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THE RADIO-PROTECTIVE EFFECTS OF *WITHANIA SOMNIFERA* AGAINST MOBILE PHONE ELECTROMAGNETIC RADIATION-INDUCED INFERTILITY IN MALE WISTAR RATS

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Keywords:

Infertility, electromagnetic radiation (EMR), Withania Somnifera, Sperm morphology, Leydig cells, Albino Rats, Antioxidants

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ABSTRACT: Introduction: The study was aimed at knowing the effect of mobile phone electromagnetic radiation (EMR) on fertility in Wistar Albino Rats and to assess the capability of polyphenolic rich *Withania somnifera* root extract in shielding rat testis against EMR-induced injuries. **Methodology:** One hundred and forty-four male Wistar Albino Rats were included in the study and grouped in to 4. Group I received a standard diet, Group II exposed to active mobile phone radiation of 2700 MHz fields for 3 hours/day, Group III exposed to 2700 MHz fields for 3 hours/day along with administration of 250 mg/kg aqueous extract of *Withania somnifera* root (Aq-Wsr) orally and Group IV received standard diet and 250 mg/kg Aq-Wsr during the experimental period of 180 days. **Results:** Group-II showed a significant decline in the sperm parameters and reduced *in-vivo* antioxidants. Group III revealed significant augmentation of sperm parameters and regulated the *in vivo* antioxidants. On microscopic examination, Group II showed irregular seminiferous tubules, atrophy of spermatogonial cells, hyper-cellularity, degenerated spermatozoa, and decreased number of Leydig cells. **Conclusion:** This research concludes that long-term exposure to EMR results in testicular trauma, which was statistically significant in sperm parameters and microscopic changes of testis in Group II. This study also proved the shielding effect of *Withania somnifera* root extract against EMR.
Keywords: Infertility, electromagnetic radiation (EMR), *Withania somnifera*, Sperm morphology, Leydig cells, albino rats, antioxidants.

INTRODUCTION: Diversity of environment and communities worldwide has been witnessed. Augmentation of male infertility has been observed in recent decades [1].

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The testis is the male gonad that produces spermatozoa under the control of various factors.

The anatomy of the testis is made up of the seminiferous tubules, the site of spermatogenesis, and the interstitial cells of Leydig that secret the male sex hormone testosterone. The whole process of sperm production is regulated by genes on the Y Chromosome and will take around 70 days to complete starting from the spermatocyte phase. The whole process of sperm production is regulated by genes on the Y chromosome and will take around

70 days to complete starting from the spermatocyte phase. Additionally, 12-21 days will be required to transport sperm from the testis together with the epididymis to the ejaculatory duct.

The aetiology of male infertility is unidentified due to considerable variability in infertility such as stress, environmental factors, radiation, and lifestyle [2]. Nonetheless, among 30-50% of sub-fertile couples, the male has sub-fertile liquefied semen quality. Because of poorly motile sperm, less number of sperm make a difference, or sperm with uncommon size and shape matters. In more than 50% of infertility in males, the aetiology remains unfamiliar and is classified as idiopathic [3]. Examination of male infertility must go beyond a straight examination of sperm, which needs to be coordinated by using a thorough background and actual physical assessment and pertinent hereditary, endocrine, and many other aspects [4].

In circulation from the epididymis, sperms mature further to formulate the ability for sustained motility [5]. The long time necessary for sperm development and transport signifies that the outcomes of your semen analysis reflect circumstances existing many weeks earlier [6]. Semen contains secretions offered from the prostate, the seminal vesicles, along the distal vas deferens. It has been encouraged that this significant cause of male infertility could be recognized to oxidative stress, and also the components that could be endangering it by inducing the same inside the testicular cells such as ionizing radiation, occupational harmful toxins, distinct atmospheric circumstances as well as many infectious conditions, oxygen metabolism, inflammation and also lifestyle stresses [7].

With the increase in electromagnetic wave techniques, the biological outcomes of electro-magnetic pulses (EMPs) have accessed the main focus [8]. Ecological, job-related, and fortunate experience to EMR influences human health its outcome on the reproductive system and the mechanisms behind this the topic of research [9]. The occurrence of male sterility put through Electromagnetic waves indicates a stable improvement over existing years [10]. In 2000 an updated comprehensive metanalysis was done that confirmed the falling trend in sperm count. AIMS reported over 12-18 million couples diagnosed with infertility every year. They reported that 3 decades ago the sperm count of a normal Indian adult male was 60 million/ml, but now it stands around 20 million/ml.

Also, the reproductive value of males working in increased voltage electronic terminals, mobile communication base stations, and other electro-magnetic situations has significantly reduced [11]. The fast development of mobile phone connections is along with a rise in radiofrequency (RF) electromagnetic rays (EMR). Subsequently, public worries have already been elevated in the possible hazardous overall health effect for being in contact with RF-EMR offered by cellular phones [12]. Recent studies have proposed that cellular phone use can be a risk aspect for brain cancers. Although evidence from human research and animal studies is limited, the International Agency for Research on Cancer (IARC) classifies RF-EMR as “possibly carcinogenic to people be in [13].

Herbal drugs provide an option on artificial materials and have already been considered either harmless or harmful [14]. It has provided driving a vehicle pressure to show for electromagnetic radiation protecting potential [15]. Natural plants and their products represent the critical supply of antioxidants. In various conventional systems of medication, they have been created consumption for thousands of years to treat many circumstances, which includes lack of ability to get pregnant, around the world [16]. *Withania somnifera* (WS), otherwise known as Ashwagandha, Indian native ginseng, winter season cherry, is a well-known medical grow in Solanaceae household found in standard treatment in lots of countries including India [17]. This herb is recognized to stop impotence and climb sexual magnetism plus infertility when produced solely or with several other medicines. Various areas of this growth, such as roots, foliage, blossoms, plant seeds, stems, and fruit, are manufactured as therapy in several countries' conventional medication. Several phytochemicals have already been slow thus far, with this plant possessing various pharmacologic and biological or commercial properties [18]. WS has become recommended to check polyarthritis, lumbago, agonizing swellings, untimely climaxing, oligospermia, torment, asthma, vitiligo, basic

debility and impotence, abscess, uterine disease, leucorrhoea, haemorrhoids and also orchitis in common Persian medication. Each one of these therapeutic usages suggests it's anti-inflammatory, aphrodisiac, semenogogue, and deobstruent features. In terms of you can find no large-variety and specific studies or organized customer feedback regarding the healing outcomes of WS, on the male and female reproductive program, the here now investigation research was trying to systemically assess WS's healing outcomes on reproductive process plus virility disorders [19]. For that reason, the objective of the investigation review is usually to assess the possible safety result of the extract of *Withania somnifera* against testis damage due to smartphone electromagnetic radiation in rats.

MATERIALS AND METHODS: The present study was a randomized control study design that included 144 Wistar Albino Rats, weighing 120-150 g of 25 days old. They were housed in an air-conditioned room (20-25 °C) and subjected to a 12/12 h daylight/darkness cycle with free access to food and water. The study was conducted for a period of 6 months after obtaining Institutional Animal Ethical Committee clearance, and all animals were housed as per the CPCSEA standard criteria (SAC/IAEC/BC/2017/PhD-003).

The root of *Withania somnifera* was collected from the Vishnu Ayurveda College, Shornur, Palakkad, Kerala and it was identified and authenticated by Centre for Medicinal Plant Research, Arya Vaidyasala, Kottackal, Malappuram District, Kerala. The roots of the gathered plant were cleaned, shade dried, and coarsely powdered. 200 g of root powder in 1200 ml of water was boiled and reduced to 1/3 volume, and the same was evaporated to dryness. The paste form of the extract obtained was stored in an airtight container at 4 ºC [20]. The study was conducted over a period of 180 days by grouping the Albino rats into four with; 36 rats in each group. Group I (control) received only a standard diet regime. Group II was exposed for a dose of 2700 MHz fields for 3 h/day throughout the experimental period. Group III was Exposed to 2700 MHz field' scell phone rays for 3 h/day through the experimental period and compounded every day for 180 days with 250 mg/kg BW aqueous extract of *Withania somnifera* root (Aq-Wsr) by gastric gavage. Group IV was administered with 250 mg/kg Aq-Wsra long with the standard diet. All animals from the control and experimental groupings were housed collectively, with each group having a total number of 36 animals with 9 animals each in four different polycarbonate cages of 30 × 40 × 40 cm dimension (W × L × H). The experimental animals were continually in contact with electromagnetic radiation (EMR) through the cell phone. The electromagnetic radiofrequency rays were generated by utilizing a cell phone with a specific absorption rate of 1.6 W/kg. A 2700 MHz, EMR near-area indicate for GSM process was utilized.

The field power was measured using the Radio-frequency meter (Cornett Electro-smog meter). The cellular phone was placed in the middle of the cage; the extended distance involving the cell phone from the bottom of the cage was 5 cm, with the maximal distance from the cage corners was 18.2 cm. Six rats were sacrificed at the end of each month from each group, and testis was harvested. Then it was preserved for antioxidant assay and histopathological examination. The left testis was dissected and instantly fixed in 10% neutral buffered formalin for 24 h. Bits were taken both transversally longitudinally along with the capsule. After fixation, the tissue was subjected to routine histopathological tissue processing, and finally, paraffin blocks were sectioned to 5 µm slices followed by hematoxylin and eosin staining [30]. Tissues were observed for lesions such as the thickness of capsule, the height of germinal epithelium, diameter and density of sertoli cell, necrotic changes, vacuolization, *etc*.

Epididymis sperms were collected by slicing the cauda region of the epididymis in 5 mL of human tubal fluid and incubated in an atmosphere of 5% CO_2 for 30 min at 37 °C to allow sperm to swim out of the epididymis tubules. After collection and liquefaction, the sperm count, motility, viability, morphology, and semen testosterone levels were evaluated using conventional methods.1:20 dilution was prepared in 1 mL microtube by pouring 190 µL of distilled water and 10 µL sperm mixture. Then, 10 µL of the mixture was dropped on a Neubauer slide, and the sperms were counted [21]. 10 µL sperm suspensions were placed on a pre-warmed slide which was covered with another

slide, and then the motility was witnessed within a light microscope (Nikon, Tokyo, Japan) with 400 × magnification [22].

Sperm Viability: It was examined by adding 20 µL of 0.05% Eosin Y-nigrosin stain into the same volume of sperm suspension. After 2 min incubation at room temperatures, slides were seen by a light microscope using a magnification of 400 × Dead sperms were discoloured pink, but the live ones had taken no colouration. Viable sperms (n = 400) were measured in each trial, and also the viability portion was computed [23].

Sperm Morphology: To evaluate the semen morphology, aniline blue staining approach was applied. The unusual morphologies percent was established. Considerably, the cytoplasmic leftover of sperms was considered as an unusual morphology [24]. The abnormality is seen in the head, middle piece, and tail of spermatozoa was noticed and categorized accordingly.

Antioxidants and Oxidative Stress: The concentration of reduced glutathione (GSH) was determined using Moron's procedure (1979) [25]. Lipid peroxidation (MDA) was estimated as thiobarbituric acid reactive substance (TBARS) according to the method of Ohkawa 1979 [26]. Catalase (CAT) activity was evaluated according to the method described by Chance and Greenstein 1992 [27]. Meanwhile, the activities of superoxide dismutase (SOD) [28] and glutathione peroxidase (GPx) were determined using the method of Misra and Fridovich (1972) [29].

RESULTS: The present study investigated the effect of EMR on the rat testes and the possible shielding effect of WS on EMR induced tissue damage. At the end of the investigation, it was

noticed the testicular changes were predominant. The decrease of epididymal sperm factors inside Group II was statistically significant compared with the management group ($p<0.05$). The outcome of epididymal sperm is essential in all groupings are shown in **Fig. 1.** The sperm count was 85.61 ± 0.28, 69.78 ± 2.67, 83.92 ± 2.01, and 86.92 ± 0.34 in control, EMR, Aq-Ws r+ EMR, and Aq-Wsr groups, respectively

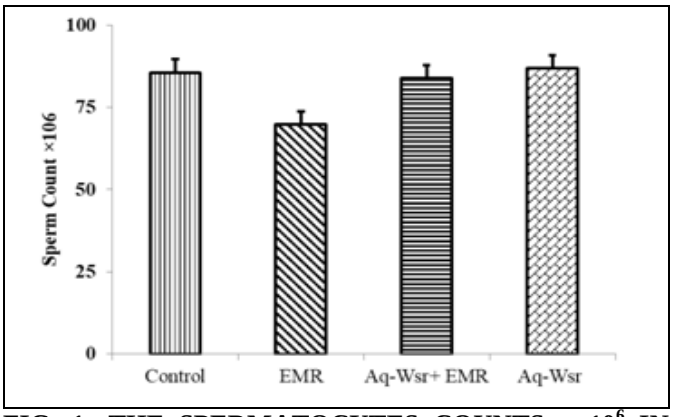

FIG. 1: THE SPERMATOCYTES COUNTS × 10^6 IN THE CONTROL AND EXPERIMENTAL GROUPS

EMR exposures led to a significant increase in the types of abnormal sperm cells observed, which were the pyriform head, detached head, coiled tail, and multiple abnormalities, where the highest numbers were 2.14 ± 0.10, 0.32 ± 0.01, 10.71 ± 0.33, and 2.08 ± 0.10 respectively in the group exposed to EMR as shown in **Table 1.** The life-to-death percentage results inside the smear analysis demonstrated how the semen with all the maximum proportion was attained inside the control Group even though the most affordable proportion was acquired in the group exposed to EMR. The sperm motility was significantly decreased, whereas the frequency percentage of dead spermatozoa was significantly ($P < 0.05$) increased in the EMR exposed animals, and amelioration was in the EMR + Aq-Wsr Group compared with the control animals. The results presented in **Fig. 2.** show the comparison between the measured values for gross motility and life to death ratio, respectively.

TABLE 1: THE SPERM ABNORMALITIES IN THE CONTROL AND EXPERIMENTAL GROUPS (MEAN ± SE)

Groups	Sperm abnormalities%			
	Pyriform head	Detached head	Coiled tail	Multiple
Control	0.58±0.02	0.55±0.02	2.45±0.07	0.64±0.02
EMR	2.14±0.10	0.32±0.01	10.71±0.33	2.08±0.10
EMR + Aq-*Wsr*	0.99±0.06	0.41±0.01	6.60±0.18	1.16±0.08
Aq-*Wsr*	0.48±0.01	0.54±0.02	1.93±0.12	0.43±0.04

* $P \leq 0.05$ is considered significant.

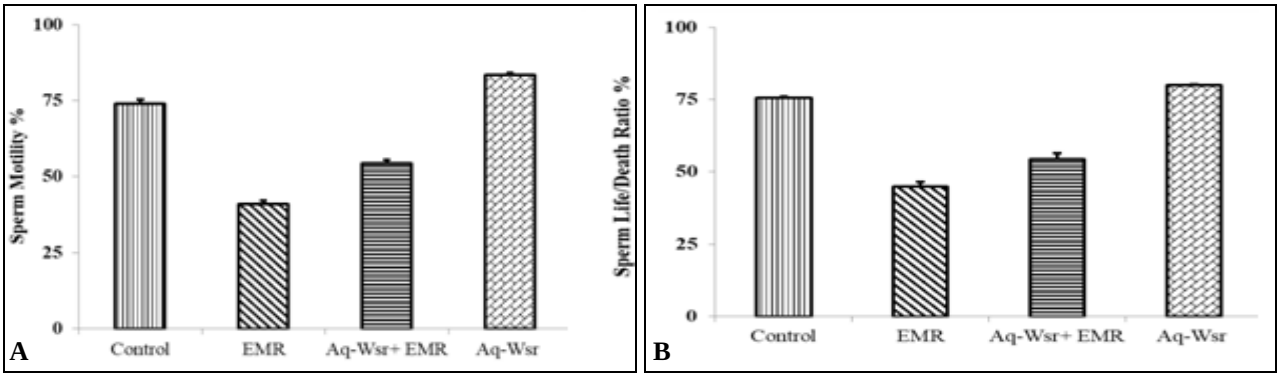

FIG. 2: THE MOTILITY OF SPERMATOCYTES PERCENTAGE (A) AND THE SPERM LIFE/DEATH RATIO PERCENTAGE (B) IN THE CONTROL AND EXPERIMENTAL GROUPS

TABLE 2: LEVEL OF ANTIOXIDANT PARAMETERS IN THE TESTIS OF RATS (MEAN ± SE)

Groups	LPO (nmol MDA·mg^{-1} protein)	CAT (U·mg^{-1} protein)	SOD (U·mg^{-1} protein)	GSH (µ (U.mg^{-1} protein	GPx(mg.g^{-1} (wet tissue))
Control	44.57±6.90	38.3±0.13	3.26±0.05	749.54±20.24	1422.74±4.76
EMR	179.17±33.63	16.53±0.16	2.64±0.55	295.21±10.63	920.74±6.77
EMR + Aq-*Wsr*	56.70±2.62	27.96±0.26	3.02±0.22	492.97±13.58	1394.72±3.67
Aq-*Wsr*	47.78±1.06	38.13±0.07	4.05±0.13	777.49±7.40	1504.69±14.16

* $P \leq 0.05$ is considered significant.

The levels of some antioxidant enzymes in the testis of the experimental rats are shown in **Table 2.** Compared to the Control Group, activities of SOD, CAT and GPx were significantly higher ($P \leq 0.05$) in Group III rats. On the other hand, the activity of SOD and concentration of GSH was significantly different between rats in Group II and III compared to control. The activity of GSH concentration was, however, significantly lower in the rats in Group II. Lipid peroxidation was significantly higher ($P \leq 0.05$) in the testis of rats in Group II. However, there was no significant difference ($P \leq 0.05$) in the level of lipid peroxidation observed in the testis of the rats between Group III and IV compared to control. Also, there was a noticeable difference in MDA, CAT, and SOD in animals treated with Aq-Wsrthan animals inside the control class.

Light Microscopic Results of the Testis: A study of hematoxylin and eosin-stained sections of control testes (Group I) proved many seminiferous tubules and interstitial tissue in-between that contain clusters of Leydig cells because of their vesicular nuclei and vacuolated acidophilic cytoplasm. Tubules were surrounded by a well-defined basement membrane lined with a stratified epithelium comprised of Sertoli cells and spermatogenic cellular material. Sertoli cellular material was acknowledged from their prominent ovoid and vesicular nuclei dispersed at intervals between spermatogenic cells. Spermatogenic cellular material included spermatogonia, primary spermatocytes, then early spermatids, later spermatids, and finally spermatozoa, which were seen in your tubules' lumen. Even the histopathology of Group III, which received Aq-Wsr, demonstrated seminiferous tubules lined by spermatogonia relaxing on basements membrane layer, combined with early on spermatids and finally delayed spermatids. The lumen of tubules contained spermatozoa. Leydig cells appeared in interstitial tissues near blood vessels in-between tubules. They made an appearance almost nearly comparable to the ones from Group I. But the histopathological stained sections of Group II (EMR) showed unusual seminiferous tubules. Many of these tubules were depleted in their spermatogenic tissue. They were lined by Sertoli tissue, a few spermatogonia and few primary spermatocytes with darkish condensed nuclei. Giant multinucleated cells were seen inside the seminiferous tubules. Also, some degenerated spermatocytes could be detected in the lumen of the seminiferous tubules. The prolonged interstitial tissues looked vacuolated with exudation and overloaded blood flow vessels. Furthermore, the study of discoloured sections of the Group III (Aq-Wsr + EMR) indicated several spermatogenic cellular material levels lined the seminiferous tubules.

Sertoli cells and Spermatogonia have been observed sleeping around the basmeent membrane accompanied by primary spermatocytes, earlier and later spermatids nearly like the handle group. EMR exposed group also showed sub-capsular congestion, necrotic debris, vacuolar degeneration of germinal epithelium, and absence of sperm within the tubular lumen, widespread tubular degeneration and testicular atrophy. No necrotic changes were observed in the testicular tissues of Group III rats instead some extent of sertoli cell proliferation were seen significantly. Group IV showed a significant rise in the number of sertoli cells.

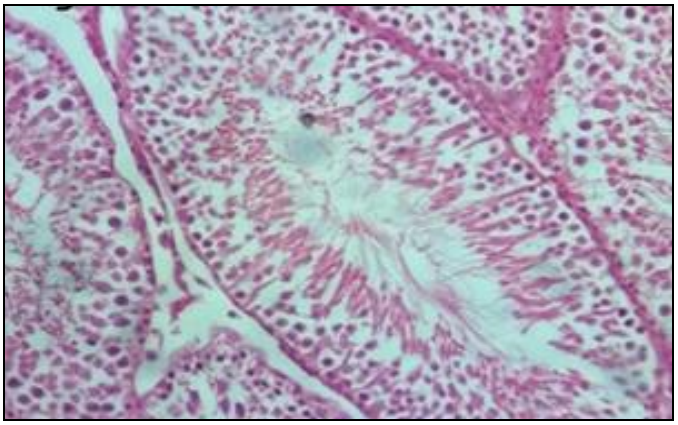

FIG. 3: H&E X100, PHOTOMICROGRAPH OF TESTIS OF GROUP I-III MONTH SHOWING NORMAL SEMINIFEROUS TUBULES AND NORMAL GERMINAL EPITHELIUM

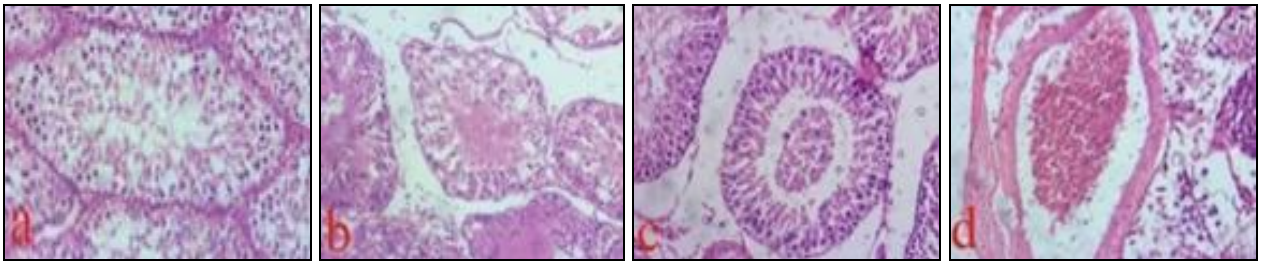

FIG. 4: H&E X100, PHOTOMICROGRAPH OF TESTIS OF GROUP II-III MONTH SHOWING SHRUNKEN TUBULES, WIDENED INTERTUBULAR SPACE, SUBCAPSULAR CONGESTION, DETACHMENT OF SPERMATOGONIAL CELLS

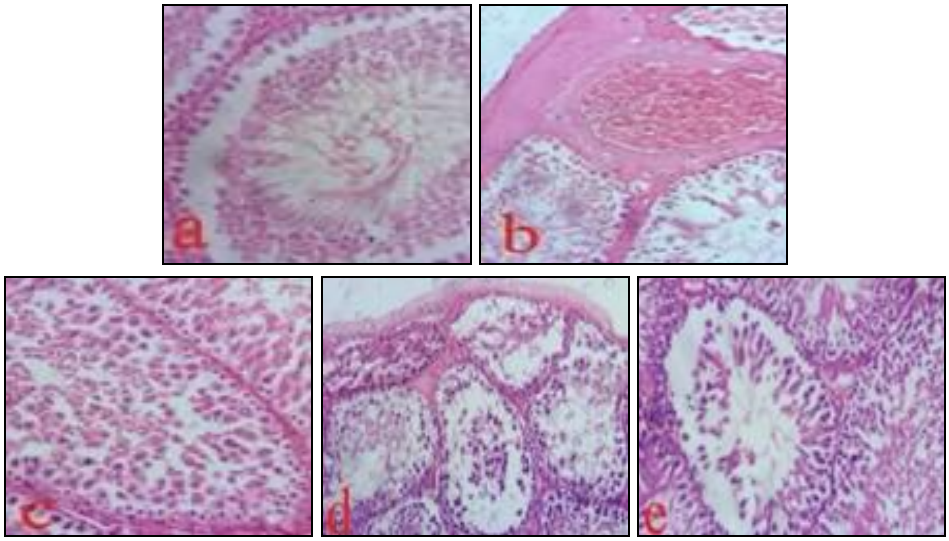

FIG. 5: H&E X100, PHOTOMICROGRAPH OF TESTIS OF GROUP III-III MONTH, a AND e SHOWING OCCASIONAL DETACHMENT OF EPITHELIUM, b SHOWING SUB-CAPSULAR CONGESTION

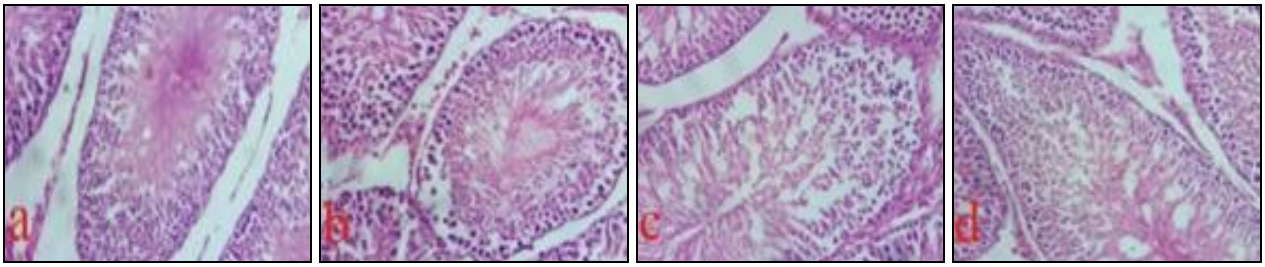

FIG. 6: H&E X100, TESTIS OF GROUP IV-III MONTH SHOWING NORMAL TUBULES, PROLIFERATION OF SERTOLI CELLS IS MORE EVIDENT AND INCREASED NUMBER OF SPERMATOZOA IN THE LUMEN OF THE TUBULES SHOWING ACTIVE SPERMIOGENESIS

DISCUSSION: Most men of reproductive age in high or midst-earning nations own cell phones, and with this increase in cellular phone management, there is egoism over the crucial adverse effects of cell phone visibility on a man's being [31]. Cellular telephones produce electromagnetic radiation (EMR), the lowest-stage radiofrequency (RF), at a volume between 800 and 2200 MHz, which the human body can absorb [32]. Cell phones are legally limited to a particular absorption amount (SAR) of 2. W/kg, and at present, most have a SAR of ~ 1.4 W/kg [33]. Around this low frequency of EMR is just not likely to ionize atoms or molecules. Cell-phones and also other electromagnetic products that produce RF-EMR rays are harmful to man's infertility [34].

Withania somnifera micronutrients consist of antitumor, contra-epileptic, contra-diuretic, contra--inflammatory and antioxidant components. *Withania somnifera* (Aq-Wsr) features specific vegetation pigments with potent anti-oxidative capacity, including natural vitamins C, E, A, caffeoylquinic acids, carotenoids-lutein, alpha-carotene, and beta carotene, kaempferol, quercetin, rutin [35]. From the existing review, Aq-Wsr was applied as anti-electromagnetic radiation-induced sterility in rats [36]. The current research results indicated that long-term consumption of GSM cell phones might cause hypo-spermatogenesis and maturation arrest in spermatozoa inside the testes of rats compared to their matched-up handle [37].

At substantial intensities, RF rays have heating system qualities creating thermal effects, increased cells or entire body heat on being exposed to EMR can cause reversible spermatogenesis interference of spermatogenesis [38]. Wang *et al.*, suggested that Leydig cells are among the most susceptible cells to EMR, and injury to these cells may affect spermatogenesis and its parameters [39]. Leydig cells create spermatozoa, and in case the Leydig cells are ruined, they ultimately affect spermatogenesis. Ozguner *et al*. revealed a reduction in seminiferous tubular diameter and epithelium fullness after implementing a radio-regularity power generator of 869-894 MHz [33]. Another recent study has also investigated the effects of exposure to cell phone rays on the testicular function and structure in the grown-up rabbit [40]. They claimed a tumble from the sperm attention showed up within the EMR treated group from the 6th week. It grew to become statistically significant with increased exposure duration from six to eight weeks compared with the control group. Also, there was a much more significant decline within the motile, viability, and surge in irregular sperm population in contract with the present examination. The final results in the present research are consistent with every one of these findings. Agarwal *et al.*, recommended that the usage of mobile phones is assigned to a decrease in semen formation [41]. The reduction in sperm viability, sperm count, motility, and the morphology of sperms were related to the time of contact with mobile devices. In the same way, inside the current animal model study, hypo-spermatogenesis and maturation arrest in the spermatozoa had been seen in rats subjected to EMR.

The outstanding decline in CAT and SOD activities concomitantly occurred in rats exposed to EMR (Group II) indicated that those animals experienced oxidative stress. Ahmad poor *et al.*, declare that oxidative stress transpired due to an imbalance between entire body antioxidant capability and reactive oxygen species (ROS) [42]. Therefore, this Phenomenon could occur due to improved significant reactive oxygen species (ROS) generation, impaired antioxidant defense system, or a combination of each. SOD and CAT are enzymes naturally developed by the mammalian system as an endogenous antioxidant system to handle the intermediates in the reactive oxygen species. SOD malfunctions the radicals of superoxide anion to H_2O_2 and H_2O. CAT catalyzes the decomposition of H_2O_2 to H_2O and oxygen [43]. The present study discovered an evident surge in SOD and CAT routines associated with a decrease in lipid peroxidation (MDA) identified by an addiction of thiobarbituric acid reactive compounds (TBARS) from Group III. Every one of these findings advises that Aq-Wsr is an effective contra-oxidant indicator.

Histological assessment proved a reduction in the size of seminiferous tubules from the telephone class than the handle team. This study's findings are consistent with Saunders and Kowalczuk's findings, which show that the primer result of micro-wave, temperature, injuries the testicular cells [44, 45].

Also, a reduction in Leydig cells' amount can clarify the destroying impact in the magnetic field in Leydig cells. The findings reveal that EMR triggered significant testicular damage. Additionally, the existing review has shown that the Aq-Wsr ameliorated EMR-caused damage of the testis cells. This result is generated by its antioxidant action and free radical scavenging process.

CONCLUSION: This research suggests that EMR exposure inflicted relevant testicular problems and histopathological change. Aq-Wsr restored the pursuits in the antioxidant enzymes, down-regulated ROS levels in the testis of EMR uncovered. In the long term, being exposed to mobile phone rays might cause hypo-spermatogenesis and maturation arrest of spermatozoa in rats' testes. Nonetheless, Aq-Wsr possessed a protective impact on radiation-induced histopathological changes on rat testis, manifested with the advancement in sperm parameters of EMR exposed rats treated with *Withania somnifera* root extract.

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