Therapeutic Efficacy of Ginger, Cisplatin and Radiation on Chemically-Induced Cancer in Male Albino Rats.

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ABSTRACT

This study aimed to investigate the in vivo effect of dietary supplementation with ginger to evaluate its therapeutic effect against lung and kidney cancer and in combination with cisplatin as chemotherapy and radiotherapy in male albino rats.

54 male albino rats were divided into nine groups of 6 animals each, all animals were allowed to food and water ad libitum. Group I was treated with 0.5 ml saline, orally for 12 consecutive weeks serve as control group. Group II injected with N-nitrosodimethylamine (NDMA) and carbon tetrachloride (CCl₄); all groups were injected with NDMA + CCl₄ for 6 weeks. Group III were given ginger for 6 consecutive weeks (200 mg/kg, b.wt./day). Group IV animals received cisplatin, group V irradiated with 2 Gy, group VI treated with ginger then irradiated, group VII treated with ginger then injected with cisplatin, group VIII injected with cisplatin then irradiated and group IX treated with ginger and cisplatin then irradiated. Antioxidant status in both kidney and lung tissues were estimated by determining the activity of antioxidant enzyme superoxide dismutase (SOD); as well as the level of reduced glutathione (GSH), Malondialdehyde (MDA) and Nitric oxide (NO). In parallel to histopathological investigations of lung and kidney tissues.

In addition, Tumor Necrosis Factor Alpha (TNF-α) level, advanced oxidative protein product (AOPP), urea, creatinine and uric acid. Remarkable disturbances were observed in the levels of all tested parameters in NDMA + CCl₄ group. On the other hand, rats injected with the cancer agents then treated with cisplatin + radiation showed moderate improvements in the studied parameters while, treatment with ginger + cisplatin + radiation ameliorated the levels of the disturbed bio-
chemical parameters. The group treated with ginger showed a remarkable improvement in comparison to the NDMA + CCl₄ treated group.

The ginger and ginger + cisplatin + radiation groups revealing an even more remarkable effect showing histopathological lung and kidney profiles close to those of the control group.

The results obtained in the current study demonstrate that the oral administration of ginger may thus be of therapeutic potential in the treatment of lung and kidney cancer.

INTRODUCTION

Cancer begins when cells in a part of the body start to grow out of control. There are many kinds of cancer, but they all start because of out-of-control growth of abnormal cells. Cancer is the second leading cause of death in the United States. About one-half of all men and one-third of all women in the US will develop cancer during their lifetimes. Today, millions of people are living with cancer or have had cancer (Hajdu, 2011).

Lung cancer is the most important cause of cancer-related death all over the world. Unfortunately, 75% of patients with lung cancer have symptoms caused by advanced disease that is incurable. Furthermore, despite progress in therapy, the five-year survival rate for all stages combined is nearly 16%. It was estimated that in 2007, the incidence and mortality of lung cancer in the United States would be more than breast, colon and prostate cancers combined during the same period (Gomez and Silvestri, 2008).

The reaction of dimethylamine with strong oxidants such as chlorine and possibly chlorine dioxide in the presence of ammonia ions leads to the formation of NDMA. N-nitrosodimethylamine (NDMA), a well studied member of the nitrosamine family, is a powerful animal carcinogen, capable of inducing benign and malignant tumors in a variety of tissues, including the liver, the kidney, the lung and the nasal cavity (Magee, 1989; Andrzejewski et al., 2005 & Sharma and Singh 2012).

CCl₄ is well-established hepatotxin which induces free radical damage in tissues. CCl₄-induced oxidation stress-related damage is dependent on its bioactivation by cytochrome P450 to trichloromethyl free radical, trichloromethyl peroxy radical and chloride free radical. These metabolites of CCl₄ can initiate free radical mediated lipid peroxidation process (Kadiiska et al., 2000) leading to oxidative damage in tissues such as liver, kidneys, heart, lung, brain, and blood (Recknagel et al., 1989 and Reinkke et al., 1992). CCl₄ treatment significantly elevated hepatic MDA and depleted GSH levels (Hwang et al., 2009 and Saad, 2013).

There are several different types of treatment, which may be used alone or in combination, either simultaneously or sequentially: surgery, radiotherapy and drugs (Poulsen et al., 2005). During the past decades, cancer chemotherapeutic agents have begun to offer major hope for chemical control of cancer. Cisplatin (cis-dichlorodiammine-platinum (II), CDDP) is an inorganic platinum compound with a broad spectrum anti-neoplastic activity against various types of tumors (Al-Majed et al., 2006). However, its therapeutic effect is dose limiting due to the presence of side effects such as gastrointestinal disturbance and specially nephrotoxicity (Yao et al., 2007).

Natural products and their active principles as sources for new drug discovery and treatment of diseases have attracted attention in recent years. Medicinal use of spices/herbs has been gradually increasing in developed countries. Zingiber officinale commonly known as ginger is one of the most commonly used spices in India and around the world. It is an indispensable component of curry, belongs to Zingiberaceae family. Rhizome of ginger has been recommended for use as carminative, diaphoretic, antispasmodic, expectorant, peripheral circulatory stimulant, astringent, appetite stimulant, anti-inflammatory agent, diuretic and digestive aid (Bliddal et al., 2000; Afzal et al., 2001 and Ali et al., 2008).

Many studies were carried out on the pungent
constituents of fresh and dried ginger rhizomes. Among the pharmacological effects demonstrated are anti-platelets, antioxidant, anti-tumor, anti-rhino viral, anti-hepatotoxicity, anti-arthritic effect and anti-inflammatory. Ginger may offer apotential adjuvant to antidiabetic medications (Kamtchoving et al., 2002; Lantz et al., 2007 and Abdul Sani et al., 2014).

Radiation therapy or (radiotherapy) is the medical use of ionizing radiation as part of cancer treatment to control malignant cells. Radiotherapy has several applications in non-malignant conditions, which is limited partly by worries about the risk of radiation-induced cancers. Radiotherapy is used for the treatment of cancer and may be used as the primary therapy. It is also common to combine radiotherapy with surgery, chemotherapy, hormonal therapy or some mixture of the three. Most common cancer types can be treated with radiotherapy in some way. The precise treatment intent will depend on the tumor type, location and stage as well as the general health of the patient (Bucci et al., 2005).

MATERIALS AND METHODS

Ginger (Zingiber officinale) was obtained from Arab company for pharmaceuticals & medicina plants Mepaco-Medifood Enshas-Sharkeya Egypt. 400 mg ginger were dissolved in 50 ml dist. water. Cisplatin was obtained from Serum Institute of India LTD. 50mg/50ml. N-nitrosodimethylamine and carbon tetrachloride was obtained from Sigma Chemical Co.

Experimental design

Fifty four adult male rats (Albino Strain) were obtained from the Animal House of the National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority, Egypt.

The animals were housed in suitable cages, under standard temperature, Pressure, humidity, ventilation and illumination conditions. Rats were fed with standard granulated chow. The animal’s weights were about 120–130 g. The rats were randomly allocated in nine groups each containing six rats.

Group I: treated with 0.5 ml saline, orly serve as control group.

Group II: treated with a single dose of N-nitrosodimethylamine (NDMA) (200 mg/kg, b.wt.), (i.p.) followed by weekly (i.p.) injections of carbon tetrachloride (CCl₄ 1 ml/kg) for 6 weeks.

Group III: treated with Ginger (Zingiber officinale) (200 mg/kg, b.wt./day), orally for 5 days per week for 6 consecutive weeks. Starting at 45 day after injection of NDMA.

Group IV: injected with a single dose of cisplatin (7.5 mg/kg, b.wt.), (i.p.) after 45 day of NDMA injection.

Group V: irradiated with 2 Gy as a whole body gamma irradiation after 45 day of NDMA injection.

Group VI: treated with Ginger (Zingiber officinale) (200 mg/kg, b.wt./day), orally for 5 days per week for 6 consecutive weeks starting at 45 day after injection of NDMA followed by irradiation with 2 Gy after one day from the last treatment.

Group VII: treated with Ginger (Zingiber officinale) (200 mg/kg, b.wt./day), orally for 5 days per week for 6 consecutive weeks starting at 45 day after injection of NDMA then injected with a single dose of cisplatin (7.5 mg/kg, b.wt.), (i.p.) after one day from the last treatment.

Group VIII: injected with a single dose of cisplatin (7.5 mg/kg, b.wt.), (i.p.) after 45 day of NDMA injection followed by irradiation with 2 Gy after one day from cisplatin injection.

Group IX: treated with Ginger (Zingiber officinale) (200 mg/kg, b.wt./day), orally for 5 days per week for 6 consecutive weeks starting at 45 day after injection of NDMA followed by a single (i.p.) injection of cisplatin (7.5 mg/kg, b.wt.) after one day from the last treatment followed by irradiation with 2 Gy after one day from cisplatin treatment.

Samples collection

After 90 day animals were anaesthetized with ether then sacrificed, blood samples obtained by heart puncture for the determination of serum Tu-
mor Necrosis Factor Alpha (TNF-α) level, advanced oxidative protein product (AOPP), urea, creatinine and uric acid. Lung and kidney tissues were quickly excised, washed with saline, blotted with a piece of filter paper, weighed and homogenized in saline. The homogenates were centrifuged at 15,000 rpm for 10 min (Hitachi model EBA 12R, Germany). Rat lung and kidney homogenates were prepared and used for determination of malondialdehyde (MDA), reduced glutathione (GSH), nitric oxide (NO) levels and superoxide dimutase activity (SOD).

**Biochemical assays**

Serum Tumor Necrosis Factor Alpha (TNF-α) level was determined according to Seriolo et al. (2006). Serum urea and serum uric acid were estimated by the method of Young et al. (1975). creatinine was determined according to Spierto et al. (1979). Advanced oxidative protein product (AOPP) of serum was estimated according to Witko-Sarsat et al. (1996) malondialdehyde in lung and kidney tissue homogenate was determined according to Yoshika et al. (1979). Glutathione contents in lung and kidney tissue homogenate was determined according to Beutler et al. (1963). Superoxide Dismutase enzyme activity was estimated by Kakkar et al. (1984) and total nitric oxide in lung and kidney tissue was determined according to Miranda et al. (2001).

**Histopathological studies**

Lung and kidney tissues from male rats were removed carefully and fixed in Bouin’s fluid for histological studies. The specimens were then dehydrated in ascending grades of alcohol and finally cleared in xylol. Embedding was performed in three changes of paraffin wax section 6 μ in thickness and stained with Ehrlich haematoxyline and eosin method (Drury and Wallington, 1980).

**Statistical analysis**

The data are presented as mean ± SEM. Analysis was performed using one way analysis of variance (ANOVA) followed by Duncan’s T test. Differences were considered significant at probability levels P> 0.05 using Statistical Package for Social Science (SPSS) version 15.0 for windows.

**RESULTS**

Table 1 show a significant decrease in serum TNF-α, AOPP, urea, creatinine and uric acid in rats treated with ginger (200 mg/kg, b.wt./day) compared to the cancer group. A significant decrease was observed in chemotherapy and radiotherapy groups also.

<table>
<thead>
<tr>
<th>Animal Groups</th>
<th>TNF-α (U/L)</th>
<th>AOPP (n mol/litre)</th>
<th>Urea (mg/dl)</th>
<th>Creatinine (mg/dl)</th>
<th>Uric acid (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C)</td>
<td>13.71±200.60</td>
<td>16.48±227.77</td>
<td>1.14±20.79</td>
<td>0.27±0.98</td>
<td>0.83±1.84</td>
</tr>
<tr>
<td>(C)*</td>
<td>10.10±701.73</td>
<td>478.20±14.65</td>
<td>47.21±4.71</td>
<td>5.02±0.23</td>
<td>5.51±0.15</td>
</tr>
<tr>
<td>(G)</td>
<td>14.55±488.33</td>
<td>380.98±11.96</td>
<td>35.71±2.56</td>
<td>3.88±0.24</td>
<td>4.14±0.31</td>
</tr>
<tr>
<td>(Cis)</td>
<td>12.39±531.66</td>
<td>423.80±14.29</td>
<td>39.18±1.70</td>
<td>4.29±0.13</td>
<td>4.73±0.25</td>
</tr>
<tr>
<td>(R)</td>
<td>17.03±540.00</td>
<td>433.00±19.00</td>
<td>40.21±0.61</td>
<td>4.69±0.29</td>
<td>4.50±0.15</td>
</tr>
<tr>
<td>(G + R)</td>
<td>15.70±478.33</td>
<td>390.60±14.93</td>
<td>34.37±0.62</td>
<td>3.38±0.25</td>
<td>4.84±0.24</td>
</tr>
<tr>
<td>(G + R)</td>
<td>15.70±478.33</td>
<td>390.60±14.93</td>
<td>34.37±0.62</td>
<td>3.38±0.25</td>
<td>4.84±0.24</td>
</tr>
<tr>
<td>(Cis + R)</td>
<td>13.98±495.00</td>
<td>403.36±18.49</td>
<td>35.24±1.50</td>
<td>3.78±0.06</td>
<td>3.67±0.26</td>
</tr>
<tr>
<td>(G + Cis)</td>
<td>15.45±456.00</td>
<td>370.33±16.48</td>
<td>33.79±0.79</td>
<td>2.88±0.37</td>
<td>3.53±0.16</td>
</tr>
<tr>
<td>(G + Cis + R)</td>
<td>15.16±431.66</td>
<td>345.76±15.16</td>
<td>32.54±0.59</td>
<td>2.58±0.39</td>
<td>3.15±0.15</td>
</tr>
</tbody>
</table>

Data are represented as mean ± standard Error (SEM)
Results in Table 2. Show a significant decrease in lung MDA and NO levels in all treated groups when compared with those of the cancer group. In the same concern, the group injected with NDMA and CCl\textsubscript{4} then treated with ginger, cisplatin and radiation recorded highly recovered value of MDA and NO levels when compared to all cancer groups. On the other hand there was a significant increase in lung GSH and SOD activity in the groups treated with ginger or cisplatin or radiation when compared with cancer group. In the same concern, rats injected with NDMA and CCl\textsubscript{4} then treated with ginger, cisplatin and radiation recorded highly recovered value of GSH level and SOD activity when compared to all cancer groups.

**Table (2)** Changes in lung MDA, NO, GSH and SOD in rats treated with Ginger, Cisplatin and Radiation.

<table>
<thead>
<tr>
<th>Animal Groups</th>
<th>Lung MDA (n mol /gm tissue)</th>
<th>Lung GSH (n mol/gm tissue)</th>
<th>Lung SOD (u g/gm tissue)</th>
<th>Lung NO (u mol/gm tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C)</td>
<td>26.88±1.27</td>
<td>31.76±0.88</td>
<td>235.73±10.36</td>
<td>36.64±3.18</td>
</tr>
<tr>
<td>(C)*</td>
<td>97.32±1.09</td>
<td>10.63±0.44</td>
<td>129.12±7.43</td>
<td>95.90±0.58</td>
</tr>
<tr>
<td>(G)</td>
<td>82.60±7.09</td>
<td>17.69±0.66</td>
<td>167.51±4.18</td>
<td>79.32±1.43</td>
</tr>
<tr>
<td>(Cis)</td>
<td>86.60±0.97</td>
<td>15.24±0.67</td>
<td>152.68±5.74</td>
<td>82.65±1.15</td>
</tr>
<tr>
<td>(R)</td>
<td>89.10±2.61</td>
<td>13.13±0.62</td>
<td>148.48±2.05</td>
<td>85.23±5.77</td>
</tr>
<tr>
<td>(G + R)</td>
<td>76.88±2.11</td>
<td>18.05±0.89</td>
<td>169.44±4.34</td>
<td>72.86±1.05</td>
</tr>
<tr>
<td>(Cis + R)</td>
<td>82.49±0.91</td>
<td>16.40±1.00</td>
<td>159.44±6.15</td>
<td>75.40±4.79</td>
</tr>
<tr>
<td>(G + Cis)</td>
<td>73.43±1.25</td>
<td>21.55±0.60</td>
<td>175.06±10.59</td>
<td>69.49±1.31</td>
</tr>
<tr>
<td>(G + Cis + R)</td>
<td>67.85±2.17</td>
<td>23.12±0.89</td>
<td>182.26±5.02</td>
<td>60.53±1.95</td>
</tr>
</tbody>
</table>

Legend as table 1.

Results in Table 3. Show a significant decrease in kidney MDA and NO levels in treated groups compared to the cancer group. In the same concern, the group that injected with NDMA and CCl\textsubscript{4} then treated with ginger, cisplatin and radiation recorded highly recovered value of MDA and NO levels when compared to all cancer groups. On the other hand there was a significant increase in kidney GSH and SOD activity in groups treated with ginger or cisplatin or radiation, compared to cancer group. In the same concern, the group injected with NDMA and CCl\textsubscript{4} then treated with ginger, cisplatin and radiation recorded highly recovered value of GSH level and SOD activity, compared to all cancer groups.

**Table (3)** Changes in kidney MDA, NO, GSH and SOD in rats treated with Ginger, Cisplatin and Radiation.

<table>
<thead>
<tr>
<th>Animal groups</th>
<th>Kidney MDA (n mol /gm tissue)</th>
<th>Kidney GSH (n mol/gm tissue)</th>
<th>Kidney SOD (u g/gm tissue)</th>
<th>Kidney NO (u mol/gm tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(C)</td>
<td>117.4±3.7</td>
<td>28.42±1.46</td>
<td>375.98±4.47</td>
<td>41.47±2.89</td>
</tr>
<tr>
<td>(C)*</td>
<td>381.62±15.29</td>
<td>9.62±1.16</td>
<td>211.16±4.23</td>
<td>107.37±1.54</td>
</tr>
<tr>
<td>(G)</td>
<td>311.87±16.04</td>
<td>17.43±0.40</td>
<td>242.66±6.87</td>
<td>86.55±1.50</td>
</tr>
<tr>
<td>(Cis)</td>
<td>316.80±1.67</td>
<td>16.90±1.11</td>
<td>232.66±6.41</td>
<td>90.55±1.40</td>
</tr>
<tr>
<td>(R)</td>
<td>323.20±2.35</td>
<td>16.94±0.89</td>
<td>228.33±0.90</td>
<td>95.69±0.73</td>
</tr>
<tr>
<td>(G + R)</td>
<td>268.15±6.78</td>
<td>18.27±1.93</td>
<td>259.33±3.15</td>
<td>79.18±2.13</td>
</tr>
<tr>
<td>(Cis + R)</td>
<td>277.25±4.78</td>
<td>16.80±0.64</td>
<td>251.00±9.54</td>
<td>82.33±0.85</td>
</tr>
<tr>
<td>(G + Cis)</td>
<td>263.97±18.35</td>
<td>17.70±0.65</td>
<td>265.33±6.92</td>
<td>75.01±1.91</td>
</tr>
<tr>
<td>(G + Cis + R)</td>
<td>258.41±19.65</td>
<td>19.37±0.40</td>
<td>275.33±3.62</td>
<td>71.33±1.21</td>
</tr>
</tbody>
</table>

Legend as table 1.
HISTOPATHOLOGICAL RESULTS

Our results showed that NDMA and CCl₄ rat’s lung showed extensive mononuclear cellular infiltration with severe blood congestion and thick interalveolar septa (fig.2). On the other hand administration of ginger showed preserved normal architecture but with few thickened interalveolar septa (fig.3). In the same concern, NDMA and CCl₄ rat’s kidney revealed dilated congested blood vessels of the lobulated glomeruli (G) with mass of pyknotic nuclei (fig.11). While in rats kidney administrated with ginger showed glomerulus with its capillary tufts surrounded by normal capsular space (fig.12). Note the proximal convoluted tubules and the distal convoluted tubules most showing nearly normal appearance of the epithelial lining of the convoluted renal tubules.

Fig.(1): photomicrograph of a section in the rats lung of control group showing the thin interalveolar septa (arrow head), alveolar sacs (S) and bronchiole (B) notice also the alveolar macrophages (two arrows). H & E (X: 100).

Fig.(2): Rats lung of cancer group showing extensive mononuclear cellular infiltration (arrow) severe blood congestion, thick interalveolar septa (arrow head). H & E (X: 100).

Fig.(3): photomicrograph of a section in the rats lung of cancer +ginger group showing normal intrapulmonary bronchus (B) and bronchioles (br) with thin of mast interalveolar septa (arrow). H & E (X: 100).

Fig.(4): photomicrograph of a section in the rats lung of cancer +cisplatin group showing preserved normal architecture but with few thickened interalveolar septa (arrow) and a congested blood vessel. H & E (X: 100).

Fig.(5): photomicrograph of a section in the rats lung of radiotherapy + cancer group showing cytoplasm of epithelium lining terminal bronchiole (B), alveolar duct (D) and alveolar sacs (S), thin walled alveoli (A). H & E (X: 100).

Fig.(6): photomicrograph of a section in the rats lung of cancer +ginger + radiotherapy group showing pulmonary blood vessels (BV) which are surrounded with thick fibrous tissue (arrow), also still showing marked thickening of the interalveolar septa while the neighboring ones are irregularly dilated, also collagen fibers around the bronchiole (arrow). H & E (X: 100).
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Fig.(7): photomicrograph of a section in the rats lung of cancer + cisplatin + radiotherapy group showing preserved normal architecture but with few thickened inter alveolar septa (arrow) and normal bronchioles (br). H & E (X: 100).

Fig.(8): photomicrograph of a section in the rats lung of cancer + ginger + cisplatin group showing thin walled alveoli (A), alveolar sacs (S), but dilated bronchiole (B). H & E (X: 100).

Fig.(9): photomicrograph of a section in the rats lung of (cancer+ ginger + cisplatin + radiotherapy) group showing mild dilated alveolar spaces, showing thin of alveolar septa showing minimal amount of collagen fibers in the per bronchiolar area (arrow) H & E (X: 100).

Fig.(10): photomicrograph of a section of a kidney of the control group showing renal corpuscle demonstrating a normal glomerulus with its capillary tufts (G) surrounded by normal capsular space. Note the proximal convoluted tubules (P) and the distal convoluted tubules (D). H & E (X: 40).

Fig.(11): photomicrograph of a section of a kidney of the cancer group showing extensive degeneration and sever of some proximal (P) and distal (D) convoluted tubules loss of normal architecture of cells. Notice congested blood vessels of the lobulated glomeruli. Hemorrhage interstitial renal tubules was also seen (H). H & E (X: 40).

Fig.(12): photomicrograph of a section of a kidney of the cancer +ginger group showing nearly normal appearance of the epithelial lining of the convoluted renal tubules. But size and appearance of Bowman's capsule and glomerulus still not normal appearance. H & E (X: 40).
Fig. (13): Photomicrograph of a section of a kidney of the cancer + cisplatin group showing nearly normal appearance of the epithelial lining of the convoluted renal tubules. The relatively normal size and appearance of Bowman’s capsule and glomerulus were also seen. H & E (X: 40).

Fig. (16): Photomicrograph of a section of a kidney of the cancer + cisplatin + radiotherapy group showing nearly normal appearance of the epithelial lining of the convoluted renal tubules. H & E (X: 40).

Fig. (14): Photomicrograph of a section of a kidney of the cancer + radiotherapy group showing nearly normal appearance of proximal convoluted tubules (P) and distal convoluted tubules. Notice the macula densa (arrow) appeared. H & E (X: 40).

Fig. (17): Photomicrograph of a section of a kidney of the cancer + ginger + cisplatin group showing mild intercellular vacuolation in the tubules with loss of architecture of renal cortex (P & D). H & E (X: 40).

Fig. (15): Photomicrograph of a section of a kidney of the cancer + ginger + radiotherapy group showing renal corpuscle atrophy with most of pyknotic nuclei and wide in renal space (*) and vacuolation in both proximal (P) and distal (D) tubules. H & E (X: 40).

Fig. (18): Photomicrograph of a section of a kidney of the (cancer + ginger + cisplatin + radiotherapy) group showing showing nearly normal appearance of the epithelial lining of the convoluted renal tubules. But size and appearance of Bowman’s capsule and glomerulus still not normal appearance. H & E (X: 40).
DISCUSSION

Reactive oxygen species (ROS) are continuously produced in vivo as a result of NDMA and CCl₄ treatment causing oxidative stress that wreak havoc in biological system by damaging tissues, altering biochemical compounds, causing chromosomal instability, corroding cell membranes and mutation which play an important role in the development of cancer (Simeonova et al., 2014). In the current study it was noticed that NDMA and CCl₄ produced a significant increase in serum TNFα, AOPP, urea, creatinine and uric acid levels. A significant elevation of NO and MDA associated to a significant decrease of SOD and GSH was recorded in lung and kidney tissues.

These results are in agreement with the results of Adewole et al. (2007) reported that administration of carbon tetrachloride (CCl₄) (1 ml/kg body weight, subcutaneously s.c.) induces oxidative stress and nephrotoxicity in male albino rats (240-260g) CCl₄ caused elevated level of serum urea, creatinine and (TBARS), NO and marked deplation of SOD and GSH kidney tissues. In the same concern, Xu et al., 2010 and Saad, 2013 Observed that intraperitoneal injection with a single dose of CCl₄ (0.5 mL/kg) on male Sprague–Dawley rats (200-210g) caused a significant elevation in serum levels of MDA, urea and creatinine and marked depletion of SOD and GSH kidney.

Ganie et al. (2011) revealed that, the injection of a single dose of CCl₄ (1 ml/kg b.wt i.p) caused a significant increase in lung and kidney MDA level with a significant decrease in lung and kidney GSH and SOD in male albino rats (200-250g). Bashandy and Awasel (2011) reported that the administration of carbon tetrachloride (CCl₄) (0.2 ml/kg b. wt, i.p twice a week for 3 months) to male Wistar rats (180-200) g caused a significant elevation in kidney MDA level with a significant decrease in kidney GSH.

Treatment with ginger showed good improvement in serum TNFα, AOPP, urea, creatinine and uric acid levels. Besides tissue parameters NO, MDA, GSH levels and SOD activity.

These results are in agreement with Habib et al. (2008) that ginger extract was able to block the elevated expression of NFκB in liver cancer-induced rats. Similarly, elevated expression of TNF-α in liver cancer rats was also blocked when treated with ginger extract (100mg/kg body weight). It is apparent that ginger may act as an anti-cancer and anti-inflammatory agent by blocking the activation of NFκB via the suppression of pro-inflammatory cytokine, TNF-α (Hudson et al., 2006 and Damiao et al., 2013).

The rhizome of ginger contains pungent vanillyl ketones, including [6]-gingerol and [6]-paradol, and these have been reported to possess a strong anti-inflammatory activity and suppress TNFα production in female mice (Surh, 1999).

As a measure of renal function status, serum urea and creatinine are often regarded as reliable markers. Thus, elevations in the serum concentrations of these markers are indicative of renal injury. In vitro and in vivo studies using Z. officinale reported the significant antioxidant activities. The exhibited renal protective activity of Z. officinale might partially be due to its antioxidant property. In the fresh ginger rhizome, the gingerols (polyphenols) were identified as the major active component (Masuda et al., 2004 and Abdul Sani et al., 2014).

Reports regarding the enzymic antioxidants status in carcinogenesis study have been highly variable. While some reports have noted increased enzymic antioxidant activities in rats and mice induced with carcinogens (Manju et al., 2005), others have reported decreased or no changes of enzymic antioxidant status (Karimov et al., 2003 & Chandra Mohan and Nagini, 2003). These results clearly exhibited the anti promoting activity of ginger extract as evidenced by the reduced number of tumors in treated rats. Since tumour promotion is closely related to oxidative stress, a compound that exhibits antioxidative properties is expected to act as antitumour. Antioxidative capacity of ginger is clearly seen when increased SOD activity as a result of superoxide free radical generation in liver cancer induced rats was abrogated by ginger oleoresin supplementation. Gin-
ger was able to attenuate the harmful effects of ethionine by scavenging the increased superoxide anions generated during hepatocarcinogenesis induced by the diet and thus sparing the endogenous SOD activity. The enhanced level of SOD activity observed during hepatocarcinogenesis may also be due to an active rate of cell proliferation that confers a selective growth advantage on cancer cells.

El-Sharaky et al. (2009) revealed also that preconditioning of rats by pre-treatment with ethanolic extract of ginger significantly reduced the extent of lipid peroxidation and improves liver antioxidant capacity. Similarly, Siddaraju and Dharmesh (2007) reported that ginger-free phenolic and ginger hydrolysed phenolic fractions exhibited free radical scavenging, inhibition of lipid peroxidation, DNA protection and reducing power abilities indicating strong antioxidant properties

Ansari et al. (2006) showed that the pretreatment for 20 days with ethanolic Z. officinale extract enhances the antioxidant defense (catalase, superoxide dismutase, and tissue glutathione) in isoproterenol-induced oxidative myocardial necrosis in rats and exhibited cardio protection property. Also, Ajith et al. (2007) reported that ginger ameliorated cisplatin-induced nephrotoxicity and this protection is mediated either by preventing the cisplatin-induced decline of renal antioxidant defense system or by direct free radical scavenging activity of ginger.

Furthermore, Amin and Hamza (2006) demonstrated that Z. officinale increased the activities of testicular antioxidant enzymes, superoxide dismutase, glutathione, and catalase and reduced level of malondialdehyde. Gingerol was found to exert inhibitory effect on xanthine oxidase responsible for generation of reactive oxygen species, such as superoxide anion.

Also, pre-treatment with ginger results in decreased production of NO. The major pungent constituent of ginger is [6]-gingerol which has been reported to exhibit antioxidative activity against linoleic acid autoxidation and peroxidation of phospholipids liposome and to scavenge trichloromethyl-peroxyl and 1, 1-diphenyl-2-picrylhydrazyl (DPPH) radicals (Sekiwa et al., 2000). In addition to these antioxidative effects, other studies (Ippoushi et al., 2003 and Ippoushi et al., 2005) revealed that [6]-gingerol inhibits nitric oxide synthesis in activated macrophages and prevents oxidation and nitrification reactions induced by peroxynitrite, a strong reactive nitrogen species (Radi et al., 2001). Besides [6]-gingerol, ginger contains a homologous series of phenolic ketones expected to have an antioxidative effect, known as [4]-, [8]-, [10]-, and [12]-gingerols.

The presence of such active components might be responsible for the exhibited renal protective activity. Recent experimental observations reported that Z. officinale is an effective anticancer agent Shukla and Singh (2007). Further, ginger can relieve the chemotherapy associated nausea and vomiting in patients (Ernst and Pittler 2000).

In the present study, administration of ginger showed preserved normal architecture but with few thickened inter alveolar septa in lung and in kidney showing glomerulus with its capillary tufts surrounded by normal capsular space. Note the proximal convoluted tubules and the distal convoluted tubules most showing nearly normal appearance of the epithelial lining of the convulated renal tubules.

Our results showed that NDMA and CCl₄ rat’s kidney revealed dilated congested blood vessels of the lobulated glomeruli (G) with mast of pyknotic nuclei. While rat’s lung of cancer group showed extensive mononuclear cellular infiltration with severe blood congestion and thick interalveolar septa.

The results obtained in this work are in agreement with the results of Adelman et al. (1981) shown that CCl₄ renal intoxication was associated with severe glomerular and tubulo-interstitial necrosis which was characterized by hydropic degeneration of the glomerular and tubular cells with complete obliteration of the tubular lumen. Examination of lung by light microscopy revealed characteristic CCl₄-induced pulmonary lesions. The most prominent feature in this group is the vascular changes. Such changes were represented by the congestion of
the blood capillaries that were engorged with erythrocytes. Most of the alveolar septa were thickened revealing the appearance of large number of type II alveolar cells, together with several fibroblasts, neutrophils, lymphocytes and macrophages (Zakaria et al., 2004).

In addition, Adewole et al. (2007) and Olagunju et al. (2009) reported that the kidneys of CCl₄-treated rats showed marked deleterious histological changes. The kidney sections showed significant glomerular and tubular degenerations varying from, glomerular basement thickening, interstitial inflammation, tubular cell swelling, pyknotic nuclei, medullary vascular congestion and moderate to severe necrosis.

Microscopically, kidney showed Glomeruli and tubules with apparently normal histological features. However in the CCl₄ (24 h) group extensive cortical damage was observed. Focal glomerular necrosis was detected in this group and the affected glomeruli showed hypocellularity and shrinkage. Most of the cortical tubules showed morphologic changes, some of them being dilated and lined with flattened epithelial cells (Ali et al., 2010).

Consequently, as observed, ginger has a therapeutic effect against lung and kidney cancer induced by NDMA and CCl₄ administration of ginger to rats was effective in reducing oxidative damages in lung and renal tissues and had a positive and potential impact on antioxidant status. Accordingly, the present work deduced that, ginger application alone would play an important role in increasing the antioxidant effect and reducing the oxidative damage formed in lung and kidney tissues.

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The Therapeutic Efficacy of Ginger, Cisplatin and Radiation on Chemically-Induced Cancer in Male Albino Rats

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The aim of this study was to evaluate the role of radiation against lung and kidney cancer and chemical treatment.

Twenty male albino rats were divided into nine groups: the control group received saline 

1. Niacinamide (200 mg/kg) was administered intraperitoneally once a week for six weeks. The third group received 6 ml/kg for three days and then received 500 mg/kg intraperitoneally for two weeks. The fourth group was treated once with cisplatin (200 mg/kg) after the last treatment. The fifth group was treated with ginger by irradiation for 45 consecutive days, starting after six days a week for five days. The sixth group was treated with Niacinamide and then irradiated with 7.5 ml/kg after the last treatment. The seventh group received 2 doses of Niacinamide and then irradiated with 7.5 ml/kg twice a week for 45 consecutive days starting after six days a week for five days. The eighth group received 500 mg/kg intraperitoneally after the last treatment. Then, 7.5 ml/kg was administered after the last treatment. The ninth group received garlic by irradiation for 45 consecutive days, starting after six days a week for five days.

The study was conducted to determine the levels of inflammatory markers in the blood serum of the rats and the changes in the histological picture of the rats.

The results of this study showed that the use of ginger by oral administration significantly improved the functions of the lung and kidney and the histological results compared to the second group. It is possible to use it as a treatment for lung and kidney cancer.

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