THDCS). DOTTED LINES: REACTIVE OXYGEN SPECIES (ROS) MEDIATED PATHWAYS. ROS GENERATION TRIGGERS CASPASE-3 ACTIVATION THEREBY CELL DEATH OF TESTICULAR CELLS. BLUE LINES: NORMAL TESTICULAR FUNCTIONS. BROKEN LINES: EXPOSURE TO THDCS NEGATIVELY TARGETS TESTICULAR FUNCTIONS THROUGH MULTIPLE MECHANISMS, EITHER DIRECTLY AT THE TISSUE LEVEL OR INDIRECTLY THROUGH ROS. EXPOSURE TO THDCS INTERFERES WITH TESTICULAR TRANSCRIPTOME THEREBY TRIGGERS GENES ASSOCIATED WITH APOPTOSIS (CASPASE-3 ACTIVATION) AND DEREGULATES GENES ASSOCIATED WITH SPERMTAOGNESIS AND STEROIDOGENESIS THEREBY CAUSES MALE INFERTILITY. LA PROTECTS MALE REPRODUCTIVE HEALTH VIA ITS ANTIOXIDANT, ANTI-APOPTOTIC OR STEROIDOGENIC ABILITIES. SUPPLEMENTATION OF LA DIRECTLY OR INDIRECTLY STIMULATES ENZYMATIC AND NON-ENZYMATIC ANTIOXIDANTS, SCAVENGES ROS IN THE TESTIS OR INHIBITS APOPTOTIC SIGNALLING THEREBY CASPASE-3 ACTIVITY IN THE TESTIS AND/OR BOTH. THESE EVENTS COULD LEAD TO LA MEDIATED PROTECTION AT THE LEVEL OF TESTIS, EPIDIDYMIS AND SPERM

These drugs are widely used during pregnancy to control hyperthyroidism [81] and other clinical issues such as nephrotoxicity, hepatotoxicity, acute pancreatitis, neurotoxicity, thyroid carcinoma and testicular toxicity [82-87]. Though promising, the use of ATDs in pregnant women is of major concern as these drugs can readily cross placenta and interfere with the fetal development [88, 89]. The thyroid hormones are not only important to sustain developing fetus but also provide additional support in terms of thyroid hormone levels after birth of the offspring [89]. Further, it has been shown that during pregnancy, PTU therapy led to congenital hypothyroidism as indicated by 25% transient neonatal hypothyroidism [90]. Animal studies have shown that the administration of

ATDs such as PTU, MMI and CBZ during critical window periods such as prenatal, perinatal periods interferes with the male reproductive tract development thereby adversely affect its functions such as spermatogensis and steroidogenesis later in life [32, 37, 75, 91-95].

α-lipoic Acid and Male Reproduction: The therapeutic efficacy of antioxidants in the management of oxidative stress-induced testicular damage is an emerging area of reproductive toxicology. α-lipoic acid (LA;1,2, dithiolane-3-pentanoic acid: **Fig. 3** is an essential cofactor for several enzymes [35] and also exhibits antioxidant properties [36].

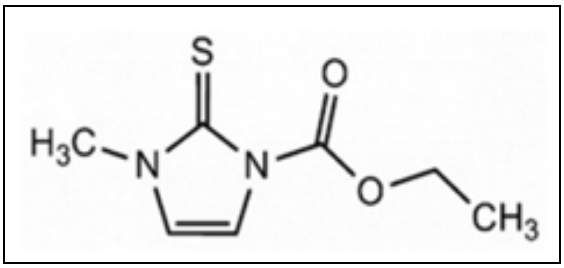

FIG. 3: CHEMICAL STRUCTURE OF ALPHA LIPOIC ACID

It can able to cross cell membranes and quench the free radicals through its redox couple, di-hydrolipoic acid (DHLA) directly by scavenging excess generation of free radicals or indirectly *via* maintaining endogenous enzymatic antioxidants such as superoxide dismutase, catalase, glutathione peroxidase or and non-enzymatic antioxidants such as α-tocopherol, ascorbate, glutathione and/or both [96-98]. The therapeutic efficacy of LA against several disorders such as diabetic neuropathy, alzheimers disease, cancer, obesity, disorders like schizophernia, and disorders of central nervous system such as multiple sclerosis is gaining importance in the field of biomedicine [36].

Thus, LA exerts its role as anti-diabetic and anti-cancerous agent [99-101]. The anticancerous properties of LA ROS mediated cell death in lung cancer [102], breast cancer [103, 104], and colon cancer [105, 106]. At the molecular level, LA can able to block the migration and invasion of metastatic breast cancer cells through ERK1/2 and AKT signalling pathway[107]. Human studies indicated that LA ameliorates endothelial functions in subclinical hypothyroidism patients [108]. Studies of Jung *et al.* [109] reported that pre-treatment of LA is beneficial in protecting thyroid gland from radiation-induced oxidative damage in rats. The beneficial effects of α-lipoic acid against a range of testicular toxicants **Fig. 2** including pharma drugs and environmental pollutants attracted the attention of scientific community and in particular, reproductive toxicologists. In a previous study, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin induced deteriorated testosterone biosynthesis was ameliorated by LA supplementation in male fetuses (gestation day 20) of dams exposed to dioxin [110]. Previously, it has been shown that LA can able to cross blood-brain barrier thereby ameliorates testosterone levels in rats exposed to 2, 3, 7, 8-tetrachrolodibenzo-*p*-dioxin prenatally [110].

Steroidogenic acute regulatory proteins (StAR) play an important role in the channelling of cholesterol into the testis across the outer and inner membranes of the testis. This step is followed by a cascade of reactions by testicular steroidogenic enzymes including 3β- and 17β-hyrdoxysteroid dehydrogenases (HSDs) which are involved in the conversion of cholesterol to testosterone.

In addition, the ameliorative effects of supplementation of LA against the deteriorative effects of pharma drugs such as cyclophosphamide [111], adriyamycin [112] and testicular toxicants such as bisphenol A [113], cadmium [114], arsenic [38], 4-tert-octylphenol[115], araclor1260 [116], acrylamide [40], di-(2etthylhexyl)-pthalate [117] methotrexate [44], ornidazole [118] and radiation [119] on testicular spermatogenesis and steroidogenesis in animal models have been reported. Mechanisms underlying male reproductive toxicity induced by chemicals occur *via* multiple routes; either they act at the level of antioxidant status or altering transcriptome and/or both.

It is well established that the oxidative stress is one of the major pathological factors for the deterioration of male fertility. The excess generation of free radicals not only attack male reproductive tract system and its functions but also deteriorate several sperm maturation events including reduced sperm motility, degradation of sperm DNA and reduced sperm capacitation events [72]. In cellular systems, a critical balance between the oxidant and antioxidants is considered important for normal biological framework.

With respect to male reproduction proper maintenance of antioxidant system is required for normal spermatogenesis. However, during oxidative stress conditions, excess generation of free radicals such as reactive oxygen species (ROS) attack the spermatogenesis and its maturation events thereby deteriorate sperm-mediated fertility.

This effect of ROS on deterioration of sperm functions may be attributed to different levels: a) at the level of testis or b) at the level of epididymis or c) at the level of sperm or a, b, and c. Testicular cells, Sertoli cells and Leydig cells mediate spermatogenesis and steroidogensis, respectively.

The metabolism in the testis leads to ROS and during normal conditions, the enzymatic (superoxide dismutase, catalase, glutathione based enzymes) and non-enzymatic (reduced glutathione, ascorbate, α-tocopherol) antioxidants mitigate the excess generation of free radicals in the testis. However, during pathological conditions, the excess generation of ROS can able to induce oxidative damage to the testis and also attacks the sperm plasma membrane, which is being rich in polyunsaturated fatty acids. On the other hand, epididymis is an important reproductive organ where the maturation event of sperm takes place.

Therefore, ROS attack at this level could lead to deterioration of DNA integrity of sperm associated with loss of sperm capacitation events. Therefore, excess generation of ROS negatively targets both spermatogenesis and its fertilizing capability [33, 72, 120, 121].

The therapeutic efficacy of antioxidants in the management of oxidative stress-induced testicular damage is an emerging area of reproductive toxicology. Many studies indicated that antioxidant therapy could ameliorate deteriorated testicular functions against wide range chemicals including pharmaceutical chemicals and or environmental toxicants with endocrine disrupting activities [33]. Among the antioxidants, supplementation of α-Lipoic acid (LA) in reducing testicular oxidative stress is well appreciated [38, 45].

The shielding effects of LA on testis and cauda epididymis against oxidative damage-induced Sertoli- and Leydig cell toxicity, reduced sperm motility, reduced sperm DNA damage, disrupted testicular and caudaepididymal structural integrity *via* enhancement of superoxide dismutase (SOD), and catalase (CAT) and restoration of glutathione system has been demonstrated [115-117, 122-124]. The positive role of GSH (reduced glutathione) GSH synthesis enzymes have been reported. Studies have shown that GSH synthesis includes two sub-units: glutamate-cysteine ligase modifier subunit and the glutamate-cysteine catalytic subunit and LA-mediated regulation of these two subunits could be one of the plausible role of LA-mediated GSH synthesis in the cellular system [125, 126]. Reports have shown that LA supplementation postnatally ameliorated SOD and GSH in hypothalamus of arsenic exposed rats [127].

As an antioxidant with its direct quenching efficacy of nictotine induced excess generation of free radicals showed protective effects on oocytes and embryos retrieved from mice [128] and gene knocking studies of lipoic acid synthase gene lead to the mortality in the foetuses of mice [129], suggesting the importance of LA during critical phases of development. These studies reflect that LA protects testis and its functions against a broad spectrum of insults where oxidative stress is part of the underlying etiology. Eventually, LA has become one of the widely used antioxidants against chemical-induced testicular toxicity [98].

Testicular antioxidant status has also been evaluated in animal models in response to ATDs. Interestingly, perinatal exposure to PTU and/or neonatal exposure to MMI also resulted in oxidative stress characterized by reduced antioxidant capacity as well as disrupted architecture of testis tissue in rats [130, 131]. Studies of Sakr *et al.* [86] demonstrated that oxidative stress and reactive oxygen species play an important role in the pathogenesis of carbimazole-induced testicular toxicity in adult rats. Our previous study [37] indicated that the embryonic exposure to CBZ resulted in sperm DNA fragmentation associated with disruption of pro- and anti-oxidant balance in the testis of rats at their adulthood.

LA supplementation on the other hand, restored suppressed testicular antioxidant status in CBZ exposed rats as evidenced by increased activity levels of SOD, CAT, GPx and GR and GSH with a reduction in the lipid peroxidation levels. Thus, LA

mediated antioxidant effects against testicular oxidative damage in CBZ exposed rats might be one of the attributable factors to negate the toxic effects of oxidative damage.

Other studies also indicated that the supplementation of LA during developmental stages also restore toxic effects of chemicals that harm brain. For example, Studies of Dixit *et al.* [127] and Shirpoor *et al.* [132] concluded that LA treatment ameliorated GSH and SOD in hippocampus of arsenic and catalase activity in different brain regions of rats exposed to ethanol, respectively. Molecular events in a precise manner are one of the key factors for proper testicular functions. Previously, a positive correlation have been proposed between the antithyroid drugs and oxidative stress induced caspase 3 levels [37].

On the other hand, the anti-apoptotic properties of LA *in-vitro* and *in-vivo* are well documented [133, 134]. Previous studies have shown that LA mediated antiapoptotic effects were mediated by maintaining optimal ratio between *bcl*-2 expression and reduced *bax* expression in the testis of rats [41] and also at the level of NF-*kB* signalling pathway [135].

Triggering activity of caspase-3 is believed to be one of the downstream events associated with the oxidative stress-induced apoptosis [136] and LA supplementation mitigated the caspase-3 mediated oxidative stress in arsenic exposed rats [107].

Antioxidant response elements binds with nrf2 (gene: *Nrf2* or nuclear factor erythroid related factor 2 like 2) thereby activates antioxidant enzymes is believed to be important for antioxidant responses towards the oxidative stress [137]. LA supplementation induced up regulation of Nrf2 gene and enhanced antioxidant status and inhibition of caspase 3 mediated oxidative stress in rodents [138, 139].

Androgen stimulation and spermatogenesis are mainly controlled and coordinated by two gonadotropins, FSH and LH, wherein sustain the Sertoli cell and the Leydig cell functions, respectively through their cognate receptors, follicle stimulating hormone receptor (FSHR; gene: *fshr*) and leutinizing hormone/chorionic gonadotropin receptors (LHCGR; gene: *lhcgr*). Interestingly, LH seems to be regulated by THs [140].

Significant up regulation of *fshr* and *lhcgr* genes have been reported *in-vitro* cultured bovine preantral follicles in the presence of LA [141]. Previously, studies of Koga *et al.* [110] and Takeda *et al.* [142] have shown that LA supplementation resulted in the circulatory levels of both FSH and LH in rats exposed to dioxins. Androgen receptors (AR; gene: *ar*) are nuclear receptors comprising of two important domains: DNA binding domain and ligand binding domain [143]. Earlier, it has been shown that neonatal testicular mitochondria of rats [130]. The pleiotropic roles of insulin like growth factor binding protein-3, (IGFBP3; gene: *igfbp3*) is well studied [144].

A possible link between the IGFBP3 mediated testicular germ cell death expression of *igfbp3* and oxidative stress has been demonstrated [145], while LA supplementation inhibited the IGFBP3 mediated death of testicular germ cells in ivermectin treated rats [146] and the protective effects have been correlated to the antioxidant properties of LA. Our studies also suggested that the embryonic exposure to CBZ deteriorated male fertility efficacy as indicated by reduced fertility index, pre- and post-implantation loss in females cohabited with CBZ expose males [37].

Surprisingly, our results also demonstrated that the LA supplementation improved sperm fertilizing ability in CBZ exposed rats and could be ascribed to the shielding effects of LA against testis, which eventually, restored spermatogenesis and testosterone biosynthesis.

CONCLUSION: In conclusion, the present review highlighted the thyroid disrupting chemicals including antithyroid drugs and their effect(s) on male reproduction especially during developmental stages. Further, the present review also emphasizes the role of lipoic acid against the testicular toxicants in general and CBZ-induced testicular toxicity in rats at their adulthood in particular. Though, most of the protective effects of α-lipoic acid on male reproductive health against testicular toxicants have been ascribed to the antioxidant properties, little or few studies projected the molecular effects of lipoic acid.

This area seems to be one of the major gaps and this review provides valuable information about the

molecular studies involving lipoic acid and male reproduction in experimental models treated with THDCs. Further, male fertility efficacy is a coordinated parameter of testicular spermatogenesis and steroidogenesis associated with other critical functions of epididymis and accessory sex organs. Thus, to develop strategies using α-lipoic acid as a protective agent to sustain male reproductive health, multifactorial approaches including molecular level factors should be addressed in addition to antioxidant properties.

ACKNOWLEDGEMENTS: The authors Prof. A. Dinakara Rao, Department of Bioinformatics, Pondicherry University, Pondicherry - 605014 for his motivation and encouragement.

CONFLICT OF INTEREST: Nothing to disclose

REFERENCES:

1. Mammadov E, Uncu M and Dalkan C: High prenatal exposure to bisphenol a reduces anogenital distance in healthy male newborns. Journal of Clinical Research in Pediatric Endocrinology 2018; 10: 25-29.
2. Rolfo A, Nuzzo AM, De Amicis R, Moretti L, Bertoli S, and Leone A: Fetal-Maternal Exposure to Endocrine Disruptors: Correlation with Diet Intake and Pregnancy Outcomes. Nutrients 2020; 12: 1744.
3. Haraux E, Tourneux P, Kouakam C, Stephan-Blanchard E, Boudailliez B, Leke A, Klein C and Chardon K: Isolated hypospadias: the impact of prenatal exposure to pesticides, as determined by meconium analysis. Environment International 2018; 119: 20–25.
4. Warembourg C, Botton J, Lelong N, Rouget F, Khoshnood B, Le Gléau F, Monfort C, Labat L, Pierre F, Heude B, Slama R, Multigner L, Charles MA, Cordier S and Garlantézec R: Prenatal exposure to glycol ethers and cryptorchidism and hypospadias: a nested case–control study. Occupational and Environmental Medicine 2018; 75: 59–65.
5. Schwartz CL, Christiansen S, Vinggaard AM, Axelstad M, Hass U and Svingen T: Anogenital distance as a toxicological or clinical marker for fetal androgen action and risk for reproductive disorders. Archives of Toxicology 2019; 93: 253–272.
6. Yilmaz B, Terekeci H, Sandal S and Kelestimur F: Endocrine disrupting chemicals: exposure, effects on human health, mechanism of action, models for testing and strategies for prevention. Reviews Endocrine and Metabolic Disorders 2020; 21: 127-147.
7. Rodprasert W, Main KM, Toppari J and Virtanen HE: Associations between male reproductive health and exposure to endocrine-disrupting chemicals. Current Opinion in Endocrine and Metabolic Research 2019; 7: 49–61.
8. Fénichel P, Chevalier N, Lahlou N, Coquillard P, Wagner-Mahler K, Pugeat M, Panaïa-Ferrari P and Brucker-Davis F: Endocrine disrupting chemicals interfere with leydig cell hormone pathways during testicular descent in idiopathic cryptorchidism. Frontiers in Endocrinology (Lausanne) 2019; 9: 786.
9. Braga LH, Lorenzo AJ and Romao RLP: Canadian urological association-pediatric urologists of canada (cua-puc) guideline for the diagnosis, management, and follow-up of cryptorchidism. Canadian Urological Association Journal 2017; 11: 251-260.
10. Cheng L, Albers P, Berney DM, Feldman DR, Daugaard G, Gilligan T and Looijenga LHJ: Testicular cancer. Nature Reviews Disease Primers 2018; 4: 29.
11. Lauretta R, Sansone A, Sansone M, Romanelli F and Appetecchia M: Endocrine Disrupting Chemicals: Effects on Endocrine Glands. Front Endocrinol (Lausanne). 2019; 10: 178.
12. Auger J, Eustache F, Chevrier C and Jegou B: Spatiotemporal trends in human semen quality. Nature Reviews Urology 2022; 19: 597–626.
13. Mishra P, Negi PSM, Srivastava M, Singh K and Rajender S: Decline in seminal quality in Indian men over the last 37 years. Reproductive Biology and Endocrinology 2018; 16: 103.
14. Bold J and Swinburne D: Pre-Conceptual Guidelines for Men: A Review of Male Infertility Experience, including Nutrition and Lifestyle Factors. Dietetics 2022; 1: 164-181.
15. Sengupta P, Borges E, Dutta S and Krajewska-Kulak E: Decline in sperm count in European men during the past 50 years. Human and Experimental Toxicology 2018; 37: 247-255.
16. Cannarella R, Condorelli RA, Gusmano C, Barone N, Burrello N, Aversa A, Calogero AE and La Vignera S: Temporal Trend of Conventional Sperm Parameters in a Sicilian Population in the Decade 2011-2020. Journal of Clinical Medicine 2021; 10(5): 993.
17. Kumar N and Singh AK: Impact of environmental factors on human semen quality and male fertility: a narrative review. Environmental Sciences Europe 2022; 34: 6.
18. Ravanos K, Petousis S, Margioula-Siarkou C, Papatheodorou A, Panagiotidis Y, Prapas N and Prapas Y: Declining Sperm Count or Rather Not? A Mini Review. Obstetrical and Gynecological Survey 2018; 73(10): 595-605.
19. Rodprasert W, Virtanen HE, Sadov S, Perheentupa A, Skakkebaek NE, Jørgensen N and Toppari J: An update on semen quality among young Finnish men and comparison with Danish data. Andrology 2019; 7(1): 15-23.
20. Dupesh S, Pandiyan N, Pandiyan R, Kartheeswaran J and Prakash B: Ejaculatory abstinence in semen analysis: does it make any sense. Therapeutic Advances in Reproductive Health 2020; 14.
21. Kumar N, Choudhari AR and Singh AK: Prevalence of male factors infertility in last ten years at a rural tertiary care centre of central India: A Retrospective analysis. Indian Journal of Obstetrics and Gynecology Research 2015; 2(3): 132-136.
22. Wang L, Zhang L, Song XH, Zhang HB, Xu CY and Chen ZJ: Decline of semen quality among Chinese sperm bank donors within 7 years (2008-2014) Asian Journal of Andrology 2017; 19: 521–525.
23. Oliveira KJ, Chiamolera MI, Giannocco G, Cabanelas Pazos-Moura C and Carvalho TMO: Thyroid function disruptors: from nature to chemicals. Journal of Molecular Endocrinology 2019; 62: 1–19.
24. Qian Y, Shao H, Ying X, Huang W and Hua Y: The Endocrine Disruption of Prenatal Phthalate Exposure in Mother and Offspring. Frontiers in Public Health 2020; 8: 366.
25. Hall C, Hansen J, Olsen J, He D, Von Ehrenstein OS, Ritz B and Heck JE: Parental occupation and childhood germ

cell tumors: a case–control study in Denmark, 1968–2016. Cancer Causes Control 2021; 32: 827–836.
26. Olsson A, Togawa K, Schüz J, Le Cornet C, Fervers B, Oksbjerg Dalton S, Pukkala E, Feychting M, Erik Skakkebæk N and Hansen J: Parental occupational exposure to solvents and heavy metals and risk of developing testicular germ cell tumors in sons (NORDTEST Denmark). Scandinavian Journal of Work, Environment and Health 2018; 1: 658-669.
27. Hernandez A and Martinez ME: Thyroid hormone action in the developing testis: intergenerational epigenetics. Journal of Endocrinology 2020; 244(3): 33-46.
28. Martinez ME, Lary CW, Karaczyn AA, Griswold MD and Hernandez A: Spermatogonial Type 3 Deiodinase Regulates Thyroid Hormone Target Genes in Developing Testicular Somatic Cells. Endocrinology 2019; 160: 2929–45.
29. Anselmo J, Scherberg NH, Dumitrescu AM and Refetoff S: Reduced Sensitivity to Thyroid Hormone as a Transgenerational Epigenetic Marker Transmitted Along the Human Male Line. Thyroid 2019; 29: 778–782.
30. Hernandez A: Thyroid Hormone Deiodination and Action in the Gonads. Current Opinion in Endocrine and Metabolic Research 2018; 2: 18–23.
31. Hernandez A: Thyroid Hormone Role and Economy in the Developing Testis. Vitamins and Hormones 2018; 106: 473–500.
32. Nittoli V, Colella M, Porciello A, Reale C, Roberto L, Russo F, Russo NA, Porreca I, De Felice M and Mallardo M: Multi Species Analyses Reveal Testicular T3 Metabolism and Signalling as a Target of Environmental Pesticides. Cells 2021; 10: 2187.
33. Asadi N, Bahmani M, Kheradmand A and Rafieian-Kopaei M: The impact of oxidative stress on testicular function and the role of antioxidants in improving it: A Review. Journal of Clinical and Diagnostic 2017; 11: 01-05.
34. Chainy GBN and Sahoo DK: Hormones and oxidative stress: an overview, Free Radical Research 2020; 54: 1-26.
35. Molz P and Schröder N: Potential Therapeutic Effects of Lipoic Acid on Memory Deficits Related to Aging and Neurodegeneration. Frontiers Pharmacology 2017; 8: 849.
36. Salehi B, Berkay Yılmaz Y, Antika G, Boyunegmez Tumer T, Fawzi Mahomoodally M, Lobine D, Akram M, Riaz M, Capanoglu E, Sharopov F, Martins N, Cho WC, and Sharifi-Rad J: Insights on the Use of α-Lipoic Acid for Therapeutic Purposes. Biomolecules 2019; 9(8): 356.
37. Prathima P, Venkaiah K Pavani R, Daveedu T, Munikumar M, Gobinath M, Valli M and Sainath SB: α-Lipoic acid inhibits oxidative stress in testis and attenuates testicular Toxicity in in rats exposed to carbimazole during embroyonic period. Toxicology Report 2017; 4: 373-381.
38. Prathima P, Pavani R, Sukeerthi S and Sainath SB: α-Lipoic acid inhibits testicular and epididymal oxidative damage and improves fertility efficacy in arsenic-intoxicated rats. Journal of Biochemical and Molecular Toxicology 2018; 32(2).
39. Kaur D, Behl T, Sehgal A, Singh S, Sharma N, Chigurupati S, Alhowail A, Abdeen A, IbrahimSF, Vargas-De-La-Cruz C, Sachdeva M, Bhatia S, Al-Harrasi A and Bungau S: Decrypting the potential role of α-lipoic acid in Alzheimer's disease. Life Sciences 2021; 284: 119899.
40. Lebda M, Gad S and Gaafar H: Effects of lipoic acid on acrylamide induced testicular damage. Material Socio Medica 2014; 26: 208–212.
41. Jana K, Dutta A, Chakraborty P, Manna I, Firdaus SB, Bandyopadhyay D, Chattopadhyay R and Chakravarty B: Alpha-lipoic acid and N-acetylcysteine protects intensive swimming exercise-mediated germ-cell depletion, pro-oxidant generation, and alteration of steroidogenesis in rat testis. Molecular Reproduction and Development 2014; 81: 833-850.
42. Gules O and Eren U: Protective role of alpha lipoic acid against polychlorobiphenyl (Aroclor 1254)-induced testicular toxicity in rats. Romanian Journal of Morphology and Embryology 2016; 57: 451–459.
43. Shaygannia E, Tavalaee M, Akhavanfarid GR, Rahimi M, Dattilo M and Nasr-Esfahani MH: Alpha-Lipoic acid improves the testicular dysfunction in rats induced by varicocele. Andrologia 2018; 50: 13085.
44. Pinar N, Çakırca G, Özgür T and Kaplan M: The protective effects of alpha lipoic acid on methotrexate induced testis injury in rats. Biomedicine and Pharmacotherapy 2018; 97: 1486-1492.
45. Najafi M, Cheki M, Amini P, Javadi A, Shabeeb D and Eleojo Musa A: Evaluating the protective effect of resveratrol, Q10, and alpha-lipoic acid on radiation-induced mice spermatogenesis injury: A histopathological study. International Journal of Reproductive Biomedicine (Yazd) 2019; 17: 907-914.
46. Wang JM, Li ZF, Yang WX and Tan FQ: Follicle-stimulating hormone signaling in Sertoli cells: a licence to the early stages of spermatogenesis. Reproductive Biology and Endocrinology 2022; 20: 97.
47. Oduwole OO, Peltoketo H and Huhtaniemi IP: Role of follicle-stimulating hormone in spermatogenesis. Frontiers in Endocrinology 2018; 9: 763.
48. D'Cruz SC, Vaithinathan S, Jubendradass R and Prakash Mathur P: Effects of plants and plant products on the testis. Asian Journal of Andrology 2010; 12: 468–479.
49. Orlowski M and Sarao MS: Physiology, Follicle Stimulating Hormone. In: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing 2023.
50. Takashima S: Biology and manipulation technologies of male germline stem cells in mammals. Reproductive Medicine and Biology 2018; 17(4): 398-406.
51. Santi D, Crépieux P, Reiter E, Spaggiari G, Brigante G, Casarini L, Rochira V and Simoni M. Follicle-stimulating Hormone (FSH) Action on Spermatogenesis: A Focus on Physiological and Therapeutic Roles. Journal of Clinical Medicine 2020; 9(4): 1014.
52. Victor E, Osarugue I, Mega Obukohwo O, Eze Kingsley N and Alexander Obidike N: Endocrine Functions of the Testes. Intech Open 2022;
53. Fénichel P, Chevalier N, Lahlou N, Coquillard P, Wagner-Mahler K, Pugeat M, Panaïa-Ferrari P and Brucker-Davis F: Endocrine Disrupting Chemicals Interfere With Leydig Cell Hormone Pathways During Testicular Descent in Idiopathic Cryptorchidism. Frontiers in Endocrinology (Lausanne) 2019; 9: 786.
54. Zirkin BR and Papadopoulos V: Leydig cells: formation, function, and regulation, Biology of Reproduction 2018; 99(1): 101–111.
55. Ivell R, Anand-Ivell R and Morley SD: Endocrinology of the Fetal Testis. In: Simoni, M., Huhtaniemi, I. (eds) Endocrinology of the Testis and Male Reproduction. Endocrinology. Springer, Cham 2017.
56. Sèdes L, Thirouard L, Maqdasy S, Garcia M, Caira F, Lobaccaro JA, Beaudoin C and Volle DH: Cholesterol: A Gatekeeper of Male Fertility? Front Endocrinol (Lausanne) 2018; 9: 369.

57. Källsten L, Almamoun R, Pierozan P, Nylander E, Sdougkou K, Martin JW and Karlsson O: Adult Exposure to Di-N-Butyl Phthalate (DBP) Induces Persistent Effects on Testicular Cell Markers and Testosterone Biosynthesis in Mice. International Journal of Molecular Sciences 2022; 23(15): 8718.
58. Lundgaard Riis M, Matilionyte G, Nielsen JE, Melau C, Greenald D, Juul Hare K, Langhoff Thuesen L, Dreisler E, Aaboe K, Brenøe PT, Andersson AM, Albrethsen J, Frederiksen H, Rajpert-De Meyts E, Juul A, Mitchell RT and Jørgensen A: Identification of a window of androgen sensitivity for somatic cell function in human fetal testis cultured *ex-vivo*. BMC Medicine 2022; 20(1): 399.
59. Selvaraj V Stocco DM and Clark BJ: Current knowledge on the acute regulation of steroidogenesis. Biology of Reproduction 2018; 99(1): 13–26.
60. Flück CE and Pandey AV: Testicular Steroidogenesis. In: Simoni M, Huhtaniemi I: (eds) Endocrinology of the Testis and Male Reproduction. Endocrinology Springer Cham 2017.
61. Tugaeva KV, Titterington J, Sotnikov DV, Maksimov EG, Antson AA and Sluchanko NN: Molecular basis for the recognition of steroidogenic acute regulatory protein by the 14-3-3 protein family. Federation of European Biochemical Societies Journal 2020; 287: 3944-3966.
62. Meinsohn MC, Smith OE, Bertolin K and Murphy BD. The Orphan Nuclear Receptors Steroidogenic Factor-1 and Liver Receptor Homolog-1: Structure, Regulation, and Essential Roles in Mammalian Reproduction. Physiological Review 2019; 99(2): 1249-1279.
63. Barbagallo F, Condorelli RA, Mongioì LM, Cannarella R, Aversa A, Calogero AE and La Vignera S: Effects of Bisphenols on Testicular Steroidogenesis. Frontiers in Endocrinology (Lausanne) 2020; 11: 373.
64. Lawrence BM, O'Donnell L, Smith LB and Rebourcet D: New Insights into Testosterone Biosynthesis: Novel Observations from HSD17B3 Deficient Mice. International Journal of Molecular Sciences 2022; 23: 15555.
65. Gu X, Li SY, Matsuyama S and DeFalco T: Immune Cells as Critical Regulators of Steroidogenesis in the Testis and Beyond. Frontiers in Endocrinology (Lausanne) 2022; 13: 894437.
66. Sainath SB, André A, Castro LFC and Santos MM: The evolutionary road to invertebrate thyroid hormone signalling: Perspectives for endocrine disruption processes. Comparative Biochemistry Physiology C Toxicology and Pharmacology 2019: 223: 124-138.
67. Feldt-Rasmussen U, Effraimidis G and Klose M: The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Molecular and Cellular Endocrinology 2021; 525: 111173.
68. Boas M, Feldt-Rasmussen U and Main KM: Thyroid effects of endocrine disrupting chemicals. Molecular and Cellular Endocrinology 2012; 355: 240-248.
69. Moog NK, EntringerS, Heim C, Wadhwa PD, Kathmann N and Buss C: Influence of maternal thyroid hormones during gestation on fetal brain development. Neuroscience 2017; 342: 68-100.
70. Alahmar A, Dutta S and Sengupta P: Thyroid hormones in male reproduction and infertility. Asian Pacific Journal of Reproduction 2019; 8: 203-210.
71. La Vignera S and Vita R: Thyroid dysfunction and semen quality. International Journal of Immunopathology and Pharmacology 2018; 32.
72. Kumar A, Shekhar S and Dhole B: Thyroid and male reproduction. Indian Journal of Endocrinology and Metabolism 2014; 18: 23-31.
73. Sarkar D and Singh SK: Inhibition of testicular steroidogenesis and impaired differentiation of Sertoli cells in peripubertal mice offspring following maternal exposure to BDE-209 during lactation suppress germ cell proliferation. Toxicology Letters 2018; 290: 83-96.
74. Lara NLM and França LR: Neonatal hypothyroidism does not increase Sertoli cell proliferation in inos -/- mice. Reproduction 2017; 154: 13-22.
75. Anbalagan A, Sashi AM, Vengatesh G, Stanley JA, Neelamohan R and Aruldhas MM: Mechanism underlying transient gestational onset hypothyroidism-induced impairment of post testicular sperm maturation in adult rats. Fertility and Sterility 2010; 193: 24-2497.
76. Romano RM, Gomes SN, Cardoso NC, Schiessl L, Romano MA and Oliveira CA: New insights for male infertility revealed by alterations in spermatic function and differential testicular expression of thyroid related genes. Endocrine 2017; 55: 607-617.
77. Ibrahim AA, Mohammed NA, Eid KA, Abomughaid MM, Abdelazim AM and Aboregela AM: Hypothyroidism: morphological and metabolic changes in the testis of adult albino rat and the amelioration by alpha-lipoic acid. Folia Morphologica (Warsz) 2021; 80(2): 352-362.
78. Sarkar D and Singh SK: Neonatal hypothyroidism affects testicular glucose homeostasis through increased oxidative stress in prepubertal mice: Effects on GLUT3, GLUT8 and Cx43. Andrology 2017; 5: 749-762.
79. Bartnik CM, Maheshwari RN and Subramanian RM: Beating the Odds: A Full-Term Delivery after Liver Transplantation of a Pregnant Hyperthyroid Patient at 19 Weeks' Gestation for Propylthiouracil-Induced Acute Liver Failure. Transplantation Proceedings 2018; 50(10): 3995-3999.
80. Abdi H, Amouzegar A and Azizi F: Antithyroid Drugs: Iranian Journal Pharmaceutical Research 2019; 18(1): 1-12.
81. Krassas GE, Poppe K and Glinoer D: Thyroid Function and Human Reproductive Health. Endocrine Reviews 2010; 31: 702–755.
82. Marazuela M, Sánchez de Paco G, Jiménez I, Carraro R, Fernández-Herrera J, María Pajares J and Gómez-Pan A: Acute pancreatitis, hepatic cholestasis, and erythema nodosum induced by carbimazole treatment for graves' disease. Endocrine Journal 2002; 49: 315-318.
83. Mittal M and Ganakumar V: Graves Disease in Childhood. Intech Open 2021; 312.
84. Calanas-Continente A, Espinosa M, Manzano-García G, Santamaria R, Lopez- Rubio F and Aljama P: Necrotizing glomerulonephritis and pulmonary hemorrhage associated with carbimazole therapy. Thyroid 2005; 15: 286–288.
85. Vilchez FJ, Torres I, Garcia-Valero A, López-Tinoco C, delos Santos A and Aguilar-Diosdado M: Concomitant agranulocytosis and hepatotoxicity after treatment with carbimazole. Annals of Pharmacotherapy 2006; 40: 2059-2063.
86. Sakr SA, Mahran HA and Nofal AE: Effect of selenium on carbimazole-induced testicular damage and oxidative stress in albino rats. Journal of trace Elements in Medicine and Biology 2011; 25: 59-66.
87. Taylor PN and Vaidya B: Side Effects of Anti-Thyroid Drugs and Their Impact on the Choice of Treatment for Thyrotoxicosis in Pregnancy. European Thyroid Journal 2012; 1: 176–185.

88. Dumitrascu MC, Nenciu A, Florica S, Nenciu CG, Petca A, Petca R and Comănici AV: Hyperthyroidism management during pregnancy and lactation (Review). Experimantal Therapeutic Medicine 2021; 22: 960.
89. Leung AM: Thyroid Emergencies. Journal of Infusion Nursing 2012; 39: 281–286.
90. Anne RP and Rahiman EA: Congenital hypothyroidism in India: A systematic review and meta-analysis of prevalence, screen positivity rates, and etiology. Lancet Regional Health Southeast Asia 2022; 5: 100040.
91. Zaidi TM, Khan AA, Hasan BM and Faruqi AN: Carbimazole induced thyroid histopathy in albino rats during development. Journal of anatomical society in India 2004; 53: 14-17.
92. Ahmed OM, Ahmed RG, El-Gareib AW, El-Bakry AM and Abd El-Tawab SM: Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: II—the developmental pattern of neurons in relation to oxidative stress and antioxidant defense system. International journal of Developmental Neuroscience 2012; 30: 517-537.
93. Kala N, Ravisankar B, Govindarajulu P and Aruldhas MM: Impact of foetal-onset hypothyroidism on the epididymis of mature rats. International Journal of andrology 2002; 25: 139-148.
94. Annapoorna K, Anbalagan J, Neelamohan R, Vengatesh G, Stanley J, Amudha G and Aruldhas MM: Transient gestational and neonatal hypothyroidism-induced specific changes in androgen receptor expression in skeletal and cardiac muscles of adult rat. Hormone and Metabolic Research 2013; 45: 197-205.
95. Kobayashi K, Kubota H, Hojo R and Miyagawa M: Dose-dependent effects of perinatal hypothyroidism on postnatal testicular development in rat offspring. Journal of Toxicological Science 2014; 39: 867–874.
96. Abdel-Aziz N, Elkady AA and Elgazzar EM: Effect of Low-Dose Gamma Radiation and Lipoic Acid on High-Radiation-Dose Induced Rat Brain Injuries. Dose-Response 2021; 19(4).
97. Li ZM: Role of antioxidants in preventing testicular ischemia reperfusion injury: a narrative review. European Review for Medical Pharmacological Sciences 2022; 26(24): 9126-9143.
98. Lv SY, He S, Ling XL, Wang YQ, Huang C, Long JR, Wang JQ, Qin Y, Wei H and Yu CY: Review of lipoic acid: From a clinical therapeutic agent to various emerging biomaterials. International Journal of Pharmaceutics 2022; 627: 122201.
99. Dugbartey GJ, Alornyo KK, N'guessan BB, Atule S, Mensah SD and Adjei S: Supplementation of conventional anti-diabetic therapy with alpha-lipoic acid prevents early development and progression of diabetic nephropathy. Biomedicine Pharmacotherapy 2022; 149: 112818.
100. Votano A, Bonofiglio A, Catalano F and Paone C: Importance of Alpha Lipoic Acid (ALA): Antidiabetic and Antioxidant Effects. Frontiers in Medical Case Reports 2021; 2(3): 1-09.
101. Yang Y, Fang E, Luo J, Wu H, Jiang Y, Liu Y, Tong S, Wang Z, Zhou R and Tong Q: The Antioxidant Alpha-Lipoic Acid Inhibits Proliferation and Invasion of Human Gastric Cancer Cells via Suppression of STAT3-Mediated MUC4 Gene Expression. Oxidative Medicine and Cell Longevity 2019; 3643715.
102. Yue L, Ren Y, Yue Q, Ding Z, Wang K, Zheng T, Chen G, Chen X, Li M and Fan L: α-Lipoic Acid Targeting PDK1/NRF2 Axis Contributes to the Apoptosis Effect of Lung Cancer Cells. Oxidative Medicine and Cell Longevity 2021; 6633419.
103. Farhat D, Léon S, Ghayad SE, Gadot N, Icard P, Romancer ML, Hussein N and Lincet H: Lipoic acid decreases breast cancer cell proliferation by inhibiting IGF-1R *via* furin downregulation. British Journal of Cancer 2020; 122 (6): 885–894.
104. Tripathy J, Tripathy A, Thangaraju M, Suar M and Elangovan S: alpha-Lipoic acid inhibits the migration and invasion of breast cancer cells through inhibition of TGF beta signaling. Life Science 2018; 207: 15–22.
105. Neitzel C, Seiwert N, Göder A, Diehl E, Weber C, Nagel G, Stroh S, Rasenberger B, Christmann M and Fahrer J: Lipoic Acid Synergizes with Antineoplastic Drugs in Colorectal Cancer by Targeting p53 for Proteasomal Degradation. Cells 2019; 8(8): 794.
106. Trivedi PP and Jena GB: Role of α-lipoic acid in dextran sulfate sodium-induced ulcerative colitis in mice: Studies on inflammation, oxidative stress, DNA damage and fibrosis. Food and Chemical Toxicology 2013; 59: 339–355.
107. Kumar H, Kumar RM, Bhattacharjee D, Somanna P and Jain V: Role of Nrf2 Signaling Cascade in Breast Cancer: Strategies and Treatment. Frontiers in Pharmacology 2022; 13: 720076.
108. Hajizadeh-Sharafabad F and Sharifi Zahabi E: Role of alpha-lipoic acid in vascular function: A systematic review of human intervention studies. Critical Reviews in Food Science and Nutrition 2022; 62(11): 2928-2941.
109. Jung JH, Jung J, Kim SK, Woo SH, Kang KM, Jeong BK, Jung MH, Kim JH and Hahm JR: Alpha lipoic acid attenuates radiation-induced thyroid injury in rats. PLoS One 2014; 9: 112253.
110. Koga T, Ishida T, Takeda T, Ishii Y, Uchi H, Tsukimori K, Yamamoto M, Himeno M, Furue M and Yamada H: Restoration of dioxin-induced damage to fetal steroidogenesis and gonadotropin formation by maternal co-treatment with α-lipoic acid. PLoS One 2012; 7(7): 40322.
111. Selvakumar E, Prahalathan C, Sudharsan PT and Varalakshmi P: Protective effect of lipoic acid on cyclophosphamide-induced testicular toxicity. Clinical Chimica Acta 2006; 367: 114-119.
112. Prahalathan C, Selvakumar E and Varalakshmi P: Lipoic acid ameliorates adriamycin-induced testicular mitochondriopathy. Reproductive Toxicology 2005; 20: 111-116.
113. El-Beshbishy HA, Aly HA and El-Shafey M: Lipoic acid mitigates bisphenol A-induced testicular mitochondrial toxicity in rats. Toxicology and Industrial Health 2013; 29: 875-87.
114. El-Maraghy SA and Nassar NN: Modulatory effects of lipoic acid and selenium against cadmium-induced biochemical alterations in testicular steroidogenesis. Journal of Biochemical and Molecular Toxicology 2011; 25: 15-25.
115. Othman AI, El-Missiry MA, Koriem KM and El-Sayed AA: Alfa-lipoic acid protects testosterone secretion pathway and sperm quality against 4-tert-octylphenol induced reproductive toxicity. Ecotoxicology and Environmental Safety 2012; 81: 76-83.
116. Aly HA, Alahdal AM, Nagy AA, Abdallah HM, Abdel-Sattar EA and Azhar AS: Lipoic acid and calligonumcomosumon attenuate aroclor 1260-induced testicular toxicity in adult rats. Environmental Toxicology 2017; 32: 1147-1157.

117. Goudarzi M, Haghi Karamallah M, Malayeri A, Kalantar M, Mansouri E and Kalantar H: Protective effect of alpha-lipoic acid on di-(2-ethylhexyl) phthalate-induced testicular toxicity in mice. Environmental Science and Pollution Research International 2020; 27: 13670-13678.
118. Zhang Y, Zhao L, Yang Y and Sun P: degradation of the antibiotic ornidazole in aqueous solution by using nanoscale zero-valent iron particles: kinetics, mechanism, and degradation pathway. RSC Advances 2018; 8: 35062.
119. Najafi M, Motevaseli E, Shitazi A, Geraily G, Rrzaeyan A, Norouzi F, Rezapoor S and Abdollahi: Mechanisms of inflammatory responses to radiation and normal tissues toxicity: Clinical implications. International Journal of Radiation Biology 2018; 94(4): 335-356.
120. Subramanian V, Ravichandran A, Thiagarajan N, Govindarajan M, Dhandayuthapani S and Suresh S: Seminal reactive oxygen species and total antioxidant capacity: Correlations with sperm parameters and impact on male infertility. Clinical and Experimental Reproductive Medicine 2018; 45: 88–93.
121. Martín-Hidalgo D, Macías-Garcíaa B, Jesús García-Marína L, Julia Bragadoa M and González-Fernández L: Boar spermatozoa proteomic profile varies in sperm collected during the summer and winter. Animal Reproductive Science 2019; 219: 106513.
122. Astiz M, Graciela E, De Catalfo H, Garcia MN, Galletti SM, Errecalde AL, De Alaniz MJT, and Marra CA: Pesticide-induced decrease in rat testicular steroidogenesis is differentially prevented by lipoate and tocopherol. Ecotoxicology and Environmental Safety 2013; 91: 129-138.
123. Hamdy BG, Nabil T, Saad NN, Abdelwahab M and Mohamed L: Protective role of alpha lipoic acid against the deleterious effects of both natural and artificial sweetener (Sucrose and Aspartame) in albino rats. Alexandria J of Veterinary Science 2016; 49: 105–115.
124. Corrêa LBNS, da Costa CAS, Ribas JAS, Boaventura GT and Chagas MA: Antioxidant action of alpha lipoic acid on the testis and epididymis of diabetic rats: morphological, sperm and immunohistochemical evaluation. International Brazilian Journal of Urology 2019; 45: 815-824.
125. Gu L, Li S, Bai J, Zhang Q and Han Z: α-Lipoic acid protects against microcystin-LR induced hepatotoxicity through regeneration of glutathione *via* activation of Nrf2. Environmental Toxicology 2020; 35(7): 738-746.
126. Glade MJ and Smith K: Oxidative stress, nutritional antioxidants, and testosterone secretion in men. Annals of Nutritional Disorders and Therapy 2015; 2: 1019.
127. Dixit S, Dhar P and Mehra RD: Protective role of exogenous α-lipoic acid (ALA) on hippocampal antioxidant status and memory function in rat pups exposed to sodium arsenite during the early post-natal period. Toxicology Mechanisms and Methods 2011; 21: 216–224.
128. Rozzana MS, Zaiton Z, Rajikin MH, Fadzilah S and Zanariyah A: Supplementation with alpha lipoic acid improves the *in-vitro* development of embryos in nicotine treated mice. BioMedical Research international 2005; 16: 28–32.
129. Yi X and Maeda N: Endogenous production of lipoic acid is essential for mouse development. Molecular and Cellular Biology 2005; 25: 8387–8392.
130. Zamoner A, Barreto KP, Filho DW, Sell F, Woehl VM and Guma FCR: Propylthiouracil-induced congenital hypothyroidism upregulates vimentin phosphorylation and depletes antioxidant defenses in immature rat testis. Journal of Molecular Endocrinology 2008; 40: 125-135.
131. Sahoo DK and Roy A: Compromised rat testicular antioxidant defence system by hypothyroidism before puberty. International Journal of Endocrinology 2012; 637825.
132. Shirpoor A, Minassian S, Salami S, Hassan Khadem-Ansari MD and Yeghiazaryan M: Alpha - Lipoic Acid Decreases DNA Damage and Oxidative Stress Induced by Alcohol in the Developing Hippocampus and Cerebellum of Rat. Cell Physiology and Biochemistry 2008; 22: 769-776.
133. Gorąca A, Huk-Kolega H, Piechota A, Kleniewska P, Ciejka E and Skibska B: Lipoic Acid Biological Activity and Therapeutic Potential. Pharmacological Reports 2011; 63: 849-858.
134. Najafi R, Sharifi AM and Hosseini A: protective effect of alpha lipoic acid on high glucose –induced neurotoxicity in PC12 cells. Holistic Integrative Oncology 2015; 30: 731-738.
135. Yue L, Ren Y, Yue Q, Ding Z, Wang K, Zheng T, Chen G, Chen X, Li M and Fan L: α-lipoic acid targeting pdk1/nrf2 axis contributes to the apoptosis effect of lung cancer cells. Oxidative Medicine and Cellular Longevity 2021; 6633419.
136. McIlwain DR, Berger T and Mak TW: Caspase functions in cell death and disease. Cold Spring Harbor Perspective in Biology 2013; 5: 008656.
137. Krajka-Kuzniak V, Paluszczak J and Baer-Dubowska W: The Nrf2-ARE signaling pathway: An update on its regulation and possible role in cancer prevention and treatment. Pharmacological Reports 2017; 69: 393–402.
138. Xia D, Zhai X, Wang H, Chen Z, Fu C and Zhu M: Alpha lipoic acid inhibits oxidative stress-induced apoptosis by modulating of Nrf2 signalling pathway after traumatic brain injury. Journal of Cell and Molecular Medicine 2019; 23: 4088-4096.
139. Prathima P, Venkaiah K, Daveedu T, Pavani R, Sukeerthi S, Gopinath M and Sainath SB: α-lipoic acid protects testis and epididymis against linuron-induced oxidative toxicity in adult rats. Toxicology Research 2020; 36(4): 343-357.
140. Visser TJ: Regulation of Thyroid Function, Synthesis and Function of Thyroid Hormones. In: Vitti P, Hegedus L, (eds) Thyroid Diseases, Endocrinology Spring 2018; 1-30.
141. Zoheir KMA, Harisa GI, Allam AA, Yang L, LiX, Liang A, Abd-Rabou AA and Harrath AH: Effect of alpha lipoic acid on *in-vitro* development of bovine secondary preantral follicles. Theriogenology 2017; 88: 124-130.
142. Takeda T, Matsuo Y, Nishida K, Fujiki A, Hattori Y, Koga T, Ishii Y and Yamada H: α- Lipoic acid potentially targets AMP-activated protein kinase and energy production in the fetal brain to ameliorate dioxin-produced attenuation in fetal steroidogenesis. Journal of Toxicological Sciences 2017; 42: 13-23.
143. Hara LO and Smith LB: Androgen receptor roles in spermatogenesis and infertility. Best Practice and Research Clinical Endocrinology and Metabolism20152015; 29: 595-605.
144. Varma Shrivastav S, Bhardwaj A, Pathak KA and Shrivastav A: Insulin-Like Growth Factor Binding Protein-3 (IGFBP-3): Unraveling the Role in Mediating IGF-Independent Effects within the Cell. Frontiers in Cell and Developmental Biology 2020; 8: 286.
145. Hu D, Ge Y, Cui Y, Li K, Chen J, Zhang C, Liu Q, He L, Chen W, Chen J, Hu C and Xiao H: Upregulated IGFBP3 with Aging Is Involved in Modulating Apoptosis, Oxidative Stress, and Fibrosis: A Target of Age-Related Erectile Dysfunction. Oxidative Medicine Cellular Longevity 2022; 6831779.

146. El-Maddawy ZK and Abd El Naby WSH: Effects of ivermectin and its combination with alpha lipoic acid on expression of IGFBP-3 and HSPA1 genes and male rat fertility. Andrologia 2018; 50 (3).

How to cite this article:
Pavani R, Prathima P, Venkaiah K and Sainath SB: Endocrine disrupting chemicalsand male reproduction: a special focus on antithyroid drugs and recuperative effects of α-lipoic acid. Int J Pharm Sci & Res 2023; 14(9): 4209-24. doi: 10.13040/IJPSR.0975-8232.14(9).4209-24.