Alterations in Lipid Peroxidation and some Trace Elements Concentrations in Sera and Tissues Homogenates of Women with Benign and Malignant Cervix and Uterine Tumors

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Abstract

The levels of sera and tissues homogenates malondialdehyde MDA (one of the lipid peroxidation products), was measured by Hirayama et.al spectrophotometry method, and the sera concentrations of some trace elements: Copper (Cu), Iron (Fe), and Zinc (Zn) were evaluated in patients with benign cervix (n=28), malignant cervix (n=20), benign uterine tumors (n=33), and malignant uterine tumors (n=28), as measured by using flame atomic absorption spectrophotometer. A significant increase (P<0.05) in MDA concentration were found in sera of all above mentioned groups when compared with that of control group. However there were a high significant increase (P<0.005) in sera of pre-menopausal groups of patients with benign, malignant cervix and uterine tumors among the other groups. Tissues homogenates MDA levels showed significant increase (P<0.05) in case of cervix pre-malignancy (n=10), cervix (n=20) and uterus cancer (n=28) groups when compared with that of the other groups (n=68). The results indicated a significant decrease (P<0.05) in sera (Zn) concentration and a significant increase (P<0.05) in both sera (Cu) and (Fe) concentration in uterus and cervix cancer groups when compared with that of the other groups.

Keywords: Malondialdehyde; Zinc; Copper; Iron; Uterus tumors; Cervix tumor.

Introduction

There has been a growing interest in studying the role of lipid peroxidation and antioxidant status in diseases. Alteration in the oxidant-antioxidant profile was reported to occur in cancer patients, where enhanced lipid peroxidation and impairment of antioxidant defence mechanism has been demonstrated [1, 2, 3].

Free radicals are formed in both physiological and pathological conditions in mammalian tissues. The uncontrolled production of free radicals is considered as an important factor in the tissue damage induced by several pathophysiology [4]. Lipid peroxidation mediated by free radicals is considered to be the major mechanism of cell membrane destruction and cell damage [5], which has been broadly defined as the oxidative deterioration of poly-unsaturated fatty acids (PUFA). Peroxidation of (PUFA) in the phospholipids bilayer of the biological membrane, leads to loss of the membrane fluidity, the membrane secretory functions and trans-membrane ionic gradient [6].

Biological free radical reactions have been inferred by identifying the products of...
lipid peroxidation, in particular, malondialdehyde (MDA)\(^7\) a by-products that has been speculated to have a crucial role in the early phases of tumor growth if they are excessively generated \(^8\). The ability of lipid peroxidation by-products in generating mutagenesis and DNA adducts formation suggest their possible role in carcinogenesis\(^9\).

It was reported that the antioxidant defence system altered in various human tumors, and a reverse relationship was found between antioxidant enzyme activities and lipid peroxidation in patients with some of these tumors\(^{10,11}\).

Generally, transition metal ions are incorporated into proteins, and they present at the active site of many enzymes. They facilitate (OH\(^-\)) radical formation, \((\text{H}_2\text{O}_2)\), lipid peroxide decomposition\(^{12}\), the transfer of single electrons to molecular oxygen \(^{11}\), and produce superoxide anion radical \((\text{O}^-)_2\) (equation 1), which in-turn is converted to hydroxyl radical through Haber-Weiss reaction or Fenton reaction (equation 2 or 3). These metals are iron and copper, and as soon as (OH\(^-\)) and lipid peroxide radicals formed, they can easily release catalytic iron from hemoglobin \(^{13}\), while \((\text{O}^-)_2\) can mobilize iron from ferritin \(^{14}\).

\[
\begin{align*}
\text{O}_2 + \text{Fe}^{2+} & \rightarrow \text{O}^-_2 + \text{Fe}^{3+} \quad (1) \\
\text{O}_2^- + \text{H}_2\text{O}_2 & \rightarrow \text{O}_2 + \text{OH}^- + \text{OH}^- \quad (2) \quad \text{Haber-Weiss reaction} \\
\text{Fe}^{2+} + \text{H}_2\text{O}_2 & \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^- \quad (3) \quad \text{Fenton reaction}
\end{align*}
\]

The formed (OH\(^-\)) will react with whatever biological molecule is in its vicinity, damage proteins, cause breakage of DNA strands, and initiate lipid peroxidation \(^{15,16}\). However, lipid peroxidation rarely seems to be the primary mechanism of the cellular damage by increased generation of \((\text{O}^-)_2\) and \((\text{H}_2\text{O}_2)\)\(^{17}\). DNA seems to be a more important target, and excessive DNA damage can contribute to a lethal depletion of nicotinamide nucleotides in the cell as ploy (ADP-ribose synthetase) becomes activated \(^{18,19}\).

Trace elements have been extensively studied to assess whether they have any modifying effects in the etiology of cancer\(^{20}\). Serum copper and zinc levels, and their clinical usefulness in malignant states have been investigated mainly in patients with different types of cancer \(^{21,22}\).

In this study, levels of MDA, as an end product of lipid peroxidation, were measured in sera and tissue homogenates of patients with benign and malignant cervix and uterine tumors in comparison with that of control women. Also some trace elements (Cu, Fe, and Zn) were measured to investigate the relationship between these trace elements and lipid peroxidation in the above indicated patients.
**Materials and methods:**

**Chemicals:**

All chemicals used throughout this work are of analar grade.

**Patients:**

Seven groups were used as a subject of this study including control healthy women, and patients with cervix and uterine diseases. Each group was subdivided to pre-menopausal, menopausal, and post- menopausal as illustrated in table 1.

**Table 1:** Samples used for lipid peroxidation and trace elements determination.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (year)</th>
<th>n</th>
<th>Samples type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>35-45</td>
<td>23</td>
<td>Blood samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-73</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Adenomyosis (Pathological control)</td>
<td>36-45</td>
<td>16</td>
<td>Blood and tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-63</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Benign uterine tumor (Leiomyoma)</td>
<td>34-45</td>
<td>19</td>
<td>Blood and tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Malignant uterine tumor (endometrial cancer)</td>
<td>35-42</td>
<td>9</td>
<td>Blood and tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-85</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Premalignancy cervix</td>
<td>34-45</td>
<td>7</td>
<td>Tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Chronic cystic cervicitis (Pathological control)</td>
<td>36-45</td>
<td>9</td>
<td>Blood and tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-66</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>35-45</td>
<td>7</td>
<td>Blood and tissue samples</td>
</tr>
<tr>
<td></td>
<td>45-55</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>55-69</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

All patients were admitted for managements to Baghdad teaching hospital, Al–Elweia teaching hospital, Al- Yarmook teaching hospital. The diagnosis was proven by cytological histopathological examination. Any patient with coexisting disease was excluded. The average age of the individuals investigated was (60) year with a range of (34-85) year.
Samples:

1- Blood

Five milliliters of blood sample were obtained from each patient, and from age matched healthy women, by vein puncture, left for (15) minute at room temperature for coagulation. Then sera were separated by centrifugation at (3000 xg) for (10) minutes and stored frozen at (- 20) °C until been used.

2- Tissues

Tissues samples were collected immediately after the operation, cut off, rinsed with normal saline, and kept frozen at (-20) °C until been used.

Tissue homogenate preparation:

From each tissue, a weight of (0.25) g was taken and cut into small pieces in a petri-dish on dry ice. The slices were homogenized by hand homogenizer in an ice bath using phosphate buffer (0.05 M; pH: 7.8) in a ratio of (1: 4 W/V). The homogenate was sonicated six cycles of (15) seconds with (30) seconds intervals in between, then filtered and centrifuged at (10,000 xg) for (30) minutes in a cooling centrifuge. The supernatant was used for protein and lipid peroxidation determination at the same day.

Protein determination:

Total protein was determined by Lowry et. al method [23] using bovine serum albumin (BSA) as a standard protein.

Lipid peroxidation in sera and tissue homogenates:

Malondialdehyde (MDA), an indicative for lipid peroxidation, was measured using Hirayama et.al. [24] method. In this method, MDA, the product of (PUFA), reacts with thiobarbituric acid (TBA) to give a pink color chromophore absorbing at (535) nm. MDA levels of tissue homogenates were determined using fresh tissue homogenate, since an increase in MDA value was found upon storage of the samples.

Calculations

MDA concentrations were calculated using its molar absorbitivity coefficient of (1.56 x10^5 M^-1 cm^-1) and the results was expressed as nmole MDA /mg protein.

MDA (nmol / mg) = A x Vt x 10^3 / Vs x 1000 x 1.56 x 10^5 x protein concentration

Where: A= Absorbance

Vt = Total volume.

Vs= Sample volume.

Determination of trace elements in serum:

Some trace elements: Iron (Fe), Copper (Cu), and Zinc (Zn) levels were determined in sera of healthy women, women with benign and malignant tumors using flame atomic absorption spectrophotometer, after five fold dilution of the sera with de-ionized water. Iron was determined at a wave length of (284.3)nm, Copper at (324.7)nm, and Zinc at (319.9) nm. The concentrations of Fe, Cu, and Zn were calculated from the corresponding standard curves.
Evaluation of results:

The results were subjected to statistical evaluation by means of the student’s t-test. Differences between means giving a probability of less than 5% were considered as statistically significant.

Results

Lipid peroxidation levels (MDA):

A- In serum:

The mean values (± SD) of sera MDA levels in the different groups are shown in Tables (2A) and (3A). The results revealed a significant increase in MDA levels in patients with benign (P < 0.05), and malignant uterine tumors (P < 0.05) when compared with that of control group, while no significant difference was found between those of benign in comparison with those with malignant uterine tumors.

Table 2: MDA levels in control women, and patients with adenomyosis, benign and malignant uterine tumors.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein (g/dL)</th>
<th>MDA nmol/mg [mean (±SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>45</td>
<td>7.28 (±1.075)</td>
<td>0.056 (±0.016)</td>
</tr>
<tr>
<td>Adenomyosis</td>
<td>35</td>
<td>7.85 (±0.75)</td>
<td>0.142 (±0.0072)</td>
</tr>
<tr>
<td>Benign uterine tumors</td>
<td>33</td>
<td>6.9 (±0.22)</td>
<td>0.1509 (±0.014)</td>
</tr>
<tr>
<td>Uterus cancer</td>
<td>28</td>
<td>7.30 (±0.113)</td>
<td>0.192 (±0.027)</td>
</tr>
</tbody>
</table>

B- Tissue homogenate

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein (g/dL)</th>
<th>MDA nmol/mg [mean (±SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenomyosis</td>
<td>35</td>
<td>1.513 (±0.20)</td>
<td>2.088 (±0.0633)</td>
</tr>
<tr>
<td>Benign uterine tumors</td>
<td>33</td>
<td>1.59 (±0.42)</td>
<td>3.01 (±0.21)</td>
</tr>
<tr>
<td>Uterus cancer</td>
<td>28</td>
<td>1.85 (±0.177)</td>
<td>4.98 (±0.187)</td>
</tr>
</tbody>
</table>

S = P< 0.05 significant compared with control group
S1= P < 0.05 significant compared with other groups
Ns= not significant compared with pathological group

Levels of MDA in sera of cervix cancer were slightly elevated than that of pathological control and premalignancy group. However no significant differences were found among them, while there was a highly significant elevation in sera of cervix cancer group when compared with that of control group (P< 0.001). No differences were found in sera MDA levels between subgroups of each group of patients used in this study as shown in figures 1 and 2.
Figure 1: Mean sera MDA levels in subgroups of control, adenomyosis, benign and malignant uterine tumors (no significant difference found among subgroups).

Figure 2: Mean sera MDA levels of control, chronic cervicitis, premalignancy, and cervix cancer (no significant difference found among subgroups).

B-In tissues homogenates:

The mean values of the tissues homogenates MDA levels of the different patients groups, and pathological control group were estimated as shown in tables (2B) and (3B). The results revealed no significant differences between pathological control, and benign uterine tumors groups. However, there was a significant increase in malignant uterine tumors group when compared with that of pathological control (P<0.05), and with that of benign uterine tumors group (P<0.05). No differences were found in tissues homogenates MDA levels between subgroups of each group of patients as shown in figure 3.
The levels of MDA of premalignancy cervix and cervix cancer groups show significant increase when compared with that of pathological control (P<0.05) and (P<0.01) respectively, while there was no significant difference between cervix cancer group and premalignancy group. Moreover no differences were found in tissues homogenates MDA levels between subgroups of patients used as shown in figure (4).

Figure 3: Mean MDA levels of tissue homogenates in subgroup of adenomyosis, benign and malignant uterine tumors (no significant difference found among subgroups).

Figure 4: Mean MDA levels of tissue homogenates in subgroup of chronic cervicitis, premalignancy, and cervix cancer (no significant difference found among subgroups).
The present results also reveal that tissues homogenates level of MDA of uterus cancer have a significant increase when compared with that of cervix cancer (P<0.05) as shown in tables (2B) and (3B).

**Table 3:** MDA levels in control women, and patients with chronic cervicitis, premalignancy cervix, and cervix cancer.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein (g/dL) [mean (±SD)]</th>
<th>MDA nmol/mg [mean (±SD)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>45</td>
<td>7.28 (±1.075)</td>
<td>0.056 (±0.016)</td>
</tr>
<tr>
<td>Chronic cervicities</td>
<td>28</td>
<td>7.39 (±0.72)</td>
<td>0.108 S (±0.002)</td>
</tr>
<tr>
<td>Premalignancy</td>
<td>13</td>
<td>7.18 (±0.517)</td>
<td>0.131S ns (±0.002)</td>
</tr>
<tr>
<td>Cervix cancer</td>
<td>20</td>
<td>7.32 (±0.56)</td>
<td>0.192S1 (±0.0055)</td>
</tr>
</tbody>
</table>

A- In serum

B- In tissue homogenate

S= P<0.05 significant compared with control group
S1= P<0.05 significant compared with control group
S2= P<0.05 significant compared with pathological group
S3= P<0.01 significant compared with pathological group
Ns= not significant compared with pathological group

**Levels of some trace elements:**

Trace elements: copper, iron and zinc in sera of control women, patients with benign and malignant cervix, and uterine tumors, were measured by flameless atomic absorption spectrophotometer. The results in table 4 showed that sera zinc levels were significantly lower (P<0.05) in uterus cancer group than that of control group, whereas no alteration were observed in sera of benign tumors group in comparison to that of the control group.

Sera copper levels were significantly higher in uterus cancer group when compared with that of control, and benign tumor groups (P<0.001), and (P <0.05) respectively.

For sera iron levels, the results showed that they were significantly higher in malignant uterine tumors groups than that of control group (P<0.05), and benign tumors group (P<0.001).
Table 4: Sera iron, zinc, and copper levels in control women, and patients with benign and malignant uterine tumors.

<table>
<thead>
<tr>
<th>Trace elements (n=10)</th>
<th>Control</th>
<th>Benign uterine tumors</th>
<th>Uterus cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (± SD) (µ mol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe</td>
<td>25.49 (±3.72)</td>
<td>23.95 (±2.87)</td>
<td>63.21 (±5.26)</td>
</tr>
<tr>
<td>Zn</td>
<td>18.2 (±2.14)</td>
<td>17.91 (±2.93)</td>
<td>11.76 (±1.84)</td>
</tr>
<tr>
<td>Cu</td>
<td>28.09 (±2.31)</td>
<td>30.12 (±3.32)</td>
<td>35.55 (±3.16)</td>
</tr>
</tbody>
</table>

S = P<0.05 significant compared with control group
S1= P<0.01 significant compared with benign tumor group
S2= P<0.05 significant compared with control group
Ns= not significant compared with control group

There were significant increase in Cu levels (P<0.05) and a significant decrease in Zn levels (P<0.01) of sera of patients with cervix cancer when compared with that of control group and benign tumors group. Iron levels were found to increase significantly (P<0.005) as compared to that of control group and patients with benign tumors as shown in table 5.

Table (5): Sera iron, zinc, and copper levels in control women, and patients with chronic cervicities (pathological control) and cervix cancer.

<table>
<thead>
<tr>
<th>Trace elements (n=10)</th>
<th>Control</th>
<th>Pathological control</th>
<th>Cervix cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (± SD) (µ mol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fe</td>
<td>25.49 (±3.72)</td>
<td>24.02 (±1.53)</td>
<td>50.29 (±4.36)</td>
</tr>
<tr>
<td>Zn</td>
<td>18.2 (±2.14)</td>
<td>18.33 (±2.62)</td>
<td>12.22 (±0.84)</td>
</tr>
<tr>
<td>Cu</td>
<td>28.09 (±2.31)</td>
<td>27.36 (±3.82)</td>
<td>36.77 (±4.56)</td>
</tr>
</tbody>
</table>

S = P<0.05 significant compared with other groups
S1= P<0.01 significant compared with other groups
S2= P<0.005 significant compared with other groups

Discussion
Several studies have been published regarding the role of pro–oxidant states in carcinogenesis. The interpretation of the results is difficult, as they seem to vary from one study to another [25, 26, 27]. The inconsistency is likely to be due to the heterogeneity of the tumor tissues. The published studies so far do not support the general hypothesis regarding the role of oxidative stress in the pathobiology of cancer. In some tumor types, including breast cancer [28, 29], and colon cancer [16], increased formation of lipid peroxidation products has been reported, while in endometrial cancer, for example, the enzymatic antioxidant defense system is altered, but the lipid peroxidation products in the tumor tissue is unchanged [30]. In contrast to our results
diminished MDA levels in patients with breast cancer and colorectal cancer have been reported [31, 32].

As it is clear from the results in table (2B and 3B) the concentration of MDA increased significantly in both malignant tissues of cervix and uterus. But the increase is much higher in the uterus cancer tissue (1.65 in comparison to that of benign tissue) than that in the cervix cancer tissue (0.899 in comparison to that of benign tissue). This difference may be due to that the cervical basal layer contains estrogen receptors (estrogen thought to play a protective role as antioxidant) [33], while among the components of endometrial mucosa is gland and stroma. The latter includes in its structure the stromal granulocyte and inconstant stromal foamy cells (lipid-containing cells of disputed histogenesis) [34]. The histochemical differences between uterus and cervix cancer tissues may be the cause for the significant increase in tissue homogenates MDA levels in uterus cancer compared with that of cervix cancer. So it was not surprising to see higher levels of MDA in these tissues since MDA is one of the by-products of lipid peroxidation.

The exact mechanism of hypercupremia in malignancy is unclear [35]. Some authors have raised the theory that this increase may be a defense mechanism against tumors since copper can retard the growth of tumors in vitro and inhibit their development in vivo [36]. Others [37,38] hypothesized that ceruloplasmin (Cp) are resialylated at the tumor cell surface and this lead to a decrease in its catabolism, a process that could account for the increase in serum copper levels in patients with neopalsia. Also, it was suggested that copper plays some role in angiogenesis, which is required for development of new tissue, as well as tumor growth is possible through the mediation of copper — dependant amine oxidases activities [14]. An increase in ceruloplasmin concentration and ceruloplasmin oxidase activity was previously reported in our laboratory in several patients with cervix and uterine tumors [39] , and breast cancer [40]. Other aspects of copper metabolism in cancer are also altered, including enhanced intestinal absorption and diminished turnover of whole — body copper, at least in rats [41]. Decreased retention of copper in intestinal mucosa and liver was also observed. Not just ceruloplasmin but also other copper — binding components (such as transcuprein) appeared to be increased in cancer [42].

As a result of the presence of free copper ions, promotion of free radicals generation occurred. This lead to oxidative damage of many biological targets, from single macromolecules such as lipoproteins, DNA, or thiol containing enzymes, to membrane, organelles, and intact cells including hepatocytes [43].

Many researchers have investigated the role of zinc in cancer growth. Direct evidence of a relation between dietary zinc levels and tumor growth were found in animals receiving Zn deficient diet, tumor weight was found to be lower and survival better than in the supplemented group [44]. In addition, it was found that high dietary levels of Zn appeared to reduce ceruloplasmin levels [7]. In biological systems, zinc is
bound to proteins with varying degrees of affinity and free zinc ion concentration is very low \[^{45}\]. Zinc may exert its antioxidant effect by decreasing the susceptibility of essential sulfhydryl groups of proteins to oxidation and by competing with pro-oxidant metals such as Fe and Cu for biological binding site \[^{46}\]. Zinc prevents production of the hydroxyl (OH\(^{\bullet}\)) and superoxide (O\(^{\bullet-}\)) free radicals through Fenton reaction. Due to its key position in the antioxidative network, superoxide dismutase SOD is of marked pathophysiological importance \[^{47}\], and it was studied primarily as a defense mechanism against the consequences of free radicals production \[^{48}\]. It was suggested that increased oxidative stress in patients with breast cancer may result from changes in the levels of certain trace elements (Se, Fe, Cu, and Mn) \[^{49}\]. As copper, and zinc ions are known as activators of Cu Zn-SOD, copper, and zinc are excellent candidates for coordinating the enzyme expression \[^{50}\]. Ec-SOD activity (the main enzymatic scavenger of (O\(^{\bullet-}\)) in extracellular matrix of tissue), and Cu Zn-SOD activity were observed to increase in plasma and tissue homogenates of breast cancer patients \[^{28,51}\]. A low serum zinc level could be a result of a deficiency caused by the concentration of zinc near the tumor site, other workers considered an intracellular protein: metallothionein, as a key component of the zinc accumulation mechanism in the liver cells, which is inducible by a variety of stress (e.g. malignancy), simultaneously depressing the serum zinc level\[^{35}\].

As far as iron is concerned, most of the iron (Fe\(^{2+}\)) is oxidized to (Fe\(^{3+}\)) by the ferroxidase activity of Cp and /or spontaneous oxidization, and then bind to transferrin to be acquired by the cells. However under pathological circumstances, the loss of Cp ferroxidase activity make it impossible for most ferrous ion to be oxidized to ferric ion accordingly, the amount of ferric ion and transferrin – bound Fe\(^{3+}\) will decrease, while non- transferrin bound iron such as citrate –Fe\(^{2+}\), ascorbate –Fe\(^{2+}\) and free ferrous iron will increase. This will induce oxidative stress and free radical formation, and trigger a cascade of pathological events leading to cell death. It is also possible that the rate of spontaneous oxidization of ferrous ion to ferric ion will increase so that more (Fe\(^{3+}\)) can be formed, as well as, generate a large amount of (ROS) \[^{52}\].

**Conclusion**

The results reported here agree with that lipid peroxidation reactions may be involved in carcinogenic processes by increase formation of ROS which cause damage to cellular macromolecules. The increased formation of ROS may be due to increased free Cu and Fe concentrations. The changes in the antioxidant enzymes activities may selectively improve the resistance of neoplastic cells to toxicity associated with tumor promotion.
References


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