The potential protective role of grape seed proanthocyanidin extract against the mixture of carboplatin and thalidomide-induced hepatotoxicity and cardiotoxicity in male rats

Mokhtar I Yousef¹, Moustafa AFH Mahdy¹ and Heba M Abdou²*

¹Department of Environmental Studies, Institute of Graduate Studies and Research, Alexandria University, Egypt
²Zoology Department, Faculty of Science, Alexandria University, Egypt

Abstract

Thalidomide is used experimentally to treat various cancers, also carboplatin is a chemotherapy drug used against some forms of cancer. Grape Seed Proanthocyanidin Extract (GSPE) has an enormously beneficial role in overcoming the adverse effects of chemotherapeutic agents due to its excellent antioxidant properties. Animals were divided into four groups as follows: The first group was used as control, the second group were treated orally for 28 consecutive days with GSPE (200 mg/kg BW), the third group were treated intraperitoneally (i.p) with thalidomide (60 mg/kg BW) for 14 consecutive days then followed by carboplatin (196 mg/kg BW) for another 14 days and the animals of the fourth group were treated with the combination of GSPE (200 mg/kg BW) and thalidomide (60 mg/kg BW) for 14-day and then followed by GSPE (200 mg/kg BW) and carboplatin (196 mg/kg BW) for other 14-day. Inflammatory cytokines, P53, oxidative stress markers, biochemical parameters, and histological analysis measured. Carboplatin and thalidomide caused oxidative stress via the elevation in free radicals and nitric oxide and the reduction in the antioxidant enzymes and glutathione in liver and heart. Tumor suppressor gene P53, tumor necrosis factor-α, and interleukin-6 were significantly increased in liver and heart. Thalidomide and carboplatin caused biochemical and histological changes in the liver and heart. Grape seed proanthocyanidin extract reduced carboplatin and thalidomide-induced liver and heart injury throughout its potent antioxidant activity. In conclusion, carboplatin and thalidomide caused hepatotoxicity and cardiotoxicity and grape seed proanthocyanidin extract showed hepatic and cardiac protective effects due to its antioxidant and anti-inflammatory potentials.

Introduction

Thalidomide was primary used as a sedative, but it was withdrawn from the market after its teratogenic effects [1]. In spite of its teratogenicity, thalidomide possesses immune-modulatory, anti-inflammatory and anti-angiogenic properties that are potentially useful in several diseases [2]. Currently, thalidomide is used experimentally to treat various cancers, dermatological, neurological and inflammatory diseases. The immunomodulatory activities, together with the anti-angiogenic, anti-proliferative and pro-apoptotic properties, are believed to mediate anti-tumor responses as observed in multiple myeloma and some solid tumors. Thalidomide and its analogs modulate the immune system in different ways [3]. Lenalidomide has shown potential in treating the bone marrow disorders multiple myeloma and myelodysplastic syndrome and is presently in Phase II and III trials [4].

Carboplatin is used against some forms of cancer, mainly ovarian carcinoma, lung, as well as endometrial, esophageal, bladder, breast and cervical; central nervous system or germ cell tumors; osteogenic sarcoma and as preparation for a stem cell or bone marrow transplant [5]. The myelosuppressive effect is the main obstruction of carboplatin. This causes the blood cell and platelet output of bone marrow in the body to decline quite massively [6].

Cancer chemotherapy induces lipid peroxidation, generates numerous electrophilic aldehydes and free radicals which can attack many cellular targets. These products of oxidative stress can delay cell cycle progression of cancer cells and cause cell cycle checkpoint arrest that may intervene with the potency of anticancer drugs to kill cancer cells [7]. The aldehydes may also inhibit drug-induced apoptosis by obstruction death receptors and suppressing caspase activity. They added, grape seed proanthocyanidin may be reduce the generation of oxidative stress-stimulated aldehydes.

Antioxidant supplements are used during treatment with chemotherapy attributable to their role in the efficacy of the chemotherapy, as well as diminish toxic side effects, allowing patients to tolerate chemotherapy for the full course of treatment and at higher doses [8]. In addition, antioxidants have several mechanisms of action depending on their use, which noted to have the potential to serve as oxidant molecules themselves [9]. The supplements have a wide range in their antioxidant mechanisms from free radical scavengers that act by the preservation of cellular defense mechanisms or could be worked as reducers [10]. Additionally, aside from their antioxidant activities, these agents may manipulate the pharmacokinetics or pharmacodynamics of chemotherapeutic agents [11].

The beneficial role of Grape Seed Proanthocyanidin Extract (GSPE) against adverse effects of chemotherapeutic agents probably owing to its excellent antioxidant properties and high nutritional values [12].

*Correspondence to: Heba Mohamed Abdou, Department of Zoology, Faculty of Science, Alexandria University, Egypt, Tel:+203-3921593; E-mail: dr.heba_abdou3000@yahoo.com

Key words: thalidomide, carboplatin, grape seed proanthocyanidin, hepatic toxicity, cardiotoxicity, cytokines

Received: November 02, 2019; Accepted: November 15, 2019; Published: November 21, 2019
Also, grape seed proanthocyanidin extract (GSPE) caused enzymatic enhancement, may be due to its antioxidative phytochemicals as flavonoids [7].

Therefore, the present study was carried out to investigate the possible protective role of grape seed proanthocyanidin extract against the mixture of thalidomide and carboplatin-induced hepatic and cardiac toxicity in male rats.

Materials and methods

Tests compounds and doses

Thalidomide (C₂₉H₄₂N₂O₈) was purchased from Sigma Chemical Company (St. Louis, MO, USA). Carboplatin (C₂H₁₄N₂O₄Pt) obtained from Vita for NV/SA, additives and pharmaceutical, Germany (www.vitafor.com). A dried, powdered grape seed proanthocyanidin extract (GSPE) was obtained from Pharco Pharmaceuticals Company, Alexandria, Egypt. The dose of thalidomide was 60 mg/kg according to the study of Ilona et al. [13]. The dose of carboplatin was 196 mg/kg according to Husain et al. [14]. The dose of grape seed proanthocyanidin extract (GSPE) was 200 mg/kg BW according to Yousef et al. [7].

Animals and experimental groups

Forty Wistar male rats weighing 160-180g were used in the current study. They were obtained from the Faculty of Medicine, Alexandria University, Alexandria, Egypt. Animals were housed in a stainless-steel wire cages, kept on basal diet and given feed and water ad libitum. Rats fed pellets which consisted of 30% berseem (Trifolium alexandrinum) hay, 25% yellow corn, 26.2% wheat bran, 14% soybean meal, 3% molasses, 1% CaCl₂, 0.4% NaCl, 0.3% mixture of minerals and vitamins, and 0.1% methionine. The vitamin and mineral premix per kg contained the following IU/gm for vitamins or minerals: Vit. A-4000,000, Vit D₃-5000,000, 000, vit E-16.7 g, K-0.67 g, vit B1-0.67 g, vit B2-2 g, B6-0.67 g, B12-0.004 g, B5-16.7 g, Biotin-0.07 g, Folic acid-1.67 g, Choline chloride-400 g, Zn-23.3 g, Mn-10 g, Fe-25 g, Cu-1.67 g, I-0.25 g, Se-0.033 g, and Mg-133.4 g (Rabbit Biodiagnostic Kit, Egypt). The vitamin and mineral premix above assays were determined according to the manual instruction of Biodiagnostic Kit, Egypt.

Statistical analysis

Results are reported as means ± SE. Statistical analysis for all examined parameters was performed using the General Linear Model (GLM) produced by the Statistical Analysis Systems Institute [20] Duncan’s New Multiple Range Test was used to test the significance of the differences between means [21]. Values of p<0.05 were considered statistically significant.

Results

Effect of grape seed proanthocyanidin extract, thalidomide, carboplatin and their combination on tumor suppressor p53, tumor necrosis factor-α, interleukin-6

Administration of thalidomide followed by carboplatin caused significant (p>0.05) increase in liver and heart p53, TNF-α and IL-6.
compared to the control group (Table 1). The combination of GSPE with thalidomide and carboplatin significant (p<0.05) decreased in liver and heart P53, TNF-α and IL-6 compared to a group of thalidomide and carboplatin. GSPE alone significantly (p<0.05) decreased P53, TNF-α and IL-6 in the liver and insignificantly (p<0.05) increased in P53, significantly (p<0.05) increased TNF-α and IL-6 in the heart compared to the control group.

Effect of grape seed proanthocyanidin extract, thalidomide, carboplatin and their combination of free radicals and antioxidant enzymes

Thalidomide followed by carboplatin significantly (p<0.05) increased in the liver and heart TBARS and NO also significantly (p<0.05) decreased in the liver and heart GSH, TAC and antioxidant enzymes (SOD, CAT, GPx, and GST) as compared to control group (Tables 2 and 3). However, the presence of GSPE with thalidomide and carboplatin significantly (p<0.05) decreased in TBARS and NO as well as significantly (p<0.05) increased in GSH, TAC and antioxidant enzymes (SOD, CAT, GPx, and GST) in liver and heart compared to thalidomide and carboplatin group. On the other hand, treatment with GSPE alone significant (p<0.05) decrease in the levels of TBARS and NO and significant (p<0.05) increase GSH and antioxidant enzymes (SOD, CAT, GPx, and GST) in the liver and heart compared to the control group. However, TAC insignificantly (p>0.05) increased in the liver and heart.

Effect of grape seed proanthocyanidin extract, thalidomide, carboplatin and their combination on heart paroxanase (PON1) and plasma biochemical parameters

The present data showed that treatment with thalidomide followed by carboplatin significantly (p<0.05) decreased PON1 in the heart compared to the control group (Table 4). The presence of GSPE with thalidomide and carboplatin significantly (p<0.05) increased the level of PON1 in the heart compared thalidomide and carboplatin group.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
</tr>
<tr>
<td>P53 (pg/mg protein)</td>
<td>11.3 ± 0.08</td>
</tr>
<tr>
<td>TNF-α (pg/mg tissue)</td>
<td>4089 ± 95 ( ^{d} )</td>
</tr>
<tr>
<td>IL-6 (pg/mg tissue)</td>
<td>4095 ± 174 ( ^{d} )</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
</tr>
<tr>
<td>P53 (pg/mg protein)</td>
<td>8.1 ± 0.07 ( ^{a} )</td>
</tr>
<tr>
<td>TNF-α (pg/mg tissue)</td>
<td>2643 ± 247 ( ^{e} )</td>
</tr>
<tr>
<td>IL-6 (pg/mg tissue)</td>
<td>10134 ± 66 ( ^{d} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>TFRARS</td>
<td>21.8 ± 1.85 ( ^{d} )</td>
</tr>
<tr>
<td>NO</td>
<td>0.47 ± 0.04 ( ^{b} )</td>
</tr>
<tr>
<td>GSH</td>
<td>6.1 ± 0.16 ( ^{d} )</td>
</tr>
<tr>
<td>SOD</td>
<td>8.5 ± 0.58 ( ^{e} )</td>
</tr>
<tr>
<td>CAT</td>
<td>62.9 ± 3.57 ( ^{e} )</td>
</tr>
<tr>
<td>GST</td>
<td>0.70 ± 0.036 ( ^{b} )</td>
</tr>
<tr>
<td>GPx</td>
<td>33.8 ± 1.87 ( ^{f} )</td>
</tr>
<tr>
<td>TAC</td>
<td>25.4 ± 0.80 ( ^{d} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Experimental groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>TFRARS</td>
<td>20.5 ± 1.73 ( ^{d} )</td>
</tr>
<tr>
<td>NO</td>
<td>0.14 ± 0.03 ( ^{b} )</td>
</tr>
<tr>
<td>GSH</td>
<td>5.8 ± 0.30 ( ^{d} )</td>
</tr>
<tr>
<td>SOD</td>
<td>6.5 ± 0.22 ( ^{e} )</td>
</tr>
<tr>
<td>CAT</td>
<td>61.2 ± 4.80 ( ^{f} )</td>
</tr>
<tr>
<td>GST</td>
<td>0.77 ± 0.012 ( ^{b} )</td>
</tr>
<tr>
<td>GPx</td>
<td>33.8 ± 1.98 ( ^{e} )</td>
</tr>
<tr>
<td>TAC</td>
<td>27.5 ± 0.33 ( ^{d} )</td>
</tr>
</tbody>
</table>

The present data showed that treatment with thalidomide followed by carboplatin significantly (p<0.05) decreased PON1 in the heart compared to the control group (Table 4). The presence of GSPE with thalidomide and carboplatin significantly (p<0.05) increased the level of PON1 in the heart compared thalidomide and carboplatin group.
heart histopathological observations

Liver histopathological observations

Microscopic examination of liver sections of thalidomide and carboplatin-treated group showed histopathological alterations; dilation and congestion in the portal vein and sinusoids, loss of the normal hepatocytes architecture, degenerated hepatocytes, hepatocyte vacuolization also, presence of inflammatory cells infiltrations around the portal area (Figure 1 C1&C2), compared to control. On the other hand, the histopathological alterations were noticeably reduced in thalidomide, carboplatin plus GSPE (Figure 1D) compared to thalidomide and carboplatin-treated group. While, treatment with GSPE significantly (p>0.05) decreased the levels of AST, ALT, ACP, and ALP while significantly (p>0.05) decrease in the concentration of total protein and albumin compared to thalidomide and carboplatin group. Furthermore, treatment with GSPE alone significantly (p>0.05) decreased the levels of total protein and albumin compared with the control group.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>GSPE</th>
<th>Thalidomide+ Carboplatin</th>
<th>Thalidomide+Carboplatin + GSPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PON1 (ng/mg protein)</td>
<td>291 ± 7.3b</td>
<td>337 ± 12.8a</td>
<td>78 ± 4.0d</td>
<td>191 ± 6.9c</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>23.7 ± 1.61c</td>
<td>21.9 ± 1.99d</td>
<td>42.0 ± 2.11a</td>
<td>38.7 ± 1.41b</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>22.9 ± 1.84c</td>
<td>20.7 ± 1.26d</td>
<td>33.5 ± 2.26a</td>
<td>27.2 ± 1.74b</td>
</tr>
<tr>
<td>ACP (U/L)</td>
<td>6.6 ± 0.36c</td>
<td>6.7 ± 0.34c</td>
<td>10.6 ± 1.72a</td>
<td>7.7 ± 0.76b</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>56.2 ± 3.5c</td>
<td>53.7 ± 3.3d</td>
<td>95.0 ± 4.8a</td>
<td>73.2 ± 4.3b</td>
</tr>
<tr>
<td>Total protein (mg/dl)</td>
<td>6.3 ± 0.16a</td>
<td>6.0 ± 0.25a</td>
<td>4.5 ± 0.19c</td>
<td>5.4 ± 0.11b</td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>4.3 ± 0.27a</td>
<td>4.4 ± 0.19a</td>
<td>2.2 ± 0.17c</td>
<td>3.3 ± 0.14b</td>
</tr>
</tbody>
</table>

Table 4. Heart paroxanase (PON1) and plasma aspartate aminotransferase (AST), alanine aminotransferase (ALT), acid phosphatase (ACP), alkaline phosphatase (ALP), total protein and albumin of male rats treated with grape seed proanthocyanidin extract (GSPE), thalidomide, carboplatin and their combination (Mean values ± SE)

Simultaneously, treatment with GSPE alone significantly (p>0.05) increased the level of PON1 in the heart compared to the control group as shown.

Heart histopathological observations

Histological examination of tissue sections from the heart muscle in thalidomide and carboplatin-treated group showed histopathological alterations; improvement of the histological alterations induced by thalidomide and carboplatin treatment with few Kupffer and lymphocytes cells (black square & green arrow) “H & E, 400 X”.

Discussion

Administration of carboplatin and thalidomide caused an elevation in liver and heart proinflammatory cytokines; tumor suppressor P53 (P53), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These results are in agreement with the report of Rehman et al. [22] and El-Awady et al. [23]. Over production of COX-2 and p53 in Cisplatin
increased the level of TBARS, NO and decreased the level of GSH and the Nrf2 expression led to modulation in antioxidant enzymes. They added, GSPE supplementation caused an elevation in normal values. This may be attributed to the anti-inflammatory role of values of various inflammatory cytokines; P53, TNF-α and IL6 near to inflammatory stimulus can increase the IL-6 concentrations [27]. As well as, IL-6 is secreted by the released by innate immune cells [27].

These results are similar [3]. This elevation in the proinflammatory cytokines also came in the same line with the reports of Kim et al. [26] who suggested that cisplatin-induced activation of proinflammatory cytokines and NF-kB directly involves c-jun N-terminal kinase and mitogen-activated protein kinases/ extracellular signal-regulated kinase (JNK and MEK/ERK) signaling pathways. TNF-α was identified as an endogenous pyrogen and a key component of an inflammatory response and one of the most potent pro-inflammatory cytokines also came in the same line with the reports of Kim et al. [26]. These results are similar [3]. This elevation in the proinflammatory cytokines and NF-kB directly involves c-jun N-terminal kinase and mitogen-activated protein kinases/ extracellular signal-regulated kinase (JNK and MEK/ERK) signaling pathways. TNF-α was identified as an endogenous pyrogen and a key component of an inflammatory response and one of the most potent pro-inflammatory cytokines also came in the same line with the reports of Kim et al. [26].

These results are similar [3]. This elevation in the proinflammatory cytokines also came in the same line with the reports of Kim et al. [26] who suggested that cisplatin-induced activation of proinflammatory cytokines and NF-kB directly involves c-jun N-terminal kinase and mitogen-activated protein kinases/ extracellular signal-regulated kinase (JNK and MEK/ERK) signaling pathways. TNF-α was identified as an endogenous pyrogen and a key component of an inflammatory response and one of the most potent pro-inflammatory cytokines also came in the same line with the reports of Kim et al. [26].

However, grape seed proanthocyanidin extract modulated the values of various inflammatory cytokines; P53, TNF-α and IL6 near to normal values. This may be attributed to the anti-inflammatory role of GSPE [28]. They added, GSPE supplementation caused an elevation in the Nrf2 expression led to modulation in antioxidant enzymes.

In the present study, carboplatin and thalidomide administration increased the level of TBARS, NO and decreased the level of GSH and TAC, as well as decline the activities of antioxidant enzymes SOD, CAT, GST and GPX in the liver and heart of male rats. These results are in the same line with those of El-Kholy et al. [29] who indicated that cisplatin increased oxidative stress, the level of malondialdehyde (MDA) accompanied with decline in reduced glutathione (GSH), antioxidant enzymes activities as superoxide dismutase (SOD) and catalase (CAT). This may be attributed to cisplatin inhibit the defense of anti-oxidative system and induce liver oxidative stress injury. Also, Bahadır et al. [30] reported that the increases in the levels of MDA designate the myocardial damage with a decline in the GSH level and SOD, CAT activities in the Cisplatin -treated rats. This may be due to Cisplatin-induced cardiotoxicity, increased activity of reactive oxygen species caused an elevation in MDA production.

Nannelli et al. [31] mentioned that a reduction in glutathione levels accompanied by an alteration in the cellular redox state occurred by carboplatin. This leads to a reduction in performance of the antioxidant enzyme defense system.

Furthermore, the elevation in the levels of TBARS, nitric oxide and proinflammatory cytokines in the thalidomide and carboplatin-treated group, as well as the depletion in the levels of glutathione (GSH). These results are concomitant with the increases in IL-6. These may be regarded as the reduction in intracellular GSH, which has been coupled with increasing cytokine biosynthesis, including the release of IL-6 [32]. The mechanism implicated a ROS-sensitive pathway since the depletion of GSH strengthened IL-6 release and the production of free radicals. Additionally, ROS-mediated activation of NF-kB can lead to upregulation of cytokine expression [33].

However, administration of GSPE caused a reduction in oxidative stress markers elevated the antioxidant enzymes activities against hepatic and cardiac damage. This may be due to GSPE increased Nrf2 nuclear translocation to promote the Nrf2 signaling pathway, thus enhancing antioxidant defense systems during hepatotoxicity [34].

In addition, Proanthocyanidins contain a large amount of H+, which can block free radical chain reaction, thus improving the activity of various antioxidant enzymes and antioxidant substances in cells [35]. GSPE considered as antioxidant, antiinflammation and antiatherosclerosis [36,37]. Also, Puiggòrs et al. [38] reported that procyanidins elicit the upregulation of a sequence of antioxidant and detoxification enzymes that enhance cellular defenses.

In the current data, administration of carboplatin and thalidomide revealed elevation in PON1, ALT, AST, ACP, ALP activities, also reduction in total protein and albumin content.

Similarly, Iseri et al. [39] indicated a significant disorder in the activities of plasma AST and ALT through treatment with platinum compounds. The alterations in the activity of these enzymes could be a secondary event following platinum-induced liver damage with the subsequent leakage from hepatocytes. Yilmaz et al., [40] reported that the involvement of oxidative stress, lipid peroxidation and mitochondria dysfunction in CDDP –induced liver toxicity. They added, oxidative stress is a common pathogenetic mechanism contributing to the initiation and progression of hepatic damage in a variety of liver disorders.

Transaminases are the most sensitive biomarkers directly implicated in the extent of cellular damage and toxicity because they are cytoplasmic in location and are released into the circulation after cellular damage [41]. Moreover, Rehman et al. [22] indicated that alterations in AST and ALT are reported in hepatic disease and in myocardial infarction.
In the current data, the reduction in total protein and albumin may be attributed to the chemotherapeutic agents caused alterations in protein, albumin and liver enzymes and this may be due to the injured kidney [42]. In addition, platinum drugs diminish DNA, RNA and protein synthesis. The inhibition of protein synthesis associated with platinum compounds may be attributed to platinum-induced transcription high jacking. So, transcription high jacking refers to the consequences of the ability of certain transcription factors to join DNA adducts caused by organ platinum compounds [43].

In addition, augmented protein metabolism, albuminuria, and microproteinuria may attribute to the reduction in serum levels of total protein and albumin. Also, high production of urea may be a result of increased proteins catabolism in the liver and plasma [44].

The presence of GSPE with carboplatin and thalidomide minimized their toxic effect on PON1, ALT, AST, ACP, ALP activities, also modulated total protein and albumin content to reach near to the control values. These results are consistent with the findings of Karthikeyan et al. [45] reported that administration of GSPE maintained the levels of the marker enzymes (AST, ALT, LDH, and CK). The maintenance of the levels of marker enzymes may be due to the free radical scavenging property of anti-oxidative phytochemicals such as flavonoids present in GSPE. A possible explanation for this is that GSPE, via its anti-lipid peroxidation activity, causes stabilization of cardiac membranes and prevents the leakage of cardiac enzymes. Moreover, the main polyphenol components in GSPE are (+)-catechin (C), (−)-epicatechin (EC), (−)-epicatechin gallate (ECC) and proanthocyanidin dimer B2 (EC-EC). Also, Phenolic antioxidants reduce lipid peroxidation through a rapid donation of a hydrogen atom to the peroxyl radical (ROO•) resultant in the creation of alkyl (aryl) hydroperoxide (ROOH). The polyphenol phenoxy radical formed can be stabilized by further donation of a hydrogen atom [46].

Administration of GSPE mitigated H2O2 -induced oxidant stress in cardiomycocytes. This action is coupled with an increase in cardiomycocyte survival. So, the cardioprotective effects of GSPE could be realized by reduction or removal of free radicals in the myocardium [47]. Likewise, Issabeagloo et al. [48] reported that GSPE treatment improves hepatic status. This attributed to cellular regeneration and stability of cell membrane which in turn, exclude the penetration of intracellular enzymes.

The biochemical parameters are confirmed by histopathological results which showed, loss of the normal hepatocytes architecture, degenerated hepatocytes with vacuolization as well as, dilatation and congestion in the portal vein and sinusoids. Moreover, distortion and degeneration in myocardial fibers with pyknotic nuclei in carboplatin hepatic damage manifested by pericentral disorganization, hepatic necrosis, and apoptotic changes.

These results agreed with Kart et al. [49] who reported that cisplatin-induced hepatic damage manifested by pericentral disorganization, hepatic necrosis, and apoptotic changes.

It was shown that cisplatin induces liver cells apoptosis by cytochrome-c release and caspase 3 release activation. Also, hepatotoxicity occurs by increasing messenger Ribonucleic Acid (mRNA) expression of nuclear factor-kappa B (NF-κb) dependent Cyclo-Oxygenase (COX-II) and inducible nitric oxide synthase (iNOS) [50].

In addition, the cardiac impairment produced after cisplatin administration revealed degeneration and necrosis of cardiac muscle fiber cells [51]. Also, cisplatin treatment may lead to degenerative changes in cardiac tissues, which may point to the possible consideration of carnitine deficiency. This result is supported by Zakhkouk et al. [52] who reported that cardiac tissue damage may be due to the elevation in the lipid peroxidation (MDA) and reduction in GSH and CAT levels.

The current data revealed that GSPE ameliorated the histological changes in liver and heart motivated by carboplatin and thalidomide. In general, these results were consistent with those of Kandemir et al. [53]. They reported that co-treatment with GSPE has been relieved hepatotoxicity since; histopathological changes were noteworthy less pronounced compared to animals treated with cisplatin alone. Supplementation of GSPE exhibited normal organization of the cardiac muscle fibers. The present results were in the same line with the results of Lian et al. [54] who reported the protective role of GSPE against cisplatin-induced cardiac toxicity and histological alteration in heart tissue of rats.

Conclusion

In spite of the efficacy of carboplatin and thalidomide treatment, there is a restriction for their use in order to their negative effects on most of the tissue functions. GSPE acts as a potent natural antioxidant due to its antioxidant properties; GSPE exhibited a protective effect on liver and heart tissues against carboplatin and thalidomide -induced damage in rats. It could improve the proinflammatory status in liver and heart. It also attenuated the lipid peroxidation, nonenzymatic and enzymatic antioxidants also, liver and heart functions near to the control values. The biochemical analysis confirmed by histopathological investigations. So, the present work indicates that GSPE has a promising therapeutic role as a preventive agent against hepatotoxicity and cardiotoxicity motivated by carboplatin and thalidomide.

Acknowledgement

This research is funded by a private partnership. Also, the research received no specific funding from any agency in the public, commercial.

References


Copyright: ©2019 Youssef MI. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.