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**Research Article**

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# Protective Effect of Antioxidants Combinations (Vit A, C, E and Selenium) (Antox Drug) against Oxidative Stress and Cellular Toxicity Induced by Sorafenib in Male Albino Rats

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**ABSTRACT**

*The present study was designed to evaluate the protective role of the antioxidants antox against Sorafenib-celllular toxicity in adult male albino rats. One hundred and twenty mature male albino rats divided into 4 equal groups were used in this study. The 1st group was kept as normal control group, the 2nd group was given anti-cancer drug sorafenib orally and daily for successive 2 weeks in adose of (10 mg/kg b.wt.), the 3rd group was administered the antioxidant drug antox orally and daily for 2 weeks in a dose of (10 mg/kg b.wt.), the 4th group was given the two drugs together in their recommended doses. Blood samples were collected from 5 rats of each group at 1st,3rd days and 1st, 2nd, 3rd and 4th weeks post end of treatment and were subjected to biochemical assays including: oxidative and antioxidative parameters (malondealdehyde (MDA), reduced glutathione (GSH) activity, (GPX) glutathione peroxidase, Catalase (CAT), souperoxide dismutase (SOD) and total antioxidants capacity and genotoxicity (Comet assay test. Treatment with sorafenib alone resulted in a significant increase in MDA, CAT, SOD and Gpx level and total antioxidants activity. The activity of reduced (GSH) is significantly decreased in sorafenib treated group compared to control group. Treatment for two weeks with antox after sorafenib elicited a significant decrease in MDA, GPX, SOD, CAT as well as a significant increase in serum GSH, total antioxidants activity and Comet assay revealed that sorafenib treated group showed a significant increase in comet %,tail length, DNA tail % and tail moment compared with control and other treated groups.*

**Keywords:** Sorafenib; Antox; Malonaldehyde; Glutathione; Catalase; Total antioxidants; Glutathione peroxidase; Comet assay test

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## INTRODUCTION

Sorafenib is an oral, biaryl urea RAF kinase inhibitor that acts against both vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptors, simultaneously targeting both tumor cell proliferation and angiogenesis This drug has an anti-angiogenic action through direct effects on vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) receptors [1].

Sorafenib was the first multikinase inhibitor to be approved for use in metastatic renal cell carcinoma in the US (2005) and in Europe (2006) [2]. Its capacity to impair the Raf/mitogen activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway [3], or inhibit the BCR/ABL kinase activity [4], as well as it demonstrated effects on STAT3 (Signal transducer and activator of transcription) [5,6]. It has been linked to its anti-proliferative effects in different tumors, which might include both growth arrest and cell death. A recent study has suggested that induction of the growth arrest DNA damage inducible gene 45β (GADD45β) might also contribute to sorafenib-

induced apoptosis in HCC cells [7]. Antox is an antioxidant contains three supplementary nutritional vitamins A, C and E with trace element selenium which is essential for normal metabolic reactions [8].
It significantly decrease the adverse effect of reactive species such as reactive oxygen and nitrogen species that can cause oxidative damage to macromolecules such as lipid, DNA and proteins, which are implicated in chronic diseases [9]. It has been reported that, vitamin A and C either individually or in combination are reported to act as an effective antioxidant of major importance for protection against diseases and degenerative processes caused oxidative stress [10,11]. Antioxidant containing drug (Antox) inhibits free radical generation in small intestine which acts as a contributing factor to the rejection process [12]. Vitamins are ideal antioxidants to increase tissue protection from oxidative stress due to their effective and safe dietary administration in a wide range of concentrations without harmful side effects [13].
This study aimed to assess the possible protective effect of the antioxidants antox and its ability to combat and ameliorate cellular-toxicity induced by anti-cancer drug sorafenib, through studying the effect on oxidative/antioxidative activities and genotoxicity parameters [14].

## MATERIALS AND METHODS

### Materials

**Experimental animals:**
One hundred and twenty mature male albino rats, obtained from Animal Breeding Unit, Faculty of Vet. Med. Zagazig University was used in this study. Their weights ranged between (150-180 gm b.wt.) They were housed in wire cages with natural ventilation, illumination and allowed free water and standard pelleted diet ad-libitum and acclimated for 2 weeks before experimentation.

**Experimental design:**
The rats were randomly divided into 4 equal groups each of 30 rats as follows:

| | |
|---|---|
| **(I) Control group** | Given 1 ml distilled water and kept as control group. |
| **(II) Sorafenib treated group** | Given orally sorafenib (10 mg/kg. b.wt.) daily for successive two weeks. |
| **(III) Antox treated group** | Given (10 mg/kg. b.wt.) of Antox in dist. water daily for two weeks. |
| **(IV) Sorafenib + Antox treated group** | Given both sorabenib and the antioxidant mixture (Antox) in their recommended doses for the same periods. |

**Drugs:**
**Sorafenib:** (Nexavar, 200® mg) obtained from Bayer Healthcare (Leverkusen, Germany) was used. Pills were ground in a tissue mill. The resulting powder was mixed with distilled water and applied via gavage to rats by stomach tube [15].
**Dose:** A dose of (10 mg/kg. b.wt.) was given orally and daily for 2 weeks [1].
**Antox:** Arab Company for Pharmaceuticals & Medicinal Plants (Mepaco-Medifood)–Egypt. A dietary Supplement, Contains the three main antioxidant vitamins A, C and E together with very important rare element, selenium. The tablets were crushed and suspended in 0.5% CMC in distilled water.
**Dose:** A dose of (10 mg/kg. b.wt.) was administrated with a stomach tube to rats [16].

**Collection of Samples**
Two blood samples were collected from 5 rats of each group at 1st and 3rd days and 1st, 2nd, 3rd and 4th weeks post end of treatment. First sample without anticoagulant for preparation of serum, blood was collected and allowed to clot and serum was separated by centrifugation at 3000 rpm and kept at -20°C for measuring antioxidants activities.
After blood collection rats were dissected out and parts from liver were collected at the 4th week and wrapped in aluminum foil and kept in freezer at -20°C and used for genotoxiciy investigation (comet assay test), (MDA), [17], Catalase Activity (CAT) [18], reduced glutathione (GSH) [19], Glutathione peroxidase (GPx) activity [20] Superoxide dismutase activity (SOD), total antioxidant capacity (TAO) [21] and Comet test Assay**,** [22,23].

**Statistical Analysis**
The obtained data were analyzed and graphically represented using the statistical package for social science [24], for obtaining [Mean value ± standard error]. The results were statistically analyzed by using one-way ANOVA test. Subsequent multiple comparisons between the different groups were analyzed by Duncan's multiple comparison tests [25] values at ($P<0.05$) were considered significant [26].

## RESULTS

The obtained results in this study revealed that oral administration of sorafenib in a dose of (10 mg/kg.b.wt.) of rats daily for 2 weeks afforded a significant decrease ($p<0.05$) in MDA,CAT,SOD,GSH,GPX and total antioxidants capacity levels together with a significant increase in GSH when compared with normal control group. Whereas, treatment for 2 weeks daily with antox (10 mg/kg.b.wt.) after sorafenib elicited a significant decrease in MDA, CAT, SOD, and GPX as well as a significant increase in serum GSH and total antioxidant activity compared with sorafenib treated group Tables 1-6. Comet assay revealed that sorafenib-treated group showed a significant increase in comet %, tail length, DNA tail % and tail moment compared with control and other treated groups (Table 7 and Figure 1)

**Table 1: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10 mg/kg.b.wt.) on MDA in male albino rats**

| Parameter / Experimental group | Value of MDA *(nmol/mL)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd day | 1st Week | 2nd Week | 3rd week | 4th Week |
| Control | 2.89 ± 0.40[a] | 2.06 ± 0.42[a] | 6.23 ± 0.38a | 3.06 ± 0.69[b] | 3.49 ± 0.27[b] | 2.62 ± 0.48[b] |
| Sorafenib | 2.99 ± 0.41[a] | 3.36 ± 0.35[a] | 4.99 ± 0.76[a] | 5.36 ± 0.35[a] | 5.34 ± 0.35[a] | 4.71 ± 0.24[a] |
| Antox | 2.86 ± 0.38[a] | 2.38 ± 0.22[a] | 4.86 ± 0.70[a] | 2.38 ± 0.22[b] | 2.82 ± 0.15[c] | 2.54 ± 0.10[b] |
| Sorafenib and antox | 2.44 ± 0.21[a] | 2.89 ± 0.52[a] | 3.77 ± 0.36[a] | 4.56 ± 0.38[a] | 4.19 ± 0.10[b] | 2.90 ± 0.30[b] |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

### Reduced Glutathione (GSH)

**Table 2: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10 mg/kg.b.wt.) on GSH in male albino rats**

| Parameter / Experimental group | Value of GSH *(mg%)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd day | 1st Week | 2ndWeek | 3rd week | 4th Week |
| Control | 77.24 ± 1.92[a] | 70.57 ± 3.43[a] | 71.24 ± 3.53[a] | 80.57 ± 2.35a | 80.57 ± 2.35[a] | 80.57 ± 2.35[a] |
| Sorafenib | 42.63 ± 2.29[c] | 36.42 ± 3.47[b] | 35.86 ± 2.04[b] | 37.32 ± 3.70c | 34.48 ± 1.50[b] | 63.61 ± 3.00[b] |
| Antox | 79.26 ± 3.56[a] | 67.64 ± 4.49[a] | 60.26 ± 3.28[a] | 59.17 ± 2.10b | 74.30 ± 5.51[a] | 78.50 ± 4.94[a] |
| Sorafenib and antox | 63.17 ± 3.04[b] | 37.13 ± 1.53[b] | 35.79 ± 1.60[b] | 50.81 ± 2.56b | 41.66 ± 3.10[b] | 61.53 ± 2.64[b] |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

### Glutathione Peroxidase (GPX):

**Table 3: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10 mg/kg.b.wt.) on GPX in male albino rats**

| Parameter / Experimental group | Value of GPX *(μ mol NADPH/mg protein)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd day | 1st Week | 2nd Week | 3rd week | 4th Week |
| Control | 14.47 ± 1.30[b] | 13.47 ± 1.55[b] | 17.13 ± 1.99[b] | 16.47 ± 1.44b[c] | 13.80 ± 1.83[c] | 17.13 ± 1.99[b] |
| Sorafenib | 21.53 ± 0.93[a] | 20.36 ± 0.66[a] | 29.16 ± 1.31[a] | 26.44 ± 1.99[a] | 27.28 ± 1.21[a] | 28.11 ± 1.57a |
| Antox | 14.09 ± 1.17[b] | 12.60 ± 1.14[b] | 17.89 ± 0.95[b] | 13.02 ± 0.78[c] | 12.92 ± 1.34[c] | 14.59 ± 1.58[b] |
| Sorafenib and antox | 20.48 ± 0.70[a] | 17.42 ± 1.05[a] | 19.82 ± 0.34[b] | 19.19 ± 0.61[b] | 21.02 ± 1.69[b] | 20.70 ± 1.21[b] |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

## Superoxide Dismutase (SOD)

**Table 4: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10 mg/kg.b.wt.) on SOD in male albino rats**

| Parameter / Experimental group | Value of SOD *(U/ml)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd Day | 1st Week | 2nd Week | 3rd week | 4th Week |
| Control | $0.71 \pm 0.10^{b}$ | $0.71 \pm 0.10^{ab}$ | $0.71 \pm 0.10^{ab}$ | $0.71 \pm 0.10^{b}$ | $0.71 \pm 0.10^{b}$ | $0.71 \pm 0.10^{b}$ |
| Sorafenib | $1.78 \pm 0.42^{a}$ | $0.71 \pm 0.11^{ab}$ | $0.81 \pm 0.10^{a}$ | $1.17 \pm 0.13^{a}$ | $1.37 \pm 0.19^{a}$ | $1.51 \pm 0.07^{a}$ |
| Antox | $0.51 \pm 0.05^{b}$ | $0.83 \pm 0.02^{a}$ | $0.41 \pm 0.12^{bc}$ | $0.48 \pm 0.06^{c}$ | $0.66 \pm 0.02^{b}$ | $0.42 \pm 0.22^{b}$ |
| Sorafenib and antox | $0.78 \pm 0.15^{b}$ | $0.70 \pm 0.03^{b}$ | $0.36 \pm 0.03^{c}$ | $0.43 \pm 0.06^{c}$ | $0.64 \pm 0.08^{b}$ | $0.85 \pm 0.07^{b}$ |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

## Total Antioxidant Capasity (TAO)

**Table 5: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10mg/kg.b.wt.) on total antioxidant in male albino rats**

| Parameter / Experimental group | Value of SOD *(U/ml)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd Day | 1st Week | 2nd Week | 3rd week | 4th Week |
| Control | 3.94 ± 0.25a | 3.60 ± 0.28a | 3.60 ± 0.28a | 3.94 ± 0.33a | 3.60 ± 0.43a | 3.94 ± 0.25a |
| Sorafenib | 2.25 ± 0.34b | 2.54 ± 0.20b | 1.41 ± 0.37c | 1.62 ± 0.37b | 1.63 ± 0.21b | 1.72 ± 0.21c |
| Antox | 3.15 ± 0.38ab | 2.85 ± 0.01b | 2.45 ± 0.30b | 3.55 ± 0.31a | 3.59 ± 0.35a | 3.29 ± 0.64b |
| Sorafenib and antox | 2.90 ± 0.08b | 2.27 ± 0.21b | 2.45 ± 0.27b | 1.96 ± 0.21b | 2.07 ± 0.06b | 2.37 ± 0.27bc |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

## Catalase (CAT)

**Table 6: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox (10 mg/kg.b.wt.)on CAT in male albino rats**

| Parameter / Experimental group | Value of SOD *(U/ml)* after | | | | | |
|---|---|---|---|---|---|---|
| | 1st day | 3rd Day | 1st Week | 2nd Week | 3rd week | 4th Week |
| Control | 1.00 ± 0.35b | 0.99 ± 0.27b | 1.24 ± 0.28b | 1.22 ± 0.27b | 0.83 ± 0.26b | 0.68 ± 0.10b |
| Sorafenib | 4.17 ± 0.33a | 3.01 ± 0.76a | 3.33 ± 0.66a | 3.40 ± 0.84a | 3.13 ± 0.68a | 3.73 ± 0.65a |
| Antox | 1.53 ± 0.53b | 1.33 ± 0.32b | 1.53 ± 0.47b | 1.50 ± 0.06b | 1.14 ± 0.24b | 0.89 ± 0.26bc |
| Sorafenib & antox | 1.64 ± 0.22b | 1.97 ± 0.13ab | 2.23 ± 0.15ab | 1.68 ± 0.26b | 1.82 ± 0.16b | 1.50 ± 0.08b |

**Mean ± S.E (n=5)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

**Table 7: Effect of sorafenib (10 mg/kg.b.wt.), antox (10 mg/kg.b.wt.) and sorafenib + antox(10 mg/kg.b.wt.) on genotoxicity in male albino rats**

| Parameter / Experimental group | Comet assay test | | | |
|---|---|---|---|---|
| | Comet percent | Tail length | DNA tail percent | Tail moment |
| Control | $11.40 \pm 0.35^{b}$ | $3.63 \pm 0.33^{c}$ | $21.73 \pm 2.04^{c}$ | $0.73 \pm 0.08^{c}$ |
| Sorafenib | $19.70 \pm 0.75^{a}$ | $7.98 \pm 0.72^{a}$ | $37.98 \pm 1.82^{a}$ | $4.15 \pm 0.53^{a}$ |
| Antox | $12.65 \pm 0.56^{b}$ | $4.50 \pm 0.30^{c}$ | $22.95 \pm 0.16^{c}$ | $1.33 \pm 0.09^{c}$ |
| Sorafenib and antox | $13.80 \pm 1.58^{b}$ | $6.18 \pm 0.64^{b}$ | $30.73 \pm 0.36^{b}$ | $3.13 \pm 0.17^{b}$ |

**Mean ± S.E (n=10)**

Means within the same column in each category carrying different litters are significant at ($P \leq 0.05$) using Duncan's multiple range test.

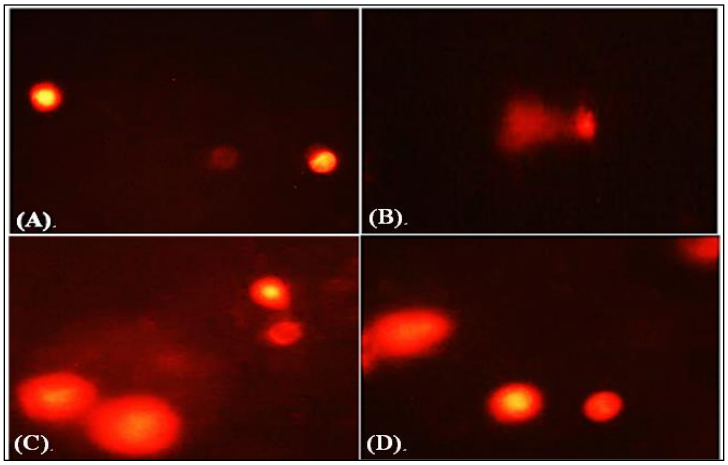


**Figure 1: Representative comet images of rat liver at the 4th week after treatment (A) control group orally recived distilled water for successive two weeks; (B) sorafenib treated group orally received sorafenib (10 mg/kg b.wt.) for two weeks; (C) antox treated group orally recived antox (10 mg/kg b.wt.) for the same period; (D) sorafenib + antox treated group as the previously aforementioned doses and duration**

## DISCUSSION

The present study showed that treatment with antox in combination with sorafenib offered considerable protection as evidenced from oxidative/antioxidative parameters and comet assay test. It has been proposed that moderate level of ROS can induce an increase in antioxidant enzyme activities [27] whereas very high level of these reactants was shown to attenuate antioxidant enzyme activities [28].

Production of oxygen radicals was parallel by an augmented lipid peroxidative index as evidenced by the significant increase in malondealdehyde (MDA) detected in serum of rats intoxicated with sorafenib compared with control rats suggesting an increased production of oxygen free radicals in rats. Highly reactive oxygen metabolites, especially hydroxyl radicals, act on unsaturated fatty acids of phospholipid components of membranes to produce malondedialdehyde, a lipid peroxidation product, where the accumulation of excess free radicals may be responsible for the increased lipid peroxidation [29]. In endogenous antioxidant systems SOD is widely distributed and plays a critical role in mammalian organism. SOD has a pivotal role against damaging effect from superoxide radical [30]. Since it is very toxic Hydrogen superoxide is then eliminated with CAT. As hydrogen superoxide is a product of SOD study it is also a strong inhibitor of this enzyme [31]. As catalase was the first antioxidant enzyme to be characterized and catalyses the two stage conversion of hydrogen peroxide to water and oxygen and sharing this function with GSH- px [32].

In the present study, there is a significant reduction in the reduced glutathione level. This reduction in GSH level may be due to either the inhibition of GSH synthesis or increased utilization of GSH for detoxification of toxicant induced free radicals. GSH was further decreased in sorafenib group. The level of GSH in sorafenib group was significantly lower than its level in either control group or antox group ($p < 0.05$). This was in accordance with [33] who reported that reduced glutathione (GSH) plays an important role in anti-oxidation of reactive oxygen species and free radicals, increasing oxidative stress accompanied by decline in GSH level. These findings are parallel with that previously reported by Omotuyll et al. who recorded a significant decrease in the reduced glutathione level after oral administration of cyfuthrin (Pyrethroid) for 15 weeks [34]. Raina et al. also recorded a significant decline in blood glutathione after 30 days of cypermethrin (Pyrethroid dermal application [35]. Sharma et al. showed that cypetrmethrin treated group, (at the dose of 3.83 mg/kg b.w. for 7 days) showed elevation in lipid peroxidation and inhibition in glutathione in Wister rat brain. In addition, Abbassy et al. observed a significant decrease in GSH after treatment of rats with lambda cyhalothrin in a dose equal 2.6 mg/kg b.w, for 6 weeks (3 doses/week) [29]. GSH and MAD levels in the liver reflect the oxidative status and the serum enzymes like AST and ALT represent the functional status of the liver. Chemical-induced cellular alteration varies from simple increase of metabolism to death of cell. The increase or decrease of enzyme activity is related to the intensity of cellular damage. Increased MAD level in the liver as well as increased serum AST, ALT and ALP levels suggest that Cyfluthrtn causes hepatic damage which may be through free radicals [36].

Oxidative stress may induce a rapid alteration in the antioxidant systems by inducing protein that participate in these systems and/or depleting cellular, stores of endogenous antioxidants such as GSH and Vitamin E [37].
According to the present data, combined supplementation of antox after sorafenib resulted in a significant reduction in ALT, AST activities. Hassan et al. reported that treatment for seven days with either antioxidants alpha lipoic acid (ALA) or Antox prior to or after LPS challenge significantly ($P<0.05$) decrease ALT, AST, MDA and NO levels when compared to LPS alone that reflect the role of Antox to overcome the oxidative stress and liver injury induced by LPS challenge [38]. This result is accompanied by improvement in the content of GSH when compared with antox treated group. This result is parallel with Hamooda et al. who reported that antox succeeded in minimizing cadmium induced toxicity in albino rats and increase the activity of endogenous antioxidants including glutathione [39]. The present study has demonstrated no sign of therapeutic effect of antox supplementation on MDA after sorafenib administration, this result agree with this result in accompanied by improvement in the content of GSH and albumin when compared with sorafenib treated group [40]. Also the total protein showed a significant increase, Antox alone improve MDA, GSH levels, activity and induce a decrease in AST activity, as compared to the control group. These results agree with the results obtained by Daoud et al. and El-Gohary et al. who reported that antox inhibited free radical generation in small intestine [12,41]. Antioxidants like vitamin E had played a protective role against the pyrethroid induced oxidative stress [42-44]. The results obtained by Pieneli-Saavedra and Das et al. who postulated that vitamin E improved the immune system by unknown ways in addition to its antioxidant properties, it may also exhibit immune-modulator effect [45,46].
Liver GPX revealed a significant decrease in sorafenib group this decrease in serum GPX level suggests that the exposure of sorafenib may lead to excessive free radical generation. These free radicals might attack the thiol group of cysteine residues and polyunsarurated fatty acids of biological membranes [34]. Moreover, Jones and El-Maghraby and Taha suggested that, the protective effect of vitamin E may be due to its lipophilic antioxidant property which may induce reduction of membrane lipid peroxidation and lipid peroxide formation [47,48]. Selenium is an essential component of GSH-Px, which is an important enzyme for process that protects lipid in polyunsaturated membrane from oxidative degradation [49]. Selenium stimulates Na, K-ATPase activity and inhibits lipid peroxidation. Since Na, K-ATPase activity is known to be inhibited by oxygen free radicals likely formed by sorafenib, selenium supplementation appears to exert its beneficial effect on Na, K-ATPase activity preventing free radical-induced damage [50].

**Effect on Genotoxicity**

The comet assay is an indicator test for the detection of DNA damage and is primarily used as a supplemental *in vivo* test for substances with positive results from *in vitro* mutagenicity tests and/or for mechanistic studies. The *in vivo* comet assay has some advantages over other *in vivo* indicator tests with regulatory acceptance, such as the unscheduled DNA synthesis (UDS) test or the alkaline elution method. The *in vivo* UDS test is generally performed in liver tissue only, while the comet assay can be applied to virtually any organ of interest provided that an appropriate cell preparation has been established for each organ and cell type. In addition, the comet assay detects a broader spectrum of primary DNA lesions, including single strand breaks and oxidative base damage, which may not sensitively be detected by the UDS test because they are not repaired by nucleotide excision repair [51].

## CONCLUSION

In this context it is extremely akin to mention that daily oral administration of sorafenib for successive two weeks resulted in significantly release comet percent, tail length, DNA tail percent and tail moment in comparison to control and or antox treated group while co administration of sorafenib with antox minimize the elevation of comet percent, tail length, DNA tail percent and tail moment although it still significant high in relation to control and antox treated rats.

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