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The Protective Effect of Ganoderma Lucidum in Mice-Exposed to Sertraline

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Abstract:
The goal of precision medicine (PM) is to provide each patient with the treatment and therapy with the optimum results without significant adverse side effects. PM play an essential role in patient care as well as therapy because it tailores the medicine on the individual basis, thus decreasing side effect associated with the drug administration and expediting the treatment as well . Antidepressant drug sertraline (SRT) is currently prescribed to treat mental disorders. This study aimed to determine how much Ganoderma lucidum protects against SRT-induced testicular damage in mice. Mice were given SRT (at a dosage of 30 mg/kg) orally for 35 consecutive days. For 35 days straight, rats receiving SRT were also given G. lucidum extract (at a dosage of 300 mg/kg). SRT therapy caused immediate testicular injury, as evidenced by the significant degeneration and necrosis of the germ cell lining and an increase in sperm malondialdehyde (MDA) levels. Additionally, evaluation of sperm parameters using computer-assisted sperm analysis (CASA) results demonstrated a substantially lower volume, movement, and survival of sperm in the SRT-treated group ($p < 0.001$). Administering G. lucidum extracts to animals that had received SRT may have reduced their histological changes. G. lucidum significantly decreased spermatozoa's lipid peroxidation, and its antioxidant defenses were strengthened. Finally, G. lucidum protects mice›s testicles from harm brought on by SRT, most likely due to its capacity to inhibit reactive oxygen species.

INTRODUCTION

Generally medical treatments are designed for the average patients in which one dose or a therapeutic strategy fits-all-approch used to treat all aptients that may benift some patients but it might have no effect or induce advese side effects on others. A wide variety of factors in patient lead to differnces in treatment response including age, gender, genetic make up, lifestyle ethnicity and environment. Percisiom medicine (PM) which aslo known as "personalized medicine" is an innovative approch to tailoring treatment and disease prevention that takes into the account diffrences in patients thereby reducing the side effects and enhancing the treatment response. PM can be very usefull in particular disease such as infertility that is associated with a variety of etiological factors. One key focus for determining the proper diagnosis and personalized treatment for each infertile couple is understanding the various molecular and pathophysiologic pathways that lead to their condition (1). Therefore, the traditional one-size-fits-all approach to infertility treatments should be rejected because it is not beneficial to everyone (2). Between 40 and 50 percent of infertility-causing reasons among couples are caused by women, 30 percent by men, and 20 percent by both men and women. Men are directly or indirectly responsible for 30 to 50 percent of infertility cases (3). The etiologic reasons causing male infertility include varicocele, congenital malfunction, urogenital infections, endocrine disorders, immunological issues and drug administrations (4).

Beside the physical disorders , mental dysfunction is also known to have a significant influence on both male and female fertility. The first line of therapy for many psychological illnesses and some non-psychological issues is selective serotonin reuptake inhibitors (SSRIs)

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(5). Sertraline (SRT) is one of the 3 SSRIs that often prescribed, and used to treat depression, anxiety, and obsessive-compulsive disorder (6). Impotence is one of the sertraline's adverse effects. Harmful effects on the reproductive system include diminished libido, delayed ejaculation, abnormal bleeding (red patches on the skin's surface), the sensation of breast enlargement or milk secretion in women, and itching skin (7). Moreover production of viable embryos, sperm motility, testicular weight, testosterone levels, and spermatogenesis are all decreased by SSRIs (8). There have been limited studies on the harmful side effects of SRT on the male reproductive system. However, prior research suggested that SRT may directly impact testicle tissue function by preventing steroidogenesis and spermatogenesis, eventually resulting in male infertility (9).

It is important to remember that selecting a substance with therapeutic and antioxidant properties is crucial for preventing malfunction caused by SRT. The substance should be able to remove SRT from the body by chelating reaction due to its solid antioxidant components. Ganoderma lucidum is a medicinal mushroom and member of the Payporaceae basidiomycete family that is frequently utilized in traditional Chinese medicine, which usually referred to the «mushroom of immortality» because of its supernatural effects(10). Over 400 bioactive substances that promote health and quality of life are present in G. lucidum(11). Among precious components found in this mushroom are polysaccharides, polyphenols, and triterpenoids, which have a number of biological characteristics, including antioxidant and radical scavenging activity, antitumor, anti-acetylcholinesterase , anti-inflammatory, and anti-aging properties(12). No thorough research has been done on the connection between G. lucidum extract and sertraline testicular toxicity, though the G. lucidum may scavenge reactive oxygen species (ROS) and improve the effectiveness of the innate antioxidant system. Therefore, the objective of this study was to examine the protective effects of G. lucidum on histopathological alterations, and oxidative measures, such as evaluation of sperm malondialdehyde (MDA) levels, as well as sperm quality metrics in mice treated with SRTduring 35 days.

MATERIALS AND METHODS

Chemical

The SRT(Zoloft) provided by Tehran Darou Company, and Iran's Fanavaran kesht Sabz served as the source for the powdered Ganoderma lucidum fruiting bodies.

Preparing hydroalcoholic extract of G. lucidum

To prepare the hydroalcoholic Ganoderma lucidum extract, 300 ml of distilled water and 700 ml of ethanol were used to suspend 150 g of mushroom dry powder. The solution was kept 48 hours at 60°C in the shaker incubator , filtered afterward, and placed in a rotary evaporator to remove the liquid under vacuum until it was completely dried after 48 hours. Total phenolic, triterpenoids, and polysaccharides were evaluated to ensure that 70% ethanol extract solution had high quality. Additionally, the extract's antioxidant activity was assessed.

Measuring the total amount of polysaccharides

The hydroalcoholic Ganoderma lucidum extract's whole polysaccharide content was determined using the phenol-sulfuric acid technique. In a nutshell, 5 ml of concentrated sulfuric acid was added to 1 ml of phenol solution (5%) and 1 ml of extract solution. The solution absorbance measured at 490 nm after 30 minutes as a benchmark, D-glucose was employed.

Total phenol content determination

Folin-Ciocalteu reagent was used to calculate total quantity of phenol and gallic acid utilized as a standard, to perform colorimetric method. 500 ml of folinciocalteu reagent was added to 80 ml of extract solution, and the mixture incubated for 5 minutes at room temperature in the dark. finally 400 ml of a %7.5 sodium carbonate solution was added, incubated for 30 minutes in the dark at room temperature, and absorbance measured at 765 nm.

Measuring the amount of all triterpenes

Using a vanillin-glacial acetic acid solution, triterpenoids were evaluated. After mixing together 0.2 ml of extract, 0.4 ml of 5 percent (W/V) vanillin-glacial acetic acid, and 1 ml of 70 percent perchloric acid solution, the mixture was incubated at 60 °C in water bath for 45 minutes. Following a 15-minute incubation period at room temp, the solution was diluted with 100% acetic acid to a final volume of 5 ml. The absorbance was measured at 548 nm and the ursolic acid solution used as a standard.

Scavenging of DPPH radicals

To assess the antioxidant capacity of the 70% ethanolic extracts of Ganoderma lucidum, diphenyl-1-picrylhydrazyl (DPPH) was utilized as a stable free radical. After diluting the DPPH solution in methanol (1 mM methanol), 1 ml of the resulting solution was added to 1 ml of extract, and the mixture left to sit at room temperature for 30 min. 517 nm was used to measure the absorbance.

Experimental groups

The experiment was conducted by following the

guideline for care and use of laboratory animals. The mice were randomly divided into the following treatment groups: control group (n = 5): the animals were given distilled water by oral gavage dailyfor 35 days and 30 mg/kg of SRT treated group (n=5): animals received 30 mg/kg of SRT orally every day for 35 days. 30 mg /kg SRT and G.lucidum extract treated group (n=5): animals were given oral doses of 30 mg/kg/day of STR and 300 mg/kg/day of G. lucidum extract, respectively. The treatment plan was based on how long the mice›s spermatogenesis took. Animals were slaughtered 24 hours after receiving their final dosage. Testis and epididymis tissues were removed to evaluate the amount of MDA, sperm parameters, and histological alterations.

Examination of the histopathologic alterations

Testicles from treatment groups and control animals were embedded in paraffin after being fixed in Bouin's solution. Hematoxylin and eosin were used to stain tissue sections with 5µm thickness, and light microscopy was used to view them. Morphometric analysis of testis micrographs taken at various magnifications with a microscope, was carried out using digital photographs .

Assessment of sperm parameters

Using CASA technique, epididymal sperm parameters were also evaluated. In this procedure, linearity, curvilinear velocity (VCL), and total motile sperm count were assessed, along with concentration, sperm motility, and hyperactivity (HYP). Whole epididymis was taken out and longitudinally sliced to extract sperm from the caud, and then , the cauda transferred to microtubes containing 1 ml of T6 solution and 25 µl BSA (bovine albumin serum). The microtubes were incubated in 5 percent CO2 incubator (37 °C) for 30 minutes or until spermatozoa formed a sperm suspension.

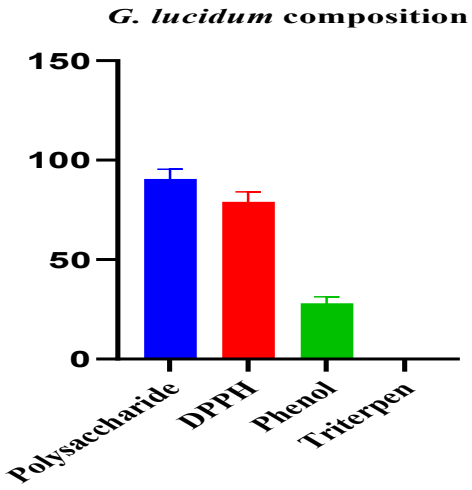

Figure 1. Alcoholic G. lucidum extract›s chemical make-up. By using the phenol-sulfuric acid, folin-ciocalteu, vanillin-glacial acetic acid, and DPPH procedures, the polysaccharides (g/ml), phenols (mg/ml), triterpenes (mg/ml), and DPPH scavenging (percent) activity, were measured respectively.

Assessment of sperm survival

50 µl of the sperm suspension and 50 µl of the 0.5 percent eosin dye were combined in a microtube. After shaking for 30 seconds, 100 µl of nigrosin was added to the initial mixture.A drop of the stained sperm suspension was deposited on slide,covered with coverslip and examined under light microscope using the 400x objective for observation. Live spermatozoa had a blue border, whereas dead spermatozoa appeared purple.

Assessment of malondialdehyde content (MDA)

The levels of lipid peroxidation were assessed according to MDA production . MDA was used as a marker for both production of free radicals and the byproduct of lipid peroxidation, which interacts with thiobarbituric acid (TBA). 400µl of sperm suspension added into 20% trichloroacetic solution was centrifuged at 10,000 RPM for 15 min. The supernatant was combined with 500 µl TBA, 0.1 HCL, and 1.5 ml Tris-KCl buffer, and then heated in a water bath for one hour. 532 nm was used to measure the absorbance of the reaction's end product.

Statistical analysis

One-way ANOVA and Tukey post hoc tests were used to examine the data in SPSS version 19. P value of 0.05 or above was deemed significant. The mean and standard deviation (SD)of all data were displayed.

RESULTS

Compound analysis of G. lucidum extract

The colorimetric technique was used to examine the G. lucidum extracts in 70 % ethanol, and the findings are shown in Figure 1. According to our research, the 70 % ethanol extract included 87 g/ml of total polysaccharides, 25.76 mg/ml of phenols, and 0.0048 mg/ml of triterpenoids. Additionally, a 70 % ethanol extract of G. lucidum had a 82.56 % of total free radical scavenging activity.

Testicular pathology findings

Testicular slices stained with hematoxylin and eosin were analyzed using a light microscope. The histological alterations in the seminiferous tubules and spermatogenic series of the mice treated with SRT and G. lucidum extract are shown in Figure 2. The control mice›s testis anatomy was expected, with mature sperm in the lumen. In contrast, the group that received 30 mg/kg of SRT had decreased interstitial tissue , significant intracellular space, reduction of

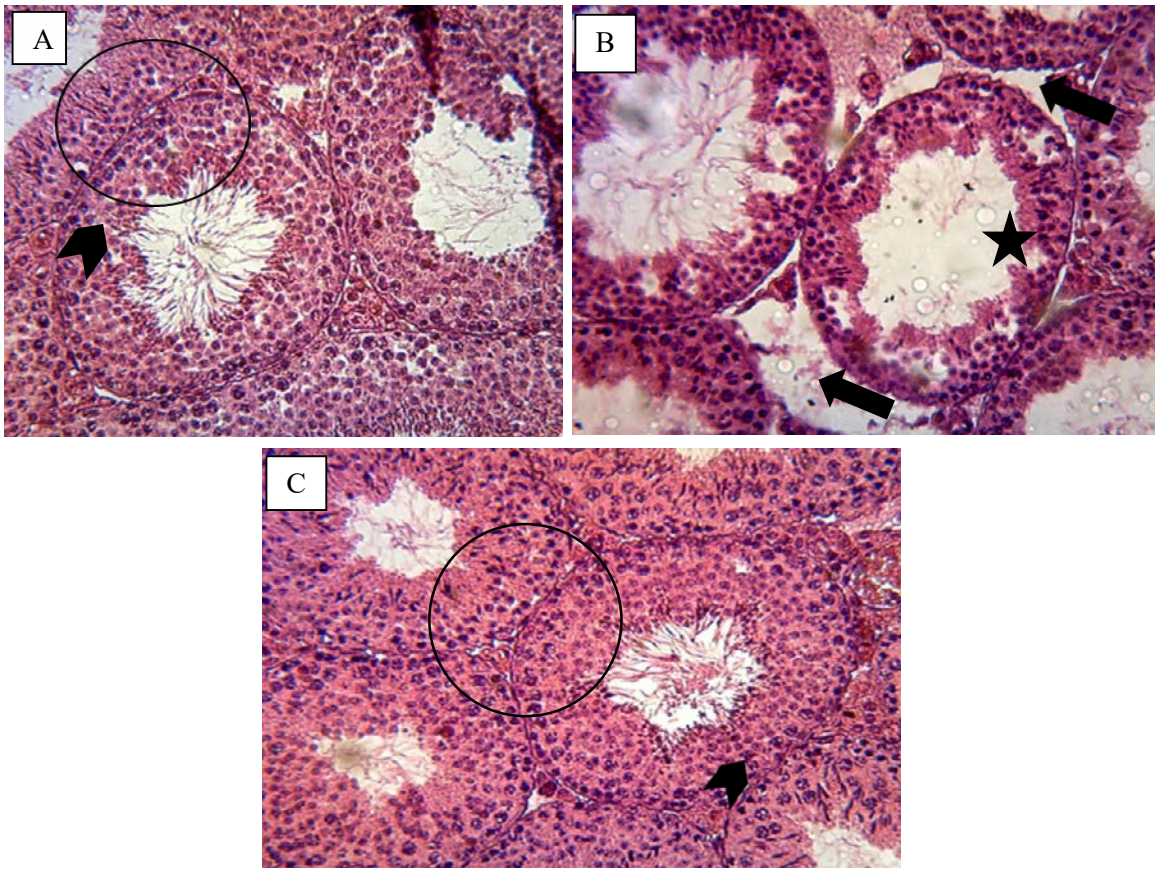

Figure 2. Testicular cross section from mice in the control and experimental groups. Seminiferous tubules with mature germ cells layers were seen in the control and SRT + G. lucidum groups to be normal and active (circle).
These groups showed acceptable intracellular spaces with complete interstitial tissue and seminiferous tubule lumen full of sperm (arrow-head). SRT testicular sections displaying striking changes, a reduced seminiferous epithelium, and an erratic basement membrane (black arrow). Seminiferous tubule lumens were devoid of sperms (star).

Table 1. Sperm parameters before and after being treated with G. lucidum extract and SRT.

Parameters	Control	SRT	SRT + G. lucidum
Volume (mL)	6.55 ± 0.73	2.56 ± 0.8 ****	7.50 ± 0.6***
PR (%)	45.64 ± 6.15	14.44 ± 8.23***	49.2 ± 5.29 ***
NP (%)	14.04 ± 6.38	10.58 ± 6.64	13.58 ± 3.96
IM (%)	38.56 ± 4.15	79.59 ± 8.76****	44.62 ± 10.37 ***
M (%)	60.10 ± 5.15	25.31 ± 10.76***	68.36 ± 9.26 ***
VCL (µm/ sec)	78.46 ± 12.26	42.50 ± 11.96*	62.23 ± 10
VSL (µm/ sec)	29.48 ± 4.68	25.68 ± 4.38	28.32 ± 6.6

PR, progressive, NP, non-progressive, IM, immotile, M, motile, VCL, curvilinear velocity, VSL, straight line velocity, VAP, average pathway velocity

mature sperms in the lumen, tubular and cellular shrinkage, and loss of the entire germinal layer. Seminiferous tubules in the group treated with SRT and G. lucidum (300 mg/kg) were completely normal and spermatogenic. Furthermore, compared to the SRT group, intercellular gaps and interstitial tissue were repaired in the SRT, and G. lucidum treated group. According to the current study, the testicular tissue of 4 mice administered SRT exhibited significant degeneration, atrophied seminiferous tubules, and a lack of differentiated spermatogenic cells that mature spermatozoa in the seminiferous lumen. Also, the

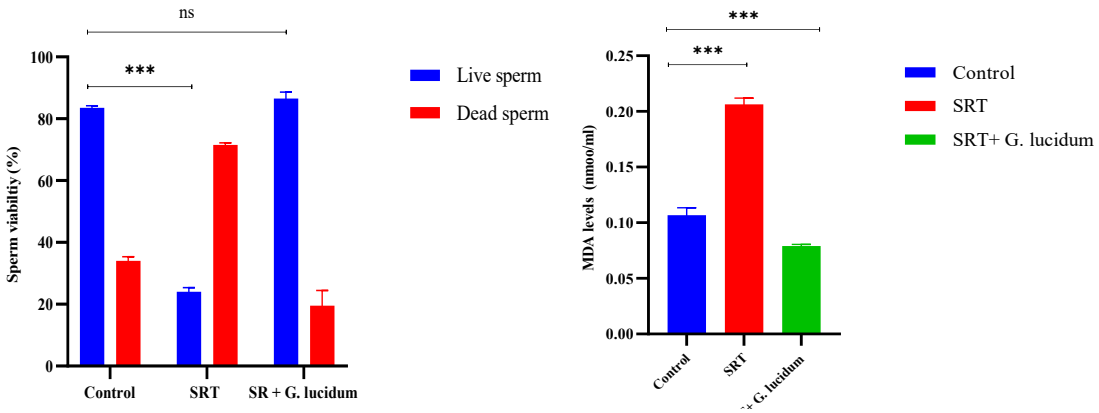

Figure 3. Sperm viability (A) and MDA levels (B) following a 35-day treatment with SRT and G. lucidum. A: significant variations between the control group and SRT was seen. Additionally, there was a significant difference between SRT and G. lucidum (300 mg/kg) assessed (***p < 0.001). B: the MDA levels in 1 ml of mouse sperm suspension after 35 days of treatment with SRT (30 mg/kg), SRT and G. lucidum (300 mg/kg), and control mice. The SRT group sample had the highest MDA level, whereas SRT + G. lucidum had the lowest amount of MDA. Data presented as mean ± SD. (***p < 0.001).

results showed that in 1 mouse, the effect of SRT on the testicular tissue was different from the other 4 mice, along with few changes in the testicular tissue.

Effects of SRT and G. lucidum treatment on mice sperm motility and quantity

The SRT (30 mg/kg/day) group's sperm concentration and mobility (progressive, nonprogressive, motile, and immotile) dramatically reduced, as shown by the CASA ($p < 0.001$). The fraction of immotile sperms significantly increased in the SRT group in comparison to the control group ($p < 0.001$). The co-administration of G. lucidum + SRT group significantly increased the sperm count and motility compared to the SRT group ($p < 0.001$). There was no discernible difference between the control group and the SRT+ G. lucidum group. Table 1 lists further alterations to sperm characteristics.

Effects of SRT treatment on sperm viability

According to Figure 3, eosin- negrosin staining results had significant differences in sperm viability between the control group and the SRT group ($P<0.001$). The percentage of epididymal sperms that were alive decreased after 35 days of oral SRT therapy (30 mg/kg) compared to the control group (27 % ± 2.21). Our results show that the proportion of surviving sperm in the G. lucidum + SRT treatment groups (30, 300 mg/kg) was higher (70 % ± 7.24) than those in the SRT group ($p<0.001$). The outcomes are shown in Figure 3A.

Measuring the MDA levels in sperm

Our findings showed that treatment with 30 mg/kg/day of SRT significantly boosted the generation of epididymal sperm MDA levels (0.276 ± 0.02 nmol/ml, $p< 0.001$) in comparison to the control group. MDA levels in mouse sperm from the SRT + G. lucidum group were 0.766 ± 0.012 nmol/ml, $p < 0.001$, compared to the SRT group. Figure 3B displays the outcomes. Our investigation revealed that 2 mice receiving a dosage of 30 mg/kg of SRT significantly increased their MDA production, whereas the other 3 mice only exhibited a little change. Also, our results showed that treatment with SRT and G. lucidum reduced the production of MDA in 3 mice. In the other 2 mice, the amount of malondialdehyde production was relatively decreased, but not like the control group.

DISCUSSION

The antidepressant drugSRT is most commonly administered to individuals suffer from depression (13)and it is regarded as a reproductive toxin,that may have adverse effects on the human reproductive system (14). In addition, numerous studies have recently been published on the harmful effects of SRT on rat fertility (14,15, 17). Due to the increased need for natural antioxidants in daily life, researchers are increasingly interested in discovering potent natural substances with extraordinary capabilities. It has been established that G. lucidum includes a wide range of bioactive substances that support several therapeutic values for various disorders(16). Therefore, this class of chemicals has been the subject of most investigations. It was, therefore, quite interesting to evaluate G. lucidum's antioxidant capacity in regard to treating the reproductive damage caused by SRT. In the present study, spermatozoa concentration and normal morphology significantly decreased, while sperm MDA levels increased dramatically, and histological abnormalities were observed, in which they all used as indicators of SRT›s reproductive toxicity. SRT treatment also caused a notable decline in the viability of sperm. These results concur with earlier data (17). In this study, the concentration of

sperm was reduced in 3 out of 5 mice in the group receiving SRT. Sperm motility was modestly decreased in 2 out of 5 mice who received 30 mg/kg of SRT. The CASA-based sperm mobility study in the SRT group exhibits a significant drop across all measured motility metrics. Case studies that support our findings show that SRT treated patients had lower spermatozoa volume and velocity but higher levels of abnormal sperm morphology (18, 19). The results of the histological analysis confirmed that SRT could cause seminiferous tubule malfunction and lowering the testosterone levels by damaging Leydig cells. The histopathological results were slightly different among the rats receiving SRT at a dose of 30 mg/kg. The results showed that the pattern of testicular tissue changes in mice was different, which indicate the importance of persolized treatment.

Our results showed that the generation of oxidative stress (OS) resulted significantly greater levels of MDA for the sperm suspension in the SRT treatment group. OS is defined as a situation in which the body creates excessive ROS, that weakens the body's built-in antioxidant defenses (20). ROS includes superoxide anions (O2), hydrogen peroxide (H2O2), peroxyl (ROO), and hydroxyl (OH) (21). Because OS impairs both the structural and functional integrity of spermatozoa, it significantly contributes to sperm dysfunction and considered the leading cause of male infertility (22). Although low levels of ROS are necessary for sperm capacitation and hyperactivation, mature spermatozoa are vulnerable to high levels of ROS that result in lipid peroxidation because of the high concentration of polyunsaturated fatty acids in their plasma membranes and their poor capacity for ROS scavenging due to the absence of cytoplasm (23). Lipid peroxidation thus reduces cell membrane fluidity and permeability, inhibits motility, and finally lessens the ability of mammalian spermatozoa to fertilize (24). Our results showed that the amount of MDA production increased by different level in mices of the SRT group. . The differences in pattern of increase in MDA production in mice can indicate the nessacity of percision and personolized management of treatment.

Also, the results of treating mice with the G. lucidum showed that only 3 mice had a decrease in MDA production. Therefore, based on concept of personalized medicine, we can conclude that antioxidant therapy may have a unique effect for each model, so, each mice's unique conditions should be taken into consideration. Also, the results of the evaluation of sperm viability in the group treated with SRT showed that the survival rate among mice in this group decreased with a slight difference. Nonetheless treatment with G. lucidum extracts increased sperm viability with a specific pattern for each mouse.

According to our findings, Ganoderma lucidum's 70% ethanol extract had significant levels of polysaccharides, triterpenoids, and polyphenols. Recent findings claim that the presence of polysaccharides and polysaccharide-complex compounds distinguishes the G. Luciduim from others (24). The results show that co-administration of G. lucidum extract with SRT at 300 mg/kg/day can reduce MDA production in sperm suspension of 3 mice. According to a specific research, G. lucidum extract increases the activity of the enzymes involved in scavenging ROS , superoxide dismutase (SOD), and catalase (CAT) (25). Additionally, sperm characteristics, including volume and movement in the G. lucidum and SRT-treated groups, were at average level compared to SRT-exposed animals. Examination of testicular tissue slices from both G. lucidum and SRT revealed that the typical shape of seminiferous tubules with several developed cells was present. We propose that SRT, which might affect individuals in different pattern, can be synergistically used with Ganoderma lucidum fungus extract to lessen its adverse effects. Interestingly seminiferous tubules and interstitial tissue repair were visible in photomicrographs taken from both the G. lucidum and SRT groups. By increasing antioxidant activity and reducing lipid peroxidation, G. lucidum may protect against OS and preserve the integrity of tissue functions brought on by SRT, according to the current evidence. However, many causes of male infertility are still unknown. For improved treatment outcomes and efficient drugs administration , physicians should employ tailore the therapy on the individual basis. Additionally, it is essential to evaluate the particular therapy requirements for each individual. Antioxidant treatment, which has been linked to a reduction in male infertility, is sometimes quite successful. Moreover, there must be more study in this field to expand and explore other effects.

CONCLUSION

The current study's findings prove that SRT harms the male reproductive system. More medical research should be conducted for advancement of fertility in in male. This study introduced personalized medicine and its possible treatment for male infertility and also to encourage the and therapeutic measures that are tailored for each individual. This study provides an overview of antioxidant therapy and the identification of biomarkers for male infertility.

Author statement

All individuals who satisfy the requirements for authorship are named as authors, and all authors have reviewed and given their approval to the submitted manuscript's final form. Additionally, each author

attests that they contributed sufficiently to the project, including the concept, design, analysis, and writing, to assume public responsibility for the work's content.

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