JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2025/51163
RESEARCH ARTICLE

Efficiency of Ethanolic Extract of *Syzygium cumini Per Se* in Preventing Silica-induced Toxicity in Male and Female Albino Rats

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Abstract

Background: Silicas, in general, are widely used in synthetic resins, plastics, cosmetics, foodstuffs, pharmaceuticals, and a wide variety of medical and dental applications. Amorphous silica has gained widespread use in the food and pharmaceutical fields since 1945. It can be made by either a wet technique that produces precipitated silica or a vapour phase approach that produces fumed silica. An increased risk of respiratory conditions such as silicosis, TB, chronic bronchitis, chronic obstructive pulmonary disease, and lung cancer is linked to prolonged work exposure to silica. **Aim:** The study aimed to evaluate the therapeutic effectiveness of simultaneous supplementation of vitamin E and vitamin C with and without the ethanolic extract of *Syzygium cumini* against silica toxicity. **Methods:** To observe the alteration of reproductive hormones and histopathological variables after silica exposure (at a dose of 40 mg/kg, *ip*) for 28 days, and also used therapeutic agents ethanolic extract of *S. cumini per se* (1000 mg/kg, *p. o.)* and its combination with Vitamin E + Vitamin C (50 mg/kg, *ip* + 100 mg/kg, *p.o.*). **Results:** Alteration was seen in the reproductive hormones after silica intoxication. After being intoxicated with silica for 28 days, experimental rats showed a significant drop in both male and female reproductive hormones. Using therapeutic agents, the readings returned to normal. **Conclusion:** Our experiment's findings clearly demonstrate that the combination of *S. cumini* with vitamin E and vitamin C worked better than *S. cumini per se*.

Major Findings: Combination of *S. cumini* with vitamin E and vitamin C was more effective than *S. cumini per se,* as both vitamins work directly with oxidizing radicals as low molecular mass antioxidants to protect cells from reactive oxygen species (ROS). Vitamin E, a naturally occurring lipophilic chain-breaking antioxidant, protects the membrane from damage. Vitamin C can help restore the antioxidant qualities of oxidized tocopherol, suggesting that one of ascorbic acid's main functions is to recycle the tocopheroxyl radical.

Keywords: Blood Parameters, Intraperitoneal, Silicon Dioxide, Testosterone, Therapeutic Agents

1. Introduction

The carbon distribution in organic materials is comparable to that of silicon in nature. About 28% of the Earth's crust is made of silicon. Due to its high reactivity, silicon does not stay in its elemental state; instead, it interacts with oxygen to produce free silica (SiO_2) or with other elements to form silicates, such as asbestos[1,2,3].

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Article Received on: 20.08.2025 Revised on: 13.10.2025 Accepted on: 06.11.2025

The diet is currently a major source of silica exposure for humans. Different types of silica are utilised as direct and indirect food additives, as well as for a variety of uses on crops and agricultural products. The Food and Drug Administration has deemed silicon dioxide and silica gel to be safe[4].

Slate, pencil, and agate grinding are among the jobs that are unique to India and have a significant risk of silicosis[5,6]. Approximately three million workers are at high risk of being exposed to silica[7].

Generally speaking, the characteristics of Precipitated Hydrophobic Silica (PHS) and Fumed Hydrophobic Silica (FHS) allow them to be used as free-flow/anti-caking agents in situations where regular silica is less successful. Accordingly, both varieties of hydrophobic silica are being explored for use as direct or indirect food additives in a range of applications[8].

The progressive lung condition known as "silicosis," which is the most prevalent of all occupational diseases, is brought on by inhaling free silica[9,10]. Silicosis is a disease from the industrial period that results in a fibrotic reaction that causes respiratory failure when silica particles are deposited in the lungs of humans and experimental animals[11-13]. The bark of *S. cumini* produces long-lasting brown dyes in a range of hues, contingent on the extract's potency and the mordant. The bark is used extensively to preserve fishing nets and tanning leather since it contains 8–19% tannin. Bark decoctions are used as a mouthwash or gargled to treat stomatitis, spongy gums, and mouth ulcers. They are also administered in situations of bronchitis and asthma. Bark ashes are either blended with oil and applied to burns or smeared over local inflammations when combined with water. Due to its ability to promote cancer and its absorption, tannin is no longer permitted for use on burned tissue in current therapy. Additionally harmful to health is excessive oral consumption of plant products high in tannins.

1.1 Silica

In the food and pharmaceutical industries, amorphous silica has been widely used since 1945. Both a wet technique that produces precipitated silica and a vapour phase approach that produces fumed silica can create it. Crystalline silica dust exposure over an extended period of time can result in granulomas, inflammation, and lung fibrosis[13,14]. The granite, sandstone, and stone quarrying and dressing industries. Among the jobs associated with silica exposure are metal grinding, sandblasting, iron and steel foundries, silica milling, flint crushing, and abrasive soap production[15,16].

At the molecular level, stress caused by toxicants is based on the generation of free radicals, which leads to chain reactions that damage membranes and cause biomolecules to cross-link. Age and stress have been linked by several groups of authors to increased generation of free radicals[17]. The sediments, which are pumped up from the lake and into the plant, are several meters thick. The material is then dried using geothermal water and sieved[18]. Silicosis was the most serious occupational danger in the 1930s and received significant federal, state, and professional attention at this time.

Toxicant-induced oxidative stress in biological systems can contribute indirectly to harm by being implicated in many sick states and toxic reactions. Free radicals are released by aqueous solutions of quartz dusts and have been linked to the pathogenicity of silica[19]. In some way, silica particles improved the permeability of alveolar macrophages' digestive vacuoles, which resulted in autodigestion. A fibroblast-stimulating factor released by the dying macrophages promotes the production of more collagen tissue. The final phases of silicosis are most likely the result of autoimmunity. As evidenced by the production of proinflammatory and profibrotic mediators, silicosis is typified by a persistent incitement of the inflammatory response[20].

Nanostructured amorphous SiO_2 can be highly toxic when inhaled, although the outcomes of studies conducted using its oral route of consumption are inconsistent[21,22]. Therefore, specifically, a dose of less than 1000 mg/kg of body weight (bw) causes some toxic consequences in rats, both local and systemic, even after a single injection of monodisperse SiO_2 NPs[23,24].

1.2 *Syzygium cumini*

Syzygium cumini (family *Myrtaceae*). Depending on the mordant and extract strength, *S. cumini* bark produces long-lasting brown colours in a range of hues. The bark, which has an 8 – 19% tannin

content, is frequently used to preserve fish and tan leather. Bark decoctions are used to treat bronchitis and asthma. They can also be gargled or used as mouthwash to treat stomatitis, spongy gums, and mouth ulcers. Bark ashes are applied to burns after being combined with water or placed over localised inflammations[15].

Common names for *S. cumini* include Indian Black Berry, Black plum, and Jamun. *S. cumini* fruits have anthocyanins, cyanidin, petunidin, malvidin glucoside, gallic acid, vitamin C, and tannins. The antihyperglycemic properties of *S. cumini* seeds have been well-established thus far, but reports of the fruit pulp's antihyperglycemic properties are scarce[17]. Jamun seeds are used to treat peptic ulcers, allergies, viral infections, inflammation, and polygenic diseases. It also has chemoprotective, cardioprotective, physiological, diuretic, and anti-nociceptive effects. Because of its impact on the pancreas, jamun seed is well recognised as having very high quality for its curative role, primarily against diabetes. Jamun seeds also contain ellagic acid, quercetin, albumen, fat, glycosides, an organic molecule called jambosine3, resin, and metals like vanadium, chromium, atomic number 11, and metallic elements. A variety of pharmacological characteristics, including antibacterial, antimicrobial, antifungal, antiviral, antioxidant, and free radical scavenging activity, cardioprotective, anti-inflammatory, neuropsychopharmacological activity, radioprotective, chemopreventive, larvicidal, gastroprotective, and antiulcerogenic activities, are possessed by the different extracts of different parts of jamun[25].

Animal models demonstrated anti-inflammatory properties in an ethanolic extract of *S. cumini* bark. Up to a dose of 10.125 g/kg, p.o., the extract did not exhibit any toxicity in mice. Rats tested for formaldehyde-induced paw oedema (sub-acute), cotton pellet granuloma (chronic), carrageenin (acute), and kaolin carrageenin (sub-acute) showed significant anti-inflammatory action. In rats' acute and chronic ulcerogenic testing, the extract did not cause any stomach lesions. Medicinal plants have been used to treat illnesses since ancient times and are a major source of both synthetic and natural medications[15,26]. The natural antioxidants found in therapeutic plants are currently gaining popularity. Scientists and clinical researchers can use plants' secondary metabolites as a vast resource to create novel medications. Indeed, it has been observed that secondary metabolites demonstrate a wide range of biological actions that support beneficial health outcomes. These activities include antibacterial, anticancer, antifungal, and antioxidant properties that are used in the food, pharmaceutical, and agricultural industries[2].

1.3 Vitamin E and Vitamin C

Vitamin E may mitigate the negative effects of Reactive Oxygen Species (ROS) at the site of free radical generation due to its potent antioxidant properties and role in plasma membranes[27].

In the present study, we aimed to measure the silica toxicity in reproductive organs (Ovary and Testis) and its recovery by plant extract of *S. cumini per se* and its combination with vitamin E and vitamin C.

The role of vitamin E supplements as antioxidants in enhancing immunological function in older women. They added that in certain animal models, vitamin E alters the appearance and behaviour of tumours and prevents the production of carcinogenic nitrosamines[1]. Supplementation of vitamin E serves as an effective method of preventing membrane damage caused by oxygen radicals. The detrimental effects of the organophosphate pesticide methidathion on antioxidant enzymes and lipid peroxidation, as well as the ameliorating benefits of a vitamin E and C combination[28].

The aim of the study is to evaluate the therapeutic effectiveness of simultaneous supplementation of vitamin E and vitamin C with and without ethanolic extract of *S. cumini* against silica toxicity.

2. Materials and Methods

Albino rats weighing 150 ±10 g, both male and female, were used for the investigation. In their conventional housing, which included a temperature of 25± 20C, a relative humidity of 60–70%, and a 12-hour photoperiod, they were given unlimited access to food and water. Animals were maintained as per the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Approval of the institutional animal ethics committee, Guru Angad

Dev Veterinary and Animal Sciences University, Ludhiana (IAEC/2018/1216-1250). SiO_2 was created as a toxicant dosage in regular saline. Olive oil was used to dissolve vitamin E, whereas distilled water was used to dissolve *S. cumini* and vitamin C.

Male and female mature animals were split up into four groups of five animals each (a Total 20 animals were used).

Group 1- Was given normal saline intraperitoneally (4 ml/kg) and acted as a standard control. **Group 2**- SiO_2 (40 mg/kg, *ip)* was administered daily for 28 days in a row as the experimental control.

Group 3- Treated with an ethanolic extract of *S. cumini per se* (1000 mg/kg, *p. o*.) for five days in a row after receiving the same toxicant as group 2.

Group 4- Treated with a combination of vitamin E (50 mg/kg, ip) + vitamin C (100 mg/kg, *p. o*.) and *S. cumini* (1000 mg/kg, *p. o*.) for five days in a row after receiving the toxicant as in group 2.

2.1 Collection of Blood and Preparation of Serum

Animal blood was drawn by puncturing the retroorbital sinus, centrifuged, and the serum refrigerated until analysis.

2.2 Necropsy of Animals

Animals were given ether anaesthesia and had their abdomens cut open 24 hours later. The testes (a male reproductive organ) and the ovary (a female reproductive organ) were removed right away. They were immediately fixed in Bouin's fixative for histology. Following their blotting and removal of unnecessary materials, they were weighed using a digital monopan electronic balance and subjected to histology.

The Kit method (CHOD-PAP method, No. 1117678.0001) from Merk was utilised to estimate the levels of reproductive hormones. Every result was given as a mean ± SE. The student's T test and P were used to compare two independent groups.

3. Result

Considerable slump in the level of estrogen on silica administration, at a dose of 40 mg/kg for 28 days. A combination of *S. cumini* with vitamin E and vitamin C was effective in the recoupment of estrogen concentration when compared to silica-exposed groups. Marginal therapeutic efficacy was also conferred by treatment of *S. cumini per se* (Figure 1 and Table 1).

The present study reveals a significant depletion in the level of progesterone in silicotic rats. Both therapeutic agents, i.e. *S. cumini* and a combination of *S. cumini* with vitamin E + vitamin C, restored the values to a considerable extent (Figure 2 and Table 1). Alterations in the activity of FSH on exposure to the toxicant at a dose of 40 mg/kg for 28 days. A significant decline in the activity of FSH is observed. Therapy of *S. cumini* with Vitamin E + vitamin C was more effective than *S. cumini per se* (Figure 3 and Table 1).

Significant depletion in the level of LH in silica-treated animals was seen when compared to control groups. A combination of *S. cumini* with vitamin E + vitamin C was more effective in the recoupment of the level of LH rather than *S. cumini per se* (Figure 4 and Table 1).

The mean testosterone level of the various groups of rats receiving 40 mg/kg silica as silicon dioxide exposed rats was statistically higher than the level of basal control animals. Both therapeutic agents, i.e., a combination of *S. cumini* with Synthetic product (vitamin E + vitamin C), and *S. cumini per se* restored the values to normal control, but the combination of *S. cumini* with vitamin E + vitamin C was found to be more effective (Figure 5 and Table 1).

3.1 Blood Parameters

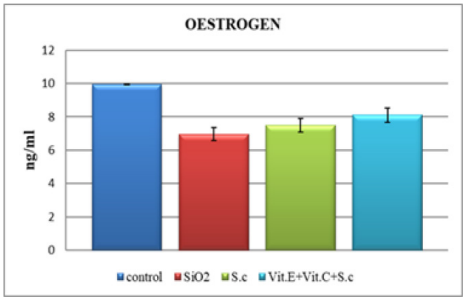


Figure 1. Comparison of oestrogen between the control and treated groups.

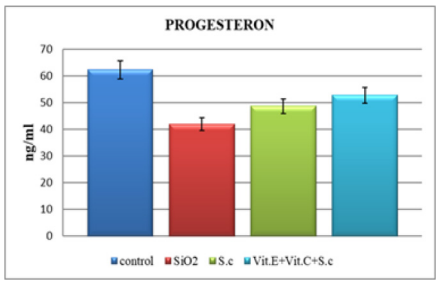


Figure 2. Comparison of progesterone between the control and treated groups.

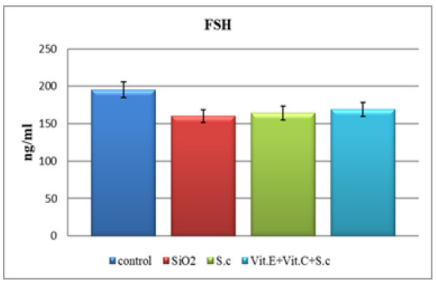


Figure 3. Comparison of FSH between the control and treated. groups

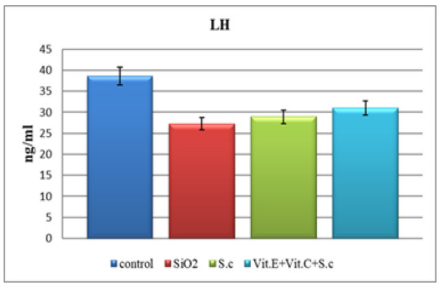


Figure 4. Comparison of LH between control and treated groups.

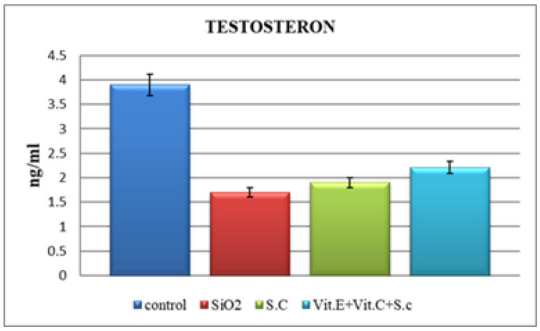


Figure 5. Comparison of testosterone between the control and treated groups.

Table 1. Blood parameters of the control and treated groups

Sr. No.	PARAMETER	CONTROL	SiO_2	S.c.
1	Testosteron (ng/ml)	3.9+0.22	1.7+0.093	1.9+0.10
2	Estrogen (ng/ml)	9.96+0.55	6.96+0.38	7.5+0.41
3	Progesteron (ng/ml)	62.21+3.43	41.9+2.32	48.6+2.68
4	FSH (ng/ml)	195.32+10.79	160.12+8.85	164.3+9.0
5	LH (ng/ml)	38.62+2.13	27.28+1.51	28.9+1.59

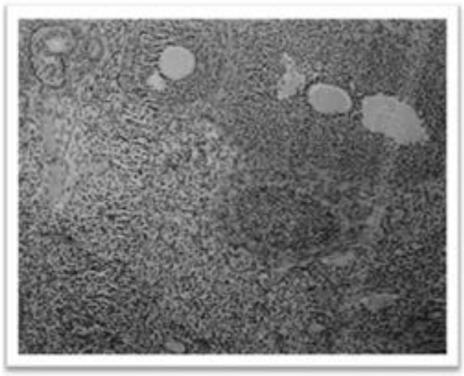


Figure 6. T.S. of the Ovary of an albino rat of the control group. the normal cellular organisation with all kinds of follicles, stroma and vascularity. X 200.



Figure 7. Silica exposure caused atrophic changes in the developing follicles and loose stroma with normal vascularity. X200.

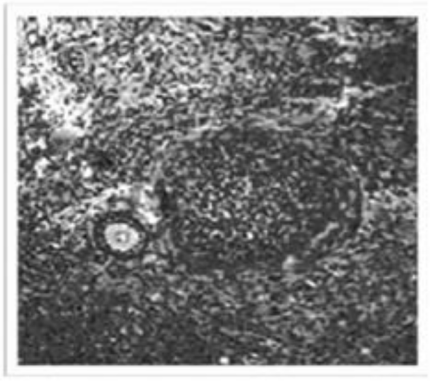


Figure 8. Treatment with S. cumini per se, slight improvement in ovarian architecture X200.

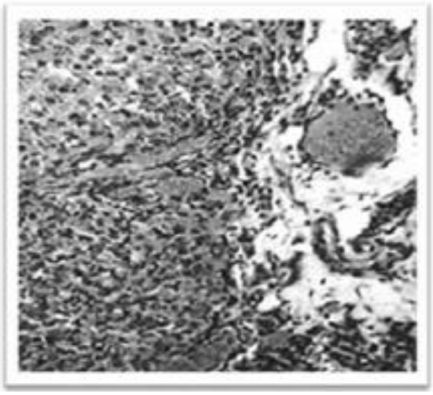


Figure 9. Treatment with a combination of S. cumini with vitamin E and vitamin C after silica administration showed significant improvement in ovarian architecture, follicles, vascularity and corpora lutea also seen. X 200.

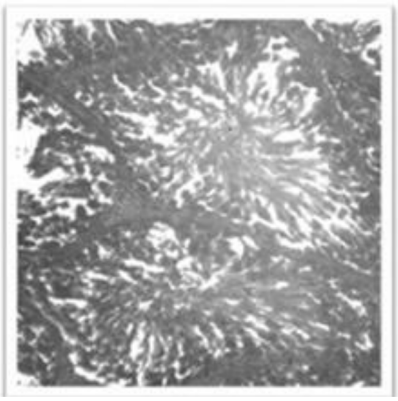


Figure 10. T.S. of the testis of the albino rat of the control group showed the tunica propria was well organised and seminiferous tubules with regular stages of spermatogenesis from spermatogonia to spermatozoa. The Leydig's cells were present in the interstitium. The vascularity of the organ was normal.



Figure 11. Silica exposure caused the testicular damage to be more generalised. In some tubules, the lumen was filled with degenerated cellular material. The remaining germ cells showed clumping to each other. The interstitium was totally devoid of Leydig's cells.

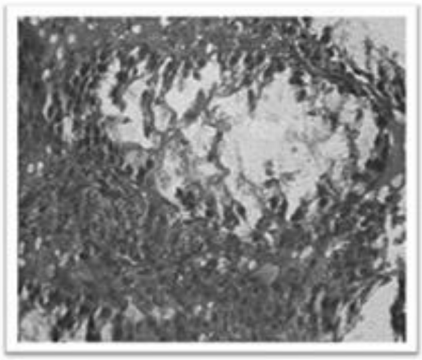


Figure 12. Treatment with S cumini per se slight improvement in testes architecture.



Figure 13. Treatment with a combination of *S. cumini* with vitamin E and vitamin C after silica administration improved the testes architecture to a great extent and showed significant improvement in testicular damage, seminiferous tubules, Leydig's cells, etc. X200.

3.2 Photograph

Photomicrograph of the T.S. of the ovary of an albino rat of the control group. Shows the normal cellular organisation with all kinds of follicles, stroma and vascularity (Figure 6). Silica exposure caused atrophic changes in the follicles and abnormal vascularity (Figure 7). Treatment with *S. cumini per se* showed slight improvement in follicles, vascularity and corpus lutea. (Figure 8). Treatment with a combination of *S. cumini* with vitamin E + vitamin C after silica administration improved the ovarian architecture to a great extent. It showed significant improvement in follicles, stroma, vascularity and corpus lutea, also seen (Figure 9). Photomicrograph of the T.S. of the testis of the albino rat of the control group showed well-organised tunica propria and seminiferous tubules with regular stages of spermatogenesis from spermatogonia to spermatozoa. The Leydig's cells were present in the interstitium. The vascularity was normal (Figure 10). The silica exposure caused severe testicular damage. The vascularisation had increased considerably in the seminiferous tubules. The interstitium was totally devoid of Leydig's cells. The vascularity was severely affected (Figure 11). When these silicotic rats were treated with the ethanolic extract of *S. cumini*, improvement was shown in the testicular architecture to a great extent. It also showed slight improvement in testicular regeneration (Figure 12). Treatment with a combination of S. *cumini* with vitamin E and vitamin C after silica administration improved the testicular architecture to a great extent. It showed significant improvement in testicular regeneration after damage caused by treatment, seminiferous tubules and Leydig's cells became normal (Figure 13).

4. Discussion

An established occupational fibrogenic agent is silica. An illness from the industrial age, silicosis is caused by silica particles depositing in the lungs of humans and experimental animals. Reexamination of the scientific literature on respirable crystalline silica led the International Agency for Research on Cancer (IARC) to classify occupational respirable crystalline silica as a human lung carcinogen[29]. During the current investigation, rats were exposed to silicon dioxide sub-chronically for 28 days. They were then given α-tocopherol, ascorbic acid, and an aqueous extract of *S. cumini* (bark). The findings of this investigation demonstrated that silica caused oxidative stress and significant changes in blood biochemical markers and histological observations. Male and female reproductive organs were found to benefit from the protective effects of α-tocopherol, ascorbic acid, and *S. cumini* extract.

The amorphous silica nanoparticle is being synthesised with highly tunable biocompatibility and stability, which is considered to be very promising for many applications, as drug delivery and molecular imaging[30]. Heavy production and excessive use of silica nanoparticles have resulted in an increased risk of human exposure. The unique nature of the male reproductive system makes the biological effect of nanoparticles on this system increasingly found as an important part of the overall toxicological studies. Mice given SiNPs had testicular regions that had various morphological alterations. The testis's seminiferous epithelium shrank and interstitial tissue degenerated after SiNPs were administered[13]. Oestrous and proestrus have high plasma levels of estrogen, whereas diestrus and metestrus, which are progesterone-dominated phases of the oestrous cycle, have low levels[31-35]. The levels of progesterone in the plasma decrease in the later stages of pregnancy, whereas the levels of estrogen increase gradually and peak near the end of pregnancy[36,37]. High plasma levels of estrogen and progesterone are associated with enhanced responsiveness of the rat uterus's alpha and beta adrenoceptors, respectively[31]. Late pregnancy and the early postpartum period are when alpha adrenoceptor responsiveness is at its highest[17,38,39]. The increase in plasma oestrogen levels that occurs toward the end of pregnancy was assumed to be the cause of this[36,37]. This is in line with earlier research showing that giving rats oestrogen beforehand improves the uterine alpha adrenoceptor responsiveness, whilst giving them progesterone beforehand decreases it[18,40]. The availability of the rat uterus's post-synaptic alpha and beta adrenoceptors is influenced by this rise or fall in hormone levels[11,39,41]. The current study shows a significant drop in estrogen levels following a 28-day dosage of 40 mg/kg of silica. Vitamin E and C combination therapy with *S. cumini* restored estrogen levels. Additionally, treating *S. cumini* alone resulted in marginal therapeutic effectiveness.

Endocrine (FSH, LH, and prolactin) and local (paracrine and autocrine) hormones control

follicular development. These latter comprise a variety of nonsteroidal regulators (luteinisation stimulator, luteinisation inhibitor, oocyte maturation inhibitor, FSH inhibitor, insulin-like growth factors, transforming growth factors, epidermal growth factor, platelet-derived growth factor, inhibin, and activin) as well as steroid hormones (estrogens, progestins and androgens) generated by various ovarian cell types[42,43,44]. The pituitary's production of FSH and LH during folliculogenesis is what allows the ovarian follicle to develop and differentiate successfully. The pituitary gonadotrophins, FSH and LH, which are controlled by their corresponding releasing factors, are responsible for the alteration in ovarian architecture[17]. Conversely, progesterone is thought to hinder ovarian steroidogenesis and has been shown to suppress post-coital ovulation in rabbits. Following 28 days of exposure to the toxicant at a level of 40 mg/kg, a notable decrease in FSH and LH activity is seen in the current investigation. *S. cumini* in combination with vitamin E and vitamin C proved to be more efficient than *S. cumini* alone.

Although both medicinal substances restored the depletion, it was shown that vitamin E + vitamin C combined with *S. cumini* was the most successful. There were alterations in the cellular organisation of the ovary's histology. The folliculogenesis process is driven by cAMP and influenced by numerous local autocrine factors and paracrine, according to numerous recent *in vivo* and *in vitro* investigations[44,45]. Non-steroidal substances like growth factors and steroid hormones are examples of these modulatory agents. A substantial decrease in the quantity of normal follicles results from atresia's disruption of the follicle selection process.

The silica exposure seriously damaged the testicles. The seminiferous tubules' vascularisation had significantly enhanced. Leydig's cells were completely absent from the interstitium. Following the administration of silica, treatment with vitamins E and C significantly enhanced the testicular architecture. It demonstrated notable recovery from treatment-induced testicular injury. Leydig's cells and seminiferous tubules returned to normal[12].

5. Conclusion

In conclusion, our experiment's results unequivocally show that a combination of *S. cumini* with vitamin E and vitamin C was more effective than *S. cumini* alone. This is because both vitamins are low molecular mass antioxidants that directly interact with oxidising radicals to shield cells from Reactive Oxygen Species (ROS). Natural lipophilic chain-breaking antioxidant vitamin E shields the membrane from harm. Restoring the antioxidant properties of oxidised tocopherol is possible with vitamin C, indicating that recycling the tocopheroxyl radical is one of ascorbic acid's primary roles. In addition to its antioxidant properties, ascorbic acid is necessary for the detoxification of harmful compounds and the microsomal oxygenation of several xenobiotics.

6. Author Contribution

Shruti Saxena: Conceptualisation, Data curation, Investigation. Kanchan Chatterjee, Formal analysis, Investigation. Priyanka Kumari: Investigation, Resources. Priyanka Rana: Supervision, Writing. Rupinder Kaur: Investigation, Software Handling Shefalee Singh: Investigation, Software Handling. All authors have read and agreed to the published version of the manuscript.

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