PROTECTIVE EFFECT OF IVERMECTIN AND VITAMIN E AGAINST TESTICULAR TOXICITY IN RATS

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ABSTRACT
The protective effect of ivermectin (IVM) and vitamin E (Vit. E) alone and in combination against testicular toxicity induced by sodium valproate (SVP) in rats was investigated. Thirty five sexually mature Sprague Dawley male rats were randomized into 7 equal groups. Group 1 was kept used as negative control and the other 6 groups were orally administered SVP (500 mg/kg) daily during the last week of experiment period (8 weeks) to induce testicular toxicity. Group 2 was positive control and groups 3,4,5,6 and 7 were orally pretreated with therapeutic or double therapeutic dose of IVM or Vit. E alone and concurrently for 8 weeks, respectively. Blood samples were withdrawn for determination of testosterone, FSH and LH serum levels. Semen samples were collected from cuta epididymis for semen analysis. Rats were sacrificed and sexual organs were removed and weighed. Histopathology of testes and superoxide dismutase and catalase antioxidant enzymes activity in testicular tissue were also performed. The results denoted that oral pretreatment with IVM concomitantly with Vit. E increased the relative weight of testes and sperm motility, count and viability in SVP-intoxicated rats. There were also significant increases in serum testosterone and FSH levels and testicular antioxidant enzymes activity associated with amelioration of degenerative changes in the testis. In conclusion, oral pretreatment with IVM and Vit. E exerts protective and antioxidant effects against testicular toxicity in rats. Further studies are needed to explore the reversibility and mechanisms of the protective action of ivermectin on male fertility and spermatogenesis.
KEYWORDS: *Ivermectin* • *Sodium valproate* • *Testis* • *Sperm* • *Antioxidant* • *Histopathology.*

INTRODUCTION

Infertility is one of the major health problems in life and approximately about 30 percent of this problem is attributed to male factors.\(^1\) Several factors can interfere with the process of spermatogenesis, reduce sperm quality and quantity and decrease male fertility. Many diseases such as coronary heart diseases, diabetes mellitus and chronic liver diseases as well as insufficient vitamins intake have deleterious effects on spermatogenesis.\(^2-5\) Chronic exposure to insecticides can also adversely affect male fertility\(^6\) and more than 90% of male infertility cases are due to low sperm count, poor sperm quality, or both. The remaining cases of male infertility can be caused by a number of factors including anatomical problems, genetic defects\(^7\) and hormonal imbalances.\(^8\) On the other side, intake of natural antioxidants with vitamins E and C was reported to protect sperm DNA from oxidative stress in rat testes and improve male fertility.\(^9\)

Ivermectin is one of macrocyclic lactones macrolide antibiotics belonging to group known avermectins and it is produced by a fungus *Streptomyces avermitilis*. Ivermectin has high potency and broad spectrum of activity against many nematode and arthropod parasites infesting sheep, cattle, dogs, horses and pigs.\(^10-12\) The mechanism of antiparasitic action of ivermectin is reported to be due to its interaction with glutamate and gama-aminobutyric acid (GABA)-gated chloride channels which cause influx of chloride ions, so it causes paralysis of many types of parasites.\(^13\) Concerning its toxicity, ivermectin has a high therapeutic index in target animals and idiosyncratic toxicity in Beagle dogs at more than 8-fold the recommended therapeutic dose of 0.6 mg/kg.\(^13\) There are few and contradictory reports on the effect of ivermectin on male fertility in Beagle dogs,\(^14\) rams,\(^15\) rabbits,\(^16, 17\) mice\(^18\) and rats.\(^19\) The present study was designed to investigate the protective effect of ivermectin and vitamin E alone and in combination against sodium valproate - induced testicular toxicity in rats.

MATERIAL AND METHODS

Drugs

**Ivermectin (Oramectin®)**

It was purchased from Pharma Swede Company, Cairo, Egypt in the form of a liquid solution containing ivermectin at 0.8 mg/ml. The oral therapeutic dose of ivermectin was 0.2 mg/kg b.wt as reported by Lytvynets et al.\(^20\)
Vitamin E (α-tocopherol)
It is purchased from Pharco Company for pharmaceuticals, Alexandria, Egypt. It is dispensed in the form of soft gelatin capsules each containing 1000 mg of vitamin E. It was administered orally to rats in a dose of 40 mg/kg b.wt according to Bansal et al.[21]

Sodium valproate (Depakine®)
It is one of products of Sanofi-Synthelabo Com., Paris, France and it is obtained as oral solution packed in dark brown bottles of 40 ml each. It is sold commercially under trade name Depakine® 200 mg/ml solution. Sodium valproate was given orally in a dose of 500 mg/kg b.wt during the last weeks of the experiment period to produce testicular toxicity as recorded by Hamza and Amin.[22]

Animals
Thirty five sexually mature male rats of Sprague Dawley strain weighing 350-360 g body weight and 10-12 weeks old were used in this study. Rats purchased from Laboratory Animal Colony, Helwan, Egypt. Rats were housed under controlled temperature at 23 ± 1°C, humidity at 52 % and 12-hr light/12-hr dark schedule. Animals were fed on commercial rat pellets manufactured by Cairo Agriculture Development Company, The 6th October City, Egypt and tape water was provided ad libitum.

Experimental design
Rats were distributed into 7 equal groups of 5 animals each. Group 1 was given orally 1 ml distilled/rat and kept as negative control. The other 6 groups were intoxicated by oral single administration of sodium valproate (SVP) at 500 mg/kg during the last week of experiment period (8 weeks) to induce testicular damage.[22] Group 2 was used as positive (intoxicated) control, while groups 3, 4, and 5 were pretreated with therapeutic dose (0.2 mg/kg) or double therapeutic (0.4 mg/kg) dose of ivermectin (IVM) or Vit. E (40 mg/kg) respectively. Groups 6 and 7 were orally pretreated with therapeutic dose of IVM and Vit E or double therapeutic dose of IVM and Vit E, respectively. At end of the experiment, the testes and accessory sex organs were removed and weighed. Blood samples were collected from the orbital plexus of veins for serum separation that used for estimation of serum testosterone, FSH and LH. Rats were the anesthetized and semen samples were collected from cuda epididymis for semen analysis. The right testes were rapidly taken on an ice bag and kept at – 70 °C till used for assaying activities of superoxide dismutase and catalase antioxidant enzymes. The left testes were preserved in 10% formalin solution till processed for histopathological examination.
Hormone assay
Serum total testosterone concentration was determined using RIA method according to Wilke and Utley.[23] Serum levels of FSH and LH hormones were determined by an enzyme-linked immunosorbent assay (ELISA) using specific commercial kits (Amersham, Buckinghamshire, UK) according the method described by Ballester et al.[24]

Semen analysis
The semen in epididymis was obtained by cutting of cuda epididymis using surgical blades and squeezed in a sterile dry Petri dish. The semen content was diluted 10 times with 2.9% sodium citrate solution and thoroughly mixed to estimate percents of sperm progressive motility and sperm count.[25] Thereafter, one drop of sperm suspension was withdrawn, smeared on a glass slide and stained by Eosin-Nigrosin. The stained seminal smears were examined microscopically to determine percentage of sperm viability (ratio of live/dead sperms) and morphological abnormalities.[26]

Antioxidant assay
Tissue specimens of the right testes after thawing were homogenized using soft tissue homogenizer (Omni International, USA) in 9 volumes of ice coold buffered 0.9% saline solution. The homogenate was then centrifuged at 8000 rpm for 15 min. at 4 °C and the supernatant was used for antioxidant enzymes assay. Activities of superoxide dismutase (SOD) and catalase (CAT) were determined as described by Nishikimi et al.[27] and Sinha[28] respectively.

Histological procedure
The fixed specimens of left testes were then trimmed, washed and dehydrated in ascending grades of alcohol. These specimens were cleared in xylene, embedded in paraffin, sectioned at 4-6 microns thickness and stained with Hematoxylen and Eosin (H & E) then examined microscopically.[29]

Statistical analysis
Data were presented as means± SE. Statistical analysis between different experimental groups was carried out using a one-way analysis of variance (ANOVA) test followed by Duncan’s multiple range tests[30] using computerized SPSS (Statistical Program of Social Sciences, Version 15, Chicago) program. Differences were considered significant at P<0.05.
RESULTS
Oral administration of sodium valproate (SVP) for 7 consecutive days during the last week of experiment caused a significant ($P < 0.05$) decrease in the relative weight of testes as compared to the negative control group. Oral pretreatments with therapeutic and double therapeutic dose of ivermectin alone and concomitantly with vitamin E significantly ($P < 0.05$) increased the relative weight of testes when compared with the positive control group as depicted in Table (1).

Table 1. Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on relative weights of sexual organs of rats with testicular damage induced by sodium valproate. (n= 5 rats).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Testes</th>
<th>Seminal vesicles</th>
<th>Prostate glands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Negative control</td>
<td>4.17±0.5&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.79±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.68±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 2 Positive control</td>
<td>1.90±0.3&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.75±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.66±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 3 IVM (Td)</td>
<td>2.45±0.4&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.74±0.04&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.67±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 4 IVM (2Td)</td>
<td>2.44±0.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.78±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.65±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 5 Vit. E</td>
<td>3.78±0.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.77±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.66±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 6 IVM (Td) + Vit. E</td>
<td>3.85±0.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.76±0.03&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.65±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Group 7 IVM (2Td) + Vit. E</td>
<td>3.60±0.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.75±0.02&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.64±0.01&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Means ± SE with different superscript letters in the same column are significant at $P < 0.05$ using one way ANOVA test. The positive control group was compared to the negative control. All pretreated groups were compared to the positive control group.

As shown in Table (2) the oral administration of SVP to male rats for 7 consecutive days caused significant ($P < 0.05$) decreases in serum levels of testosterone and FSH hormones as compared with the negative control group. Oral pretreatments with therapeutic and double therapeutic dose of ivermectin alone and concomitantly with vitamin E significantly ($P < 0.05$) increased serum levels of testosterone and FSH when compared with the positive control group.

Sodium valproate when given orally to male rats for 7 consecutive days induced significant ($P < 0.05$) decreases in sperm cell count, motility and viability as compared with the negative control group. Oral pretreatments with Oral pretreatments with therapeutic and double therapeutic dose of ivermectin alone and concurrently with vitamin E caused significant ($P < 0.05$) increases in sperm cell count, motility and viability when compared with the positive
control group, but decreased sperm cell abnormalities when compared to positive control group as recorded in Table (3).

Table 2. Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on serum levels of sex hormones testosterone (T), FSH and LH in rats with testicular toxicity induced by sodium valproate. (n= 5 rats).

<table>
<thead>
<tr>
<th>Sex hormones Groups</th>
<th>T (ng/mL)</th>
<th>FSH (ng/mL)</th>
<th>LH (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Negative control</td>
<td>3.90 ± 0.4a</td>
<td>2.21 ± 0.2a</td>
<td>0.55 ± 0.02a</td>
</tr>
<tr>
<td>Group 2 Positive control</td>
<td>1.80 ± 0.5c</td>
<td>1.15 ± 0.3b</td>
<td>0.53 ± 0.01b</td>
</tr>
<tr>
<td>Group 3 IVM (Td)</td>
<td>3.52 ± 0.2b</td>
<td>1.19± 0.4b</td>
<td>0.52 ± 0.03a</td>
</tr>
<tr>
<td>Group 4 IVM (2Td)</td>
<td>2.50 ± 0.1c</td>
<td>1.18± 0.2b</td>
<td>0.51 ± 0.03a</td>
</tr>
<tr>
<td>Group 5 Vit. E</td>
<td>3.60 ± 0.2b</td>
<td>1.16 ± 0.2b</td>
<td>0.52 ± 0.01a</td>
</tr>
<tr>
<td>Group 6 IVM (Td) + Vit. E</td>
<td>3.61 ± 0.1b</td>
<td>1.19± 0.4b</td>
<td>0.54 ± 0.03a</td>
</tr>
<tr>
<td>Group 7 IVM (2Td) + Vit. E</td>
<td>2.65 ± 0.3c</td>
<td>1.17 ± 0.1b</td>
<td>0.53 ± 0.02a</td>
</tr>
</tbody>
</table>

Means ± SE with different superscript letters in the same column are significant at $P < 0.05$ using one way ANOVA test. The positive control group was compared to the negative control. All pretreated groups were compared to the positive control group.

Table 3. Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on sperm parameters of rats with testicular damage induced by sodium valproate. (n= 5 rats)

<table>
<thead>
<tr>
<th>Sperm parameters</th>
<th>Count (10^6/ml)</th>
<th>Motility (%)</th>
<th>Viability (%)</th>
<th>Abnormality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Negative control</td>
<td>73.09±2.25a</td>
<td>92.20±1.77a</td>
<td>90.00±2.2a</td>
<td>5.20±0.37a</td>
</tr>
<tr>
<td>Group 2 Positive control</td>
<td>58.20±3.45a</td>
<td>68.20±2.17d</td>
<td>75.6±2.8a</td>
<td>6.20±0.37a</td>
</tr>
<tr>
<td>Group 3 IVM (Td)</td>
<td>62.15±1.64c</td>
<td>71.30±3.27a</td>
<td>77.6±2.6c</td>
<td>5.40±0.25a</td>
</tr>
<tr>
<td>Group 4 IVM (2Td)</td>
<td>63.25±2.46c</td>
<td>72.50±2.17c</td>
<td>79.6±1.8c</td>
<td>5.30±0.27a</td>
</tr>
<tr>
<td>Group 5 Vit. E</td>
<td>66.24±2.62c</td>
<td>75.20±4.27c</td>
<td>80.6±2.8c</td>
<td>5.10±0.25c</td>
</tr>
<tr>
<td>Group 6 IVM (Td) + Vit. E</td>
<td>68.24±1.75c</td>
<td>77.20±2.17c</td>
<td>86.6±3.5c</td>
<td>5.20±0.27a</td>
</tr>
<tr>
<td>Group 7 IVM (2Td) + Vit. E</td>
<td>70.28±2.35b</td>
<td>80.20±1.22b</td>
<td>87.6±2.4b</td>
<td>5.10±0.47a</td>
</tr>
</tbody>
</table>

Means ± SE with different superscript letters in the same column are significant at $P < 0.05$ using one way ANOVA test. The positive control group was compared to the negative control. All pretreated groups were compared to the positive control group.

Oral administration of SVP to male rats for 7 consecutive days significantly ($P < 0.05$) decreased the activity of superoxide dismutase (SOD) and catalase (CAT) enzymes in testicular tissue when compared with the negative control group. Oral pretreatments with therapeutic and double therapeutic dose of ivermectin alone and together with vitamin E
significantly \((P < 0.05)\) increased the activity of SOD and CAT in the rat testes when compared to the positive control group as shown in Table (4).

Table 4. Effect of ivermectin (IVM) at therapeutic and double therapeutic (Td and 2Td) dose and vitamin E (Vit. E) on activity of testicular superoxide dismutase (SOD) and catalase (CAT) in rats with testicular damage induced by sodium valproate. (n= 5 rats).

<table>
<thead>
<tr>
<th>Groups</th>
<th>SOD (U/mg protein)</th>
<th>CAT (nmol/min/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 Negative control</td>
<td>179.6±2.3</td>
<td>0.32 ±0.1</td>
</tr>
<tr>
<td>Group 2 Positive control</td>
<td>99.2± 1.3</td>
<td>0.01±0.2</td>
</tr>
<tr>
<td>Group 3 IVM (Td)</td>
<td>144.15±4.9</td>
<td>0.13±0.1</td>
</tr>
<tr>
<td>Group 4 IVM (2Td)</td>
<td>140.25±3.6</td>
<td>0.14±0.1</td>
</tr>
<tr>
<td>Group5 Vit. E</td>
<td>168.25±2.7</td>
<td>0.17 ±0.1</td>
</tr>
<tr>
<td>Group 6 IVM (Td) + Vit. E</td>
<td>167.25±5.9</td>
<td>0.21±0.2</td>
</tr>
<tr>
<td>Group 7 IVM (2Td) + Vit. E</td>
<td>164.25±0.6</td>
<td>0.19±0.1</td>
</tr>
</tbody>
</table>

Means ± SE with different superscript letters in the same column are significant at \(P < 0.05\) using one way ANOVA test. The positive control group was compared to the negative control. All pretreated groups were compared to the positive control group.

The testes of negative (normal) control rats showed normal histological structure of active mature functioning seminiferous tubules associated with complete spermatogenic germ cell series (Fig. 1A). Testes of rats given sodium valproate (positive control) revealed severe testicular degeneration with marked decrease in spermatogonial cells to complete loss of spermatogenic series (Fig. 1B). Severe testicular hemorrhage, intertubular edema and severe congestion of blood vessels were also seen (Fig. 1C). In rats pretreated with vitamin E, the testes showed mild to moderate hemorrhage with intertubular edema and congestion of intertubular blood vessels (Fig. 1D). Rats pretreated with the therapeutic dose of ivermectin and vitamin E, showed only mild testicular degeneration (Fig. 1E). The tests of rats pretreated with the double therapeutic dose of ivermectin and vitamin E showed moderate intertubular edema and hemorrhage, moderate testicular degeneration represented by decrease in the number of spermatogonial cells in seminiferous tubules and some tubules contained spermatid giant cell (Fig. 1F).
Figure (1): Photomicrographs of rat testes: A. Testis of a rat from the negative control group showing normal histological findings of mature seminiferous tubules and normal spermatogenic series; B. Testis of a rat given sodium valproate showing severe testicular degeneration with decreased in spermatogonial cells to complete loss of spermatogenic series (arrow); C. Testis of a rat given sodium valproate showing severe testicular hemorrhage (arrow) with marked dilation of the blood vessels(arrow); D. Testis of a rat pretreated with vitamin E alone showing moderate intertubular edema (arrow) with moderate testicular degeneration; E. Testis of a rat pretreated with therapeutic dose of ivermectin and vitamin E showing mild testicular degeneration and F. Testis of a rat pretreated with double therapeutic dose of ivermectin and vitamin E showing intertubular edema and hemorrhage, some tubules contained spermatid giant cell (arrow) with degenerated and necrotic cells.

DISCUSSION

The current study was designed to investigate the protective and antioxidant effects of ivermectin, at therapeutic and double therapeutic dose, concomitantly with vitamin E against sodium valproate-induced testicular toxicity and oxidative stress in male rats.
The results of this study revealed that oral administration of sodium valproate (SVP) to male rats in a dose of 500 mg/kg b.wt for consecutive 7 days produced marked reproductive toxicity. The toxic effect of SVP characterized by decreased relative weight of testes, lowered semen quantity and quality, decreased serum levels of testosterone and FSH as well as marked degenerative changes (hemorrhage, edema and degeneration of most seminiferous tubules) in the testis. The results of our study nearly correlate with results of the previous reports. The previous authors found that oral administration sodium valproate to male rats significantly decreased the relative weight of testes and epididymis and sperm numbers and viability. Serum and testicular concentrations of testosterone, FSH and LH hormones levels were also dropped and severe testicular degenerative lesions were also seen.

Mechanisms of toxicity of SVP on the male reproduction and spermatogenesis were attributed to its direct cytotoxic effect on the testis and/or indirectly via decreasing level of testosterone, FSH and LH in the serum. Moreover, SVP induced oxidative stress in the rat testis as evident by significant decreases in the activity of antioxidant SOD and CAT enzymes in this study. The toxic effect of SVP reported in this study was similar to that reported by Bairy et al. who concluded that SVP induced oxidative stress and reproductive toxicity in male rats.

The present study showed that vitamin E produced protective and antioxidant effects against sodium valproate-induced testicular injury in rats. These findings were in accordance with the previous findings. The previous authors concluded that vitamin E can protect sperm DNA from oxidative stress in the rat testis and enhance spermatogenesis and male fertility due to its powerful antioxidant activity. Moreover, it has been reported that combination of vitamin E and selenium improved semen parameters and pregnancy rates in infertile men. A recent study confirmed the protective effect of vitamin E against lead acetate-induced reproductive toxicity in Wistar rats. Findings of the previous were nearly similar to the results of our study. The previous results showed that vitamin E increased sperm count, motility and viability and increased serum testosterone, FSH, and LH levels and alleviation of testicular degenerative changes induced by lead in vitamin E-administered rats was also seen.

Concerning ivermectin (IVM), our results showed that its oral pretreatment at 0.2 and 0.4 mg/kg b.wt which were within its recommended dose (0.2 to 0.8 mg/kg b.wt) to male rats with testicular damage significantly evoked protective and antioxidant activities of in rats with testicular damage. The protective effect of IVM was manifested by increased the relative
weight of testes, serum levels of testosterone and FSH hormones, semen quality and quantity and ameliorated the testicular degeneration. The activity of antioxidant SOD and CAT enzymes was also increased in the testicular tissue. There were contradictory findings on the effect of IVM on male reproduction and spermatogenesis in different animal species. IVM at low oral doses of 0.2 to 0.6 had no adverse effects on spermatogenesis, fertility, or reproductive performance male fertility in Beagle dogs\textsuperscript{[14]} and rats.\textsuperscript{[19]} The authors concluded that the standard therapeutic doses of IVM can be used without producing side effects on sexual behavior. On the other hand, IVM was reported to produce deleterious effects on male fertility and spermatogenesis in rams\textsuperscript{[15]}, rabbits\textsuperscript{[16, 17]} and mice\textsuperscript{[18]} when larger doses up to 1.0 mg/kg b.wt were used. Our results was partially similar to that of El-Far\textsuperscript{[19]} who reported that chronic oral administration of ivermectin at therapeutic and double therapeutic doses significantly increased serum testosterone and free testosterone levels in male rats and thus might improve male fertility.

The increase of serum testosterone and FSH hormones caused by coadministration of IVM in combination with vitamin E, in this study, might be responsible for improving semen quality and quantity as it has been established that testosterone is essential for spermatogenesis, and also FSH and LH play a valuable role in germ cell progression and improved fertility in animal models.\textsuperscript{[15]} The amelioration of degenerative changes testes of rats administered by IVM in combination with vitamin E were confirmed by the improvement in semen parameters and testicular weight that reported in this study. To the best of our knowledge the results of the present study concerning concomitant use of IVM and vitamin E were for the first time to be recorded.

In conclusion, sodium valproate induces testicular toxicity and oxidative stress in male rats and reduces male fertility. Oral administration of ivermectin at therapeutic and double therapeutic doses and vitamin E alone and in combination exhibits protective and antioxidant effects against reproductive toxicity induced by sodium valproate in rats. Further studies are necessary to explore the reversibility and exact mechanisms of the protective action of ivermectin on male reproduction and spermatogenesis.

REFERENCES


