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Recuperative Effects of Resveratrol on Male Reproductive Health against Testicular Toxicants

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Abstract: ***Resveratrol (3, 5, 4' - trihydroxy - trans - stilbene), a polyphenol that belongs to stilbenoids group and is well recognized for its antioxidant properties and in addition, it exerts vasorelaxant, anti - inflammatory, anti - carcinogenic properties. These extraordinary properties of resveratrol underlie its therapeutic potential and eventually elaborated its medical benefits to protect various tissues such as pancreas, brain, kidney, heart, and liver. The unique chemical structure of resveratrol possessing phenol rings linked to each other through ethylene bridge underlies its antioxidant properties. In the current study, recuperative effects of resveratrol at the level of testicular functions against the oxidative damage induced by toxic insults was highlighted. This review comprises of three aspects. The first aspect emphasizes the structure, sources, and health benefits of resveratrol. The second aspect covers the adverse effects of environmental pollutants and their mechanisms involved in the deterioration of spermatogenesis and testosterone biosynthesis. The third aspect highlights the protective role of resveratrol on male reproductive health against toxic insults. Finally, the pros and cons of resveratrol were presented.***

Keywords: Apoptosis, epididymis, resveratrol, sperm, testis, testosterone

1. Introduction

Male infertility among the population of the youth is one of the alarming global problems and this notion is supported by many andrological studies over the past decades (Arbuckle et al., 2018; Warembourg et al., 2018; Schwartz et al., 2019). Decline in the sperm number over the past 60 years raised concerns and drawn public and scientific attention. Studies of Carlsen et al. (1992) specified that during the past five decades (i. e.1938 As a result of these male reproductive disorders there has been a decrease in the quality and quantity of sperms resulting in male infertility (Rodprasert et al., to 1990) the sperm concentration reduced to 66 million/ml from 113 million/ml. In consistent to his study, meta - analysis data conducted by various andrologists also indicated the same (Warembourg et al., 2018; Schwartz et al., 2019; Mishra et al., 2018). However, the exact mechanisms are not clarified. Antioxidant therapy is one of the preferrable choices to protect the testicular functions against chemical/toxic insult induced oxidative injury (Asadi et al., 2017). Among the antioxidants, resveratrol (3, 5, 4' - trihydroxy - trans - stilbene), a polyphenol that belongs to stilbenoids group is well recognized for its antioxidant properties. In addition, it exerts vasorelaxant, anti - inflammatory, anti - carcinogenic properties. These extraordinary properties of resveratrol underlie its therapeutic potential and eventually elaborated its medical benefits to protect various tissues such as pancreas, brain, kidney, heart, and liver. The unique chemical structure of resveratrol possessing phenol rings linked to each other through ethylene bridge underlies its antioxidant properties. In the current study, recuperative effects of resveratrol at the level of testicular functions against the oxidative damage induced by toxic insults was highlighted.

In view of the above, the present review emphasizes three aspects. The first aspect covers the structure, sources, and health benefits of resveratrol. The second aspect covers the adverse effects of environmental pollutants and their mechanisms involved in the deterioration of spermatogenesis and testosterone biosynthesis. The third aspect highlights the protective role of resveratrol on the male reproductive health against toxic insults. Finally, the merits and demerits of resveratrol were summarized.

Resveratrol: Structure, sources and health benefits

Resveratrol (RES: *trans* - 3, 5, 4′ - trihydroxystilbene) is a stillbenoid polyphenolwith well appreciated antioxidant properties. Since its discovery in the year 1940, research owing to the resveratrol (RES) is increasing day - by - day as RES exhibit diverse health benefits. RES was isolated from the roots of two plant species, *viz*., white hellebore (*Veratrum grandiflorum* O. Loes) and *Polygonum cuspidatum* in the years 1940 and 1963, respectively. The later plant is widely used as anti - inflammatory and anti - platelet agent in Chinese and Japanese medicine. RES synthesis from plants occurs due to stress conditions such as infections and ionizing radiations. The high percentage of RES are present in *Vitis vinifera* (grapes) against the fungal infections. Published reports indicated that the plants belong to the family, *Dipterocarpaceae* synthesize 50 RES compounds. RES [IUPAC: *E* - 5 - (4 - hydroxystyryl) benzene - 1, 3 - diol] occurs in two isoforms: *cis* - and *trans* - resveratrol, wherein *trans* RES unequivocally dominant form as compared to *cis* RES in terms of biological properties. However, its low biological abundance hampered its therapeutic abilities and hence, several modified RES have been synthesized. Among the modifications, glycosylated RES attracted the attention of researchers as glycosylation prevents enzymatic oxidation of RES thereby sustain its biological activity.

RES offers several health benefits such as antiaging, antioxidant, antimicrobial, anticancer, anti - inflammatory and protects brain, liver, kidney, pancreas against oxidative stress. Further, it promotes blood - sugar lowering properties (Salehi et al., 2018). It is also widely used against the reproductive disorders such as cryptorchidism,

dyszoospermia, enhancing testosterone production, penile erection triggering, improving spermatogenesis in males (Juan et al., 2005; Rolando et al., 2020; Revel et al., 2003; Uguralp et al., 2005; Shin et al., 2008). The role of RES in the protection of male reproductive health against chemical induced oxidative toxicity is well noticed (Fahim et al., 2019). Thus, in view of its extraordinary properties RES is sold as a nutritional supplement. Due to increased usage, its demand necessitated the synthesis of RES using chemical and biotechnological approaches from yeasts *Saccharomyces cerevisiae*.

Environmental pollutants: Mechanisms underlying deterioration of male reproductive health

The testicular functions viz., spermatogenesis and testosterone biosynthesis are major targets for chemical with endocrine disrupting properties and oxidative stress induced damage. Therefore, it is appropriate to acquire knowledge about the spermatogenesis and testosterone biosynthesis in mammals which acts as a platform to address the plausible mechanism (s) of action of environmental pollutants/ toxicants.

Spermatogenesis and steroidogenesis

Testicular spermatogenesis is a complex process and starts during puberty. The major events are of spermatogenesis are spermatogoniogenesis (formation of spermatogonia), spermatocyte (primary and secondary) formation, spermiogenesis (spermatid formation) and spermiation (formation of sperm cells) (D'Cruz et al., 2010) and from basal to lumen region of seminiferous tubule, spermacytogenesis to sperm cell formation occurs. There are two cell division events, mitosis and meiosis take place for the conversion of spermatogonia to sperm cell. Mitotic division take place at the stage of spermatogonia and meiotic division takes place at the spermatocyte and spermatid post meiotic differentiation stage. These stages end at spermatogenesis and spermiation leading to mature spermatozoa (haploid) from germinal epithelium to tubular structure. Spermatogonia are the immature cells which undergo mitosis and transform into primary spermatocyte and undergo meiotic division for secondary spermatocyte formation and forms spermatids. Two haploid spermatids are produced by each secondary spermatocyte which in turn gives four haploid spermatids. Spermatogenesis consists of a final step known as spermiogenesis wherein spermatozoa are formed from spermatids. In human, spermatogenesis (one cycle) takes around 65 to 75 days, but in rats spermatogenesis takes around 54 to 60 days' time. For mature sperm production and availability, spermatogenesis is carried out at different places of testis at different times simultaneously. The spermatogenesis events take place in a step wise manner which are synchronised by the Sertoli cells and Leydig cells secretions and also pituitary gland endocrine factors also assist spermatogenesis.

The Leydig cells are also known as the steroidogenic cells which are located in the interstitium of testis (Svechnikov et al., 2010a; b). Leydig cells are involved in the synthesis of testosterone, which is a male hormone. The testosterone production involves a cascade of events including enzymatic reactions and proteins. Testosterone, male hormone plays a vital role in the regulation of physiological processes which also includes spermatogenesis. Hence, insufficient amount of testosterone leads to many pathological issues which also comprise of male fertility issues. At the time of development, Leydig cells occur as two different populations i. e. fetal Leydig cells and adult Leydig cells. The significant controllers of virilisation of male urinogenital tract are the fetal Leydig cells. A very important role is played by the secretions of fetal Leydig cells in the induction of testis descent. The decline of these Leydig cells occurs after birth. On the other side, precursors which are present undifferentiated after birth transform into adult Leydig cells and achieve steroidogenic capacity at the age of puberty. The paracrine and endocrine factors together regulate the fetal and adult Leydig cell population differentiation.

The Precursor of steroid hormones is cholesterol (Carr et al, 1983; Landschulz et al, 1996). The cholesterol transport from the outer membrane of mitochondria to the inner membrane of mitochondria is a rate limiting step. It is so, as the space present in the middle of the internal and external membrane is occupied with aqueous fluid and therefore permits only the molecules which are soluble in water (Thompson et al, 2004; updated by Scott et al, 2009). For this purpose of binding and transportation of the cholesterol, steroidogenic acute regulatory protein plays a major role. (Arakane et al, 1998; Miller, 2002; Stocco and Clark, 1996). Most of the transcription factors along with Sf1 are known to be condemnatory for enzymes regulation that intervene cholesterol synthesis as well as StAR (Mascaro et al, 2000; Scott et al, 2009). After transportation, conversion of cholesterol to testosterone consists of two vital pathways namely delta 4 pathway or progesterone pathwayand delta 5 pathway or dihydroepiandrosterone pathway. In human testis, the latter pathway appears to be the most common. First cleavage of cholesterol events are carried out by cytochrome p450 enzymes such as CYP11a1 and CYP17a1 that favor hydroxylation reactions using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron source. The second cleavage of cholesterol is mediated by 17 - hydroxylase and 17, 20 - lyase. The first steroidogenesis enzymatic processes happen in the inner mitochondrial membrane, where CYP11a1 cleaves a six - carbon cholesterol chain to produce the steroid pregnenolone (Thompson et al, 2004). Pregnenolone is then converted into progesterone and catalyzed by 3β - hydroxysteroid dehydrogenases (3β - HSD) in the smooth endoplasmic reticulum. Furthermore, progesterone is metabolized to 17 - hydroxyprogesterone with the help of 17α - hydrolase, which is further converted to androstenedione by 17, 20 - lyase (Scott et al, 2009). Androstenedione is eventually transformed to testosterone by the enzyme 17β - hydroxysteroid dehydrogenases 17β - HSD (O'Shaughnessy et al, 2000). Pregnenolone is transformed to 17α - hydroxypregnenolone by 17α - hydrolase, and 17α - hydroxypregnenolonewhich is turned to delta 5 androstenediol by 17β - HSD in the delta 5 route. Finally, 3β - HSD converts androstenediol to testosterone in delta 5 pathway (Kinnelly et al., 2023).

Endocrine regulation of spermatogenesis and steroidogenesis

The hormones generated and secreted by the hypothalamic - pituitary - testicular (HPG) axis control and coordinate male reproduction. Hypothalamus is a vital gland correlated with pituitary gland stimulation, consequently gonadotropins. It is present beneath the thalamus and consists of diencephalon. It amalgamates and releases gonadotropin releasing hormone (GnRH), which is a decapeptide and helps in boosting anterior part of the pituitary gland for gonadotropins secretion. Hence, the classical name HPT - axis master controlling gland to hypothalamus. Pituitary gland is popularly known as master of endocrine glands, a special name given to pituitary gland, as it regulates many of the biological functions of the body through its secretions. After stimulation by GnRH, the anterior part of the pituitary gland releases two vital hormones namely: follicle stimulating hormone (FSH) and luteinizing hormone (LH) to reach the particular tissue and gonad through circulation.

LH and FSH binds their cognate receptors leutinzing hormone chorionic gonadotropin receptor and follicle stimulating hormone receptor present on the Leydig cells and the Sertoli cells, respectively and eventually control spermatogenesis and testosterone biosynthesis (Sriraman et al., 2005; Oduwole et al., 2018). FSH plays a crucial role in controlling the Sertoli cell differentiation and proliferation, thus the Sertoli cell number in testis. Furthermore, FSH - mediated regulation of structural genes of cell - cell junctions and genes that govern regulatory and nutritional factors from Sertoli to germ cells is well appreciated at the molecular level (Abel et al., 2008; Oduwole et al., 2018). FSH in coordination with testosterone helps in the stimulation of Sertoli cells which leads to regulatory molecules and nutrients production which is necessary for continuation of spermatogenesis (Walker and Cheng, 2005). Membrane bound receptors present on the Sertoli cells helps in the regulation of spermatogenesis. FSH regulates the quantity of Sertoli cells and their ability to support growing germ cells, therefore spermatogenesis (Ruwanpura et al., 2010). FSH is an important component of the feedback processes that regulate testicular function through the HPT - axis (Hayes et al., 2001). Therefore, the hormones from the brain (gonadotropin releasing hormone and pituitary gland) influence Sertoli cell sustained spermatogenesis and Leydig cell steroidogenesis (gonadotropin: FSH and LH). Additionally, testosterone regulates spermatogenesis through Sertoli cells. As a result, a healthy HPT axis is essential for testicular function (Oduwole et al., 2018).

Mechanisms underlying repro - toxicity in males by environmental toxicants

Many toxicants mediate diverse routes such as endocrine disruption, and oxidative stress and interfere with the male fertility via impairing structural and functional integrity of reproductive organs. These events directly or indirectly affect the spermatogenesis and testosterone biosynthesis with double edge sword like activities such as disruption of molecular networks on one hand and irregularities at the level of enzymes and proteins (Cheng et al., 2011). Cellular disruption at the level of testis and epididymis lead to the improper sperm production and its maturation events, whereas at the level of vas deferens, seminal vesicles and ventral prostate lead to improper transport and seminal fluid secretions that sustain the nourishment to the sperm cell (Gao et al., 2015).

With respect to the endocrine disruption, broad spectrum of environmental toxicants as well as pharmaceutical compounds can able to interfere with the endocrine system thereby negatively affect the physiological processes. For example chemicals such as polychlorinated biphenyls, alkylphenols, polybrominated biphenyls, plasticizers such as bisphenol A, phthalates, and perfluoroalkyl compounds, pesticides including methoxychlor, dichlorodiphenyl trichloroethane, chloropyrifos, fungicides including vinclozolin, persistent organic pollutants designed for industrial purpose with long half - lives such as dichlorodiphenyl dichloroethylene, dioxin, hexachlorobenzene, organochlorine and organophosphorus pesticides and pharmaceutical drugs including diethylstilbesterol are playing a major role in the deterioration of the male reproductive system thereby male infertility (Schwartz et al., 2019; Manoj et al., 2020). Such chemicals with endocrine disrupting mechanisms are broadly categorized into EDs. They may perturb the biological functions via blocking the synthesis of endogenous hormone synthesis, binding to the endogenous receptors via their mimicking property, obstruction of the transport of endocrine factors (Boas et al., 2012; Warembourg et al., 2018). The endocrine disruptors mechanism of action can be divided into different categories, they are: a. Endogenous hormones mimicking; b. They can act as endogenous hormone receptors resulting in the blockage of the natural hormones; c. modification of receptors production and function and d. inhibition of endogenous hormones secretion and synthesis. Male reproductive system is very sensitive to endocrine disruption as minute changes in the hormones may adversely affect testicular and epididymal functions (Rodprasert et al., 2019).

With respect to the oxidative stress, it has been shown that the OS is one of the etiological factors that underlie male infertility. Homeostasis between the generation of free radicals and endogenous antioxidants is essential for normal cellular/tissue physiological functions and therefore, an imbalance between the excess generation of free radicals and endogenous antioxidants, a condition known as oxidative stress may cause free radical attack at the level of vital components of the cells, DNA, lipids, and proteins thereby alter normal physiological events (Kumar et al., 2011). Many studies claimed that the exposure to EDs at least in part mediate oxidative stress as a weapon to deteriorate male reproductive health, in addition to their hormone disrupting properties (Eggert et al., 2019). It is now well documented that oxidative stress caused by a range of pollutants is one of the etiological factors of chemical - induced deterioration of spermatogenesis, sperm maturation events and testosterone biosynthesis (Mathur et al., 2008). The testis and the epididymis are equipped with intrinsic antioxidants such as enzymatic and non - enzymatic antioxidants to over come excess generation of free radicals thereby cellular pro - and antioxidant status is maintained and hence, toxicants that perturb the testicular and epididymal redox status through several mechanisms including triggered apoptosis may

inhibit their functions such as spermatogenesis and post - testicular sperm maturation events (Asadi et al., 2017).

Resveratrol induced recuperative effects on male reproduction

In male reproduction, appropriate antioxidant system maintenance is necessary for normal spermatogenesis. During oxidative stress, however, free radicals such as reactive oxygen species (ROS) assault spermatogenesis and its maturation events, causing sperm - mediated fertility to decline. This effect of ROS on sperm function deterioration can be attributed to multiple levels: a) at the testis level, b) at the epididymis level, or c) at the sperm level, or a, b, and c. During pathological situations, however, excessive ROS production can cause oxidative damage to the testis and assault the sperm plasma membrane, which is rich in polyunsaturated fatty acids. The epididymis, on the other hand, is a key reproductive organ where sperm maturation occurs. As a result, a ROS attack at this level could result in sperm DNA integrity deterioration and sperm capacitation events being lost. As a result, excessive ROS production inhibits spermatogenesis and fertilisation (Birben et al., 2010). Studies have shown that the RES when supplemented exogenously can able to negate the effects of oxidative stress via boosting enzymatic and non - enzymatic antioxidants (Avdatek et al.2016; Rafaela et al.2018,). In all living cells, there are two different defence antioxidant systems occurs endogenously. They are enzymatic antioxidant enzymes: glutathione - based enzymes, superoxide dismutase and catalase and non - enzymatic antioxidants including low molecular antioxidants such as thioredoxin, vitamin A, C, E, lutein, lycopene, quercetin. which protect the cells from oxidative stress (Salehi et al., 2018). Previously, it has been shown that the supplementation of RES ameliorated testosterone levels, spermatogenesis, activity levels of 3β - and 17β - HSDs and restored testicular architecture in animal models against a range of chemicals including doxorubicin, cisplatin, nitric oxide, benzo (a) pyrene, combination of streptozotocin - nicotinamide, 2, 3, 7, 8 - tetrachlorodibenzo - *p* - dioxin, malathion, nicotine, finasteride, and sulfoxaflor (Turedi et al., 2004; Pratap Reddy et al., 2016; Hamdy et al., 2020; Jalili et al., 2017; Liu et al., 2017; Bahmanzadeh et al., 2019; Banerjee et al., 2019; Jalili et al., 2019; Shalaby et al., 2020; Said et al., 2021). These studies at least in part suggest that the RES supplementation promote spermatogenesis, sperm maturation events and testosterone biosynthesis.

Pros and cons of resveratrol supplementation

Though, undoubtedly RES is one of the supreme nutraceutical drugs with promising health benefits, RES is often associated with side effects (Shaito et al., 2020). Thus, RES is associated with hormetic effect i. e. at low doses exhibit beneficial effects, while at higher doses exerts toxic effects. Moreover, dose dependent biphasic effect at the level of cellular pro - and anti - oxidant status revealed that RES at low doses promote antioxidant properties, whereas at high doses exert pro - oxidant properties. One answer to address biphasic effect of RES is through elaborate its effect by considering a greater number of clinical studies, and to appraise its harmful effects, if any, to abate hermetic aspect of RES. This can be achieved by designing uniform clinical approaches/regimens. Finally, as RES is one of the frequently used antioxidants to protect the male reproductive health, more studies at the level of molecular aspects is required to define its protective role against the testicular toxicants.

2. Conclusion

Resveratrol, a potent antioxidant, has shown promising potential in addressing male reproductive disorders induced by various physical and chemical agents. Its cytoprotective efficacy is primarily attributed to its antioxidant properties, which inhibit apoptosis in germ cells, Sertoli cells, and Leydig cells, thereby promoting spermatogenesis and maintaining adequate testosterone levels. Additionally, resveratrol safeguards the epididymis from chemical - induced oxidative toxicity, thereby enhancing post - testicular sperm maturation processes. Despite its promising benefits, the hormetic effect of resveratrol, beneficial at low doses and potentially toxic at high doses, necessitates further investigation through comprehensive clinical studies.

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