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EFFECT OF *PIPER NIGRUM* (LINN.) ON INFERTILITY INDUCED BY ETHIONAMIDE AND PARA AMINO SALICYLIC ACID IN MALE SPRAGUE-DAWLEY RATS

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ABSTRACT: Tuberculosis is a global problem. The tuberculosis is the common cause of male infertility in developing countries due to the use of second-line anti-tuberculosis drugs (ATB). The experiments were conducted at Unique Bio diagnostic Enterprise Veterinary Pathology Laboratory Parel, Mumbai for chemiluminescence immunoassay to study the levels of testosterone in male Sprague-Dawley rats. The histological analysis was also carried out to confirm the study. From the study it was found that the body weights are inversely proportional to the weight of the testis. It was also found that Ethionamide administered rats showed lowest levels of testosterone, which may lead to infertility. To increase fertility potential we have administered *Piper nigrum* (Linn.) (PnS) seed ethanolic extract in combination with Ethionamide (ETH) + Para aminosalicylic acid (PAS) drugs. From the above results it is found that *Piper nigrum* increases the level of testosterone by maintaining the fertility potential in male Sprague-Dawley rats, it is also confirmed that the histological reconciliation of testis was appreciably restored in Sprague-Dawley rats administered with *Piper nigrum*.

INTRODUCTION: World health organizations acknowledged tuberculosis (TB) as a global problem. The drugs of tuberculosis affect the individual mind as well as physically in many ways. Good health and sexual life is an important aspect of modern human life. The tuberculosis is the common cause of male and female infertility in developing countries [1]. It affects sexual function of male and female patients. Long term exposure to tuberculosis drugs causes sexual problems including infertility.

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Therefore, it is necessary to monitor reproductive health during antituberculosis chemotherapy [2]. Ethionamide (ETH) (eth eye on a mide) is most frequent drug used as an antimycobacterial function. ETH drug has been responsible for many cases of clinically illusive acute liver injury that arise in up to 5% of patients which can be fatal and malefic cases are also reported [3]. Side effects associated with the use of this drug are gynecomastia, gastrointestinal upset, nausea, anorexia, diarrhea, metallic taste, depression, drowsiness, and fatigue. It causes teratogenicity and hence it is avoided in pregnancy [4].

Para-amino salicylic acid (PAS) is the first antibiotic found to be efficient in the treatment of tuberculosis in the 1940s [5]. PAS enhances the activity of drug isoniazid and streptomycin and is extensively used in the combinations against

Mycobacterium tuberculosis [6]. PAS treatment is uncommon, and a highly drug-resistant strain seems to have limited resistance to this drug. Thus, PAS became the principle second-line agent for the treatment of MDR-TB [7]. There are insufficient animal and human safety data on the use of PAS, and it is not used in pregnancy as there were reports on-ear and limb deformities [4].

The use of plants in medicine is an age-long practice in various parts of the globe for both prevention and curative purpose. Today, about 80% of the world population dependent on botanical agents as medicine to meet their health issues [8]. In developing countries, traditional plant remedies are widely used to treat various ailments. Many varieties of plants have been used for treating different kinds of diseases including male fertility problems because of their androgenic and spermatogenic effects or potentials [9]. Nowadays the dietary supplements and herbal remedies have increased the interest of researchers to treat different kinds of diseases.

Piper nigrum Linn. (family Piperaceae) is one of the most commonly used spices and considered as ''The King of spices'' among various spices. *Piper nigrum* is an effective anti- *M. tuberculosis* and is active against both drug-sensitive and resistant strains of TB [10]. *Piper nigrum*, along with other phytoconstituents contains major pungent alkaloid Piperine, which is known to possess many interesting pharmacological actions. It is widely used in different traditional systems of medicine like Ayurvedic and Unani System of medicines [11, 12]. Piperine exhibits diverse pharmacological activities like antihypertensive and antiplatelets [13], antioxidant, antitumor [14], antiasthmatics [15], antipyretic, analgesic, anti-inflammatory, anti-diarrheal, antispasmodic, anxiolytic, anti-depressants [16], hepato-protective [17], immuno-modulatory, antibacterial, antifungal, anti-thyroids, antiapoptotic, anti-metastatic, antimutagenic, anti-spermatogenic, anti Colon toxin, insecticidal and larvicidal activities *etc*.

Piperine has been found to enhance the therapeutic efficacy of many drugs, vaccines and nutrients by increasing oral bioavailability by inhibiting various metabolizing enzymes [18]. It is also known to enhance cognitive action and fertility [19].

In view of the severe undesirable side effects of synthetic drugs, there is a need to focus on systematic research methodology and to study the scientific basis for the traditional herbal medicines that are claimed to show fertility potential. Therefore, because of the above literature survey it was found that ETH and PAS used as antituberculosis drugs, but at the same time these drugs are responsible for sterility in human beings leading to disturbances in androgenic hormonal balance. Therefore, in the present study, attention has been given on the aspects of enhancement of fertility potential due to *Piper nigrum* against ETH and PAS induced sterility in the Sprague-Dawley rats.

MATERIALS AND METHODS:

Collection of Sample: Fresh seeds of *Piper nigrum* were procured from the botanical garden of Kokan Krushi Vidyapeeth, Dapoli, Ratnagiri. The initial identification was made by referring related literature survey, and final identification and confirmation were done at the department of horticulture, Kokan Krushi Vidyapeeth, Dapoli, Ratnagiri before process the sample at the department of Zoology S. S. & L. S. Patkar College Goregaon (west), Mumbai India.

Extraction: The ethanolic extract of the seeds was carried out by Soxhlet extraction method. The sample was evaporated to dryness and powder was weighed and the yield so obtained was collected in a sterile container and kept at -20 ºC till further use. The weight of the powder was calculated based on weight of the seeds.

Experimental Design: Thirty (32) male Sprague-Dawley rats (average weight 150 - 240 g) were used for the experiment. They were purchased and procured from the National Toxicological Centre, APT Testing & Research Pvt. Ltd. (ATR) Pune. The experimental study was approved by Ethical committee at APT Research Foundation, Pune before the experimentation (CPCSEA NO. 40/PO/ReBi Rc/S/99/.11.03.2014) the animals were acclimatized, maintained and housed in APT laboratory for a week.

The controlled humidity and temperature at 24 ºC; humidity, 12-h light/12 h dark cycle was also maintained by feeding the rats with commercial rat

pallets and water available *ad libitum*. The drugs ETH (Macleods Pharmaceuticals Ltd) and PAS (Lupin Ltd.) were purchased following the Prescription of Physician from B.J. Medical College and Sassoon General Hospital, Pune, Maharashtra. ETH (132 mg/Kg bw,) PAS (400 mg/Kg bw), *Piper nigrum* (500 mg/kg bw) was administered to each rat by a single oral gavage. The animals were dosed using a stainless steel intubation needle fitted onto a suitably graduated syringe.

The dose-volume administered orally/per day to individual rat to 28 days. After 28 days of drugs and *Piper nigurm* administered rats were weighed for their body weight and blood of all the animals were withdrawn for hormonal assay prior to the scarification of the animals. The animals were dissected and absolute weight of testis was recorded before the histopathological analysis.

Hormonal Assay: Blood samples of the above groups were drawn after 28th day from cardiac puncture into heparinised bottles and was analyzed at the Unique Bio Diagnostics Enterprises (UBE) Veterinary Pathology Laboratory, B-20, Bhuvaneshwar, Dr. V. K. Valimbe Road, Near Gururani Nagkanya Chowk, Parel Village, Mumbai, for Chemiluminescence immunoassay of testosterone as proposed by [20, 21] by using Immulite 2000 immunoassay system, (Siemens).

Histological Analysis: Testes were removed and immersed in Bouins solution for fixation and processed until the embedded in paraffin for histological analysis. Five micron thick sections were prepared using microtome and staining using Hematoxylin and Eosin (H&E) method as proposed by Davidson, [22] and histological specimens were examined under the Biological digital microscope-Motic B1 Series.

TABLE 1: THE EFFECT OF *P. NIGRUM* ADMINISTRATION ON INFERTILITY INDUCED BY ETHIONAMIDE AND PARA AMINO SALICYLIC ACID IN MALE RATS

Groups	Number of Male Animals	Treatment	Doses mg/kg.p.o./day	No. of Days
A	4	Rat Pellets and Ordinary water	*ad libitum*	
B	4	PnS	500	
C	4	ETH	132	
D	4	PAS	400	28
E	4	ETH+PAS	132+400	
F	4	ETH+PnS	132+500	
G	4	PAS+PnS	400+500	
H	4	ETH+PAS+PnS	132+400+500	

ETH = Ethionamide. PAS=Para amino salicylic acid. PnS = *Piper nigrum* mg/kg/per. oral /per day

TABLE 2: BODY WEIGHTS IS EXPRESSED AS MEAN READINGS

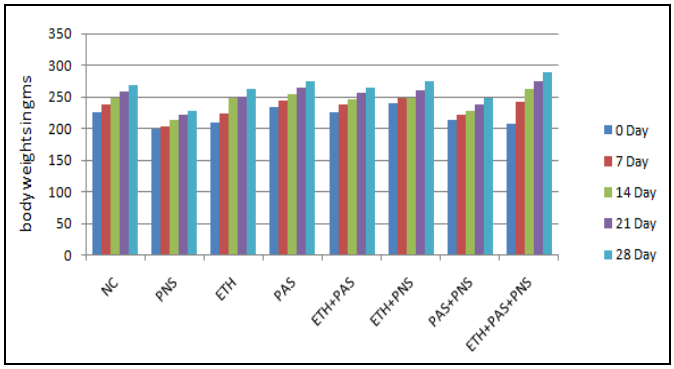
Group	Treatment	0 Day	7 Day	14 Day	21 Day	28 Day
A	NC	226.75	238	247.75	258.5	269.25
B	PnS	198.875	203.25	213	221.5	228.25
C	ETH	209.75	224.25	248.25	251	261.75
D	PAS	234.5	243.25	253.75	264.5	274.25
E	ETH+PAS	225.25	238.75	247	257	264.5
F	ETH+PnS	239.25	248.5	247.75	260	274.75
G	PAS+PnS	214.5	221.5	228.75	237.5	248.75
H	ETH+PAS+PnS	207.75	241.25	263.25	274.25	288.5

TABLE 3: TESTES WEIGHTS IS EXPRESSED AS MEAN WHERE N=4

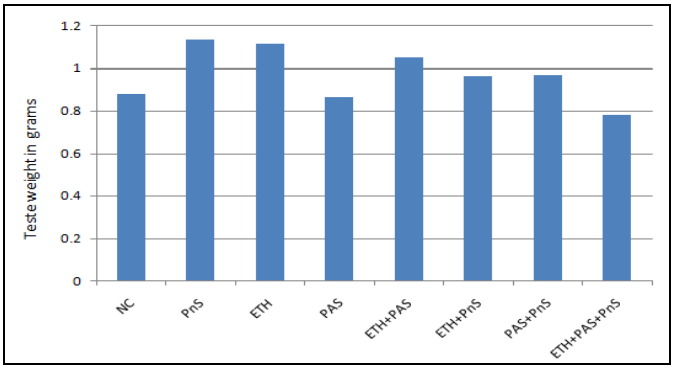
Group	Treatment	Testes (grams)
A	NC	0.884
B	PnS	1.138
C	ETH	1.118
D	PAS	0.868
E	ETH+PAS	1.053
F	ETH+PnS	0.967
G	PAS+PnS	0.972
H	ETH+PAS+PnS	0.786

TABLE 4: REPRESENTING MEAN TESTOSTERONE IN ng/dl BY CHEMILUMINESCENCE ASSAY

Group	Treatment	Testosterone ng/dL
A	NC	81.6975
B	PnS	90.55
C	ETH	17.68
D	PAS	114.185
E	ETH+PAS	220.8
F	ETH+PnS	458.815
G	PAS+PnS	241.775
H	ETH+PAS+PnS	108.702



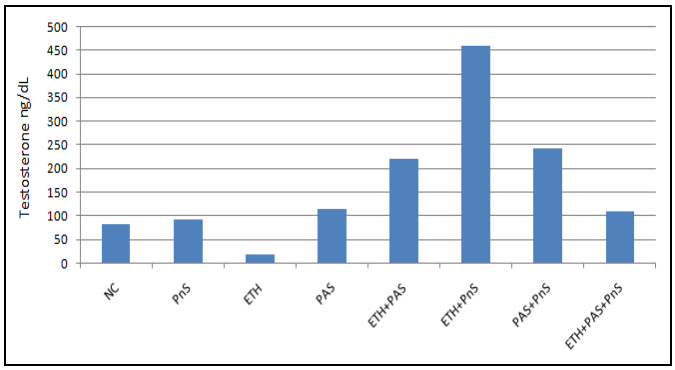
GRAPH 1: SHOWING THE CHANGES IN MEAN BODY WEIGHTS MEASURED AT THE INTERVAL OF EVERY 7 DAYS TILL 28 DAYS STUDY OF GROUPS A-H



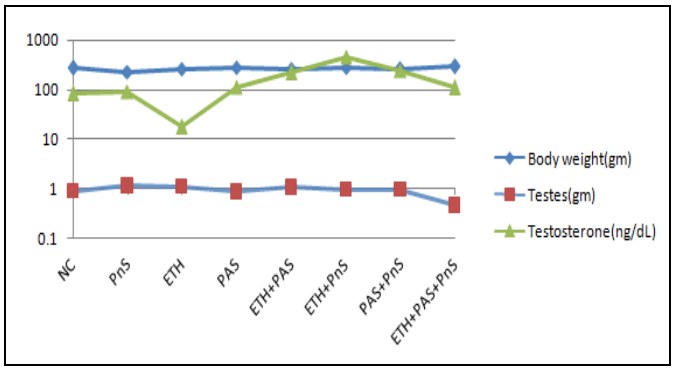
GRAPH 2: THE MEAN WEIGHTS OF TESTES AFTER SCARIFICATION AT THE END OF 28 DAYS OF GROUP A TO H

TABLE 5: SHOWING MEAN BODY WEIGHT, MEAN TESTES WEIGHT AND TESTOSTERONE IN MALE RATS AFTER 28 DAYS OF STUDY

Group	Treatment	Body weight /gm	Testes/gm	Testosterone ng/dL
A	NC	269.25	0.884	81.6975
B	PnS	228.25	1.138	90.55
C	ETH	261.75	1.118	17.68
D	PAS	274.25	0.868	114.185
E	ETH+PAS	264.5	1.053	220.8
F	ETH+PnS	274.75	0.967	458.815
G	PAS+PnS	248.75	0.972	241.775
H	ETH+PAS+PnS	288.5	0.457	108.702

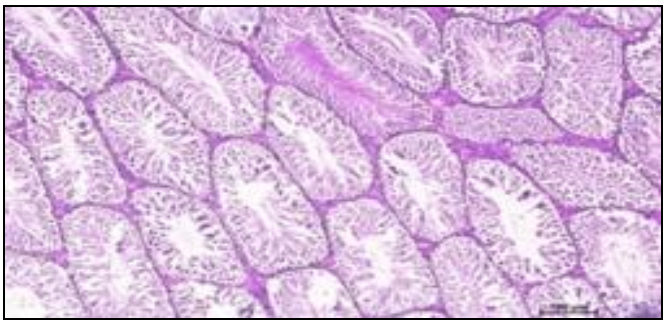


GRAPH 3: REPRESENTING THE MEAN TESTO-STERONE BY CHEMILUMINESCENCE ASSAY AFTER 28 DAYS IN THE TESTES OF MALE SPRAGUE-DAWLEY RATS OF GROUP A-H

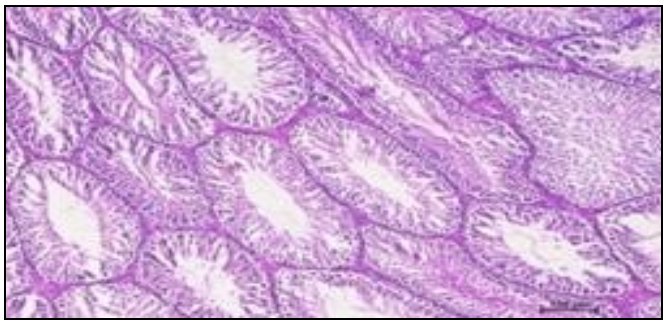


GRAPH 4: SHOWING THE CORRELATION IN MEAN BODY WEIGHT, MEAN TESTES WEIGHT AND TESTOSTERONE IN MALE RATS AFTER 28 DAYS OF STUDY

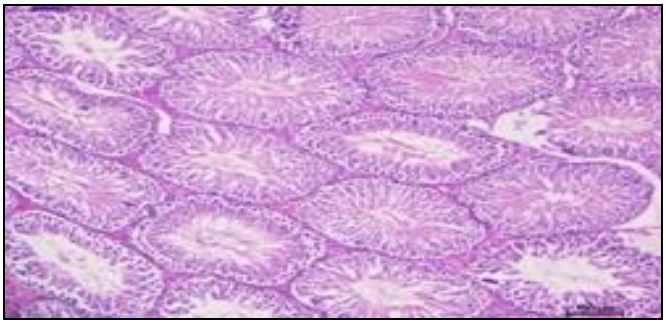
Histopathological Analysis:



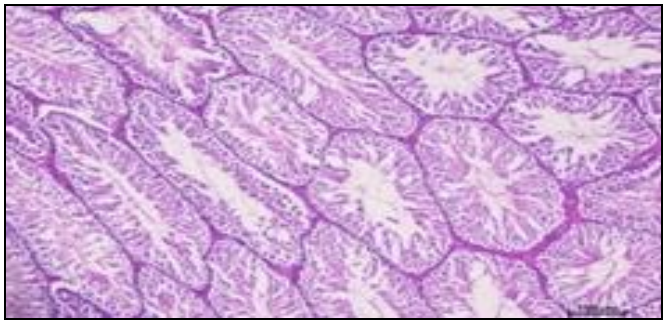
GROUP A: NC NORMAL HISTOMORPHOLOGY OF SEMINIFEROUS TUBULES WITH INTACT CELLULAR FEATURES OF GERMINAL LAYERS. NORMAL CELLULAR FEATURES OF SPERMATOGENESIS WITH FORMATION OF SPERMS IN TUBULES. ABSENCE OF DEGENERATIVE OR NECROTIC OR INFLAMMATORY CHANGES IN THE SECTION



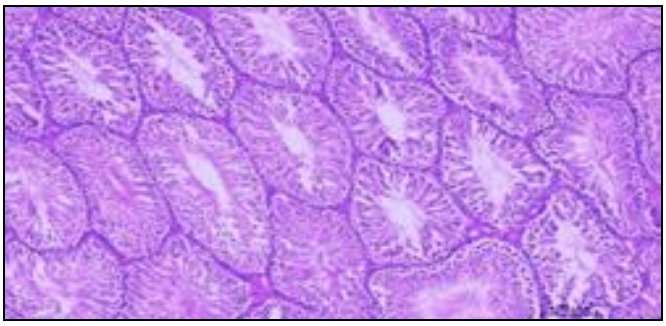
GROUP B: PnS-SLIGHT INCREASE IN HISTOMORPHO-LOGY OF SEMINIFEROUS TUBULES WITH INTACT CELLULAR FEATURES OF GERMINAL LAYERS. NORMAL CELLULAR FEATURES OF SPERMATO-GENESIS WITH FORMATION OF SPERMS IN TUBULES. ABSENCE OF DEGENERATIVE OR NECROTIC OR INFLAMMATORY CHANGES IN THE SECTION



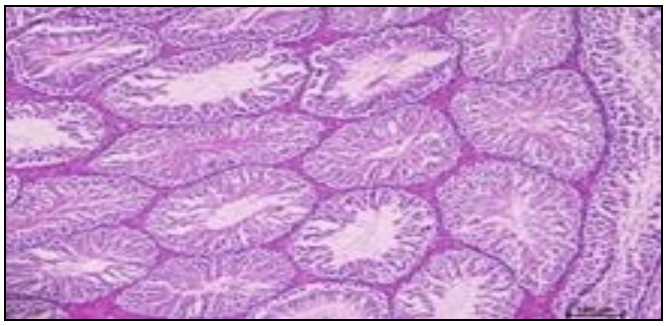
GROUP C: ETH- DISSARRANGEMENT OF SEMINI-FEROUS TUBULE IS OBSERVED WITH ABNORMAL SPERMATOGENIC MORPHOLOGY OF CELLS



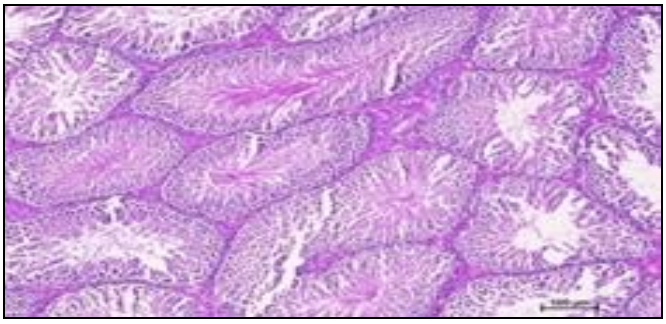
GROUP D: PAS- CONGESTED ARRANGEMENT OF SEMINIFEROUS TUBULES IS OBSERVED



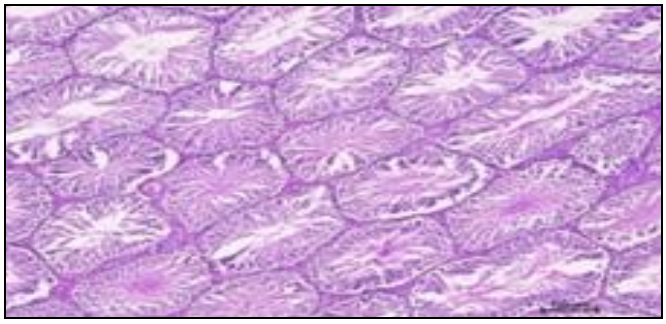
GROUP E: ETH+PAS-NORMAL HISTOMORPHOLOGY OF SEMINIFEROUS TUBULES WITH INTACT CELLULAR FEATURES OF GERMINAL LAYERS. NORMAL CELLULAR FEATURES OF SPERMATO-GENESIS WITH FORMATION OF SPERMS IN TUBULES. ABSENCE OF DEGENERATIVE OR NECROTIC OR INFLAMMATORY CHANGES IN THE SECTION



GROUP F: ETH+PNS- NORMAL HISTOMORPHOLOGY OF SEMINIFEROUS TUBULES WITH INTACT CELLULAR FEATURES OF GERMINAL LAYERS NORMAL SPERMATOGENITC CELLS



GROUP G: PAS + PnS- DISSARRANGEMENT OF EPITHELIAL LININGS SEMINIFEORUS TUBULES ARE SEEN



GROUP H: ETH + PAS + PnS- MORPHOLOGY OF SEMINIFEORUS TUBULE IS CHANGED, NORMAL SPERMAGENTIC CELLS ALIGNMENT IS OBSERVED

Statistical Analysis: Obtained data were statistically analyzed by one-way analysis of variance (ANOVA) by F –Test. The value $p< 0.05$ considered as significant.

DISCUSSION: Table 1 represents the treatment of *Piper nigrum* administration on infertility induced by ETH and PAS in male Sprague-Dawley rats. As can be seen in **Table 2** and graph 1 represents the mean body weights. After 28 days, the lowest recorded mean body weight is 228.25 grams in group B administered with *Piper nigrum* whereas highest recorded mean body weight is 288.5 grams in group H administered with ETH + PAS + PnS.

In **Table 3** and **Graph 2** it was found that the lowest recorded mean weight of testis was 0.457 grams found in group H administered with ETH + PAS+ PnS whereas the highest recorded weight 1.138 grams was found in group B administered with *Piper nigrum*. From the above results it is concluded that body weights are inversely proportional to the weight of the testes. **Table 4** and **Graph 3** represents the weight of testosterone hormone in ng/dL. The lowest recorded weight of testosterone hormone in group C, administered with ETH is 17.68 ng/dL & highest testosterone hormone level is 458. 81 ng/dL in group F, animals

administered with ETH + PnS. From the above results it was found that the ETH administered animals leads to gynecomastia and other associated effects like gastrointestinal upset, nausea, anorexia, diarrhea, metallic taste, depression, drowsiness and fatigue as stated by [23]. Whereas, it was found that, combine dose of (ETH + PnS) recovered the animals by increasing the level of testosterone to maintain fertility of male rats. **Table 5** and graph 4 showed ETH and PAS effects on the body weights and testicular weight, which affect the testosterone secretion in the treated groups from B to H as compared with group A was found significant at $p < .05$.with the p-value < .00001.

The rare case study carried by, [24] studied the effect of ETH on human being and they recorded a decreased level of testosterone in male. Our results are in agreement with the results of Sharma and Bansal. Here above our, results are also correlated with histological architecture of male rats it is clearly found that the group administered with ETH showed disarrangement of seminiferous tubules with abnormal spermatogenic morphology. From the above results we found that after administration of *Piper nigrum* in combination with ETH and PAS, the morphology of seminiferous tubules has changed and showed normal spermatogenic cell alignment which confirms that *Piper nigrum* has fertility potential.

The study carried out by [25] concluded that *Piper nigrum* is dose-dependent and they have also shown the decreased weight of organs. Our study is in agreement with the study carried out by Mishra. In our study, we found that the body weights are inversely proportional to the weight of testis. In addition to body weights we also found the reversal changes in the histological architecture of the reproductive organs. Our study is also is in the agreement with the study carried by [26] where they have given the clear cut evidence that *Piper nigrum* enhances the reproductive functioning in male mice by significantly increasing testosterone. *Piper nigrum* contains a verity of nutrients including zinc has been reported by many authors. These nutrients are responsible for numerous physiological processes in organisms [27, 28]. Zinc supplementation can improve the antioxidative status in goats and proved to increased serum levels of sex hormones including testosterone in rats [29, 30].

In the present investigation, the increased level of testosterone may be because of zinc and anti-oxidant property of *Piper nigrum*, which may also be responsible for the improvement of histological architecture of the testis of rats.

CONCLUSION: In the present investigation we have examined the role of *Piper nigrum* against infertility induced by ETH and PAS in male Sprague-Dawley rats. In our study it is found that body weights are inversely proportional to the weight of the testis. It is also found that *Piper nigrum* enhances the reproductive functioning in male Sprague-Dawley rats by significantly increasing weight of testosterone. The results of the above study are also correlated with histological architecture of male Sprague-Dawley rats it is clearly found that the group administered with ETH showed disarrangement of seminiferous tubules with abnormal spermatogenic morphology. We found that after administration of *Piper nigrum* in combination with ETH and PAS, the morphology of seminiferous tubules has changed towards normal spermatogenic cell alignment, which confirms that *P. nigrum* has fertility potential. The combined dose of (ETH + PnS) recovered the animals by increasing the level of testosterone to maintain fertility of male rats.

This study suggests that the antituberculosis drugs in combination with *Piper nigrum* are effective to cure the disease and to maintain the fertility in rats. The study further suggests that clinical investigations are needed to find the active component in *Piper nigrum*, which is responsible for the enhancement of testosterone in male rats.

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CONFLICT OF INTEREST: There is no conflict of interest in the present work.

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