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Neuro- and nephroprotective effect of grape seed proanthocyanidin extract against carboplatin and thalidomide through modulation of inflammation, tumor suppressor protein p53, neurotransmitters, oxidative stress and histology

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ABSTRACT

The combination of thalidomide and carboplatin is one of the most potent chemotherapeutic strategies for the treatment of cancer. However, limited studies have been conducted on the neurotoxicity and nephrotoxicity of both chemotherapeutic agents. The aim of our study was to assess the toxicity of thalidomide and carboplatin combination on brain and kidney and investigate the protective effect of grape seed proanthocyanidin extract (GSPE). Thalidomide and carboplatin induced up-regulation of the expression of p53, tumor necrosis factor-α and interleukin-6 in brain and kidney. Acetylcholinesterase, dopamine and serotonin were decreased and norepinephrine was increased. Thiobarbituric acid reactive substances, nitric oxide, lipid profile, bilirubin and creatinine were elevated, while antioxidants enzymes (GST, GPX, CAT and SOD), total antioxidant capacity and the levels of glutathione were decreased. A microscopic examination showed shrinkage of capillaries, degeneration with pyknotic nuclei, loss of normal structure and neuronal degeneration. GSPE co-treatment with thalidomide and carboplatin reduced their brain and renal damage, oxidative stress, diminished cytokines, p53, neurotransmitters and biochemical parameters, and inhibited brain and renal cell apoptosis. It can be concluded that, the protective effects of GSPE against thalidomide and carboplatin induced-brain and renal damage was associated with the minimization of oxidative stress.

1. Introduction

Chemotherapy drugs have many mechanisms of actions and may belong to more than one group. One group of chemotherapeutic drugs is alkylating agents that directly damage DNA. Alkylating agents include the platinum drugs (cisplatin, carboplatin and oxalaplatin) [1]. High dose of carboplatin induces ototoxicity in cancer patients and oxidative injury in rats *via* the generation of free radicals and the depletion of antioxidants [2].

Immunomodulating drugs such as thalidomide, lenalidomide and revlimid is another group of chemotherapeutic agents. Thalidomide was used as a sedative drug to treat morning sickness in pregnant women in the 1950s, but was subsequently withdrawn from the market in 1961 because of severe teratogenicity and neurotoxicity [3]. Interestingly, subsequent studies on the mechanisms of thalidomide teratogenicity revealed that the compound was an effective anticancer and anti-inflammatory agent. The US Food and Drug Administration approved thalidomide for the treatment of lepromatous leprosy and multiple myeloma in 1998 and 2006, respectively [4]. Thalidomide is used experimentally to treat various cancers, dermatological, neurological and inflammatory diseases. Thalidomide and its immunomodulatory analogues have numerous effects on the body's immune system, including potential anti-cancer and anti-inflammatory activities [5].

Antineoplastic agents induce oxidative stress in biological systems. During cancer chemotherapy, oxidative stress induced lipid peroxidation generates numerous electrophilic aldehydes that can attack many cellular targets. These products of oxidative stress can slow cell cycle progression of cancer cells and cause cell cycle checkpoint arrest, effects that may interfere with the ability of anticancer drugs to kill cancer cells. The aldehydes may also inhibit drug-induced apoptosis (programmed cell death) by inactivating death receptors and inhibiting

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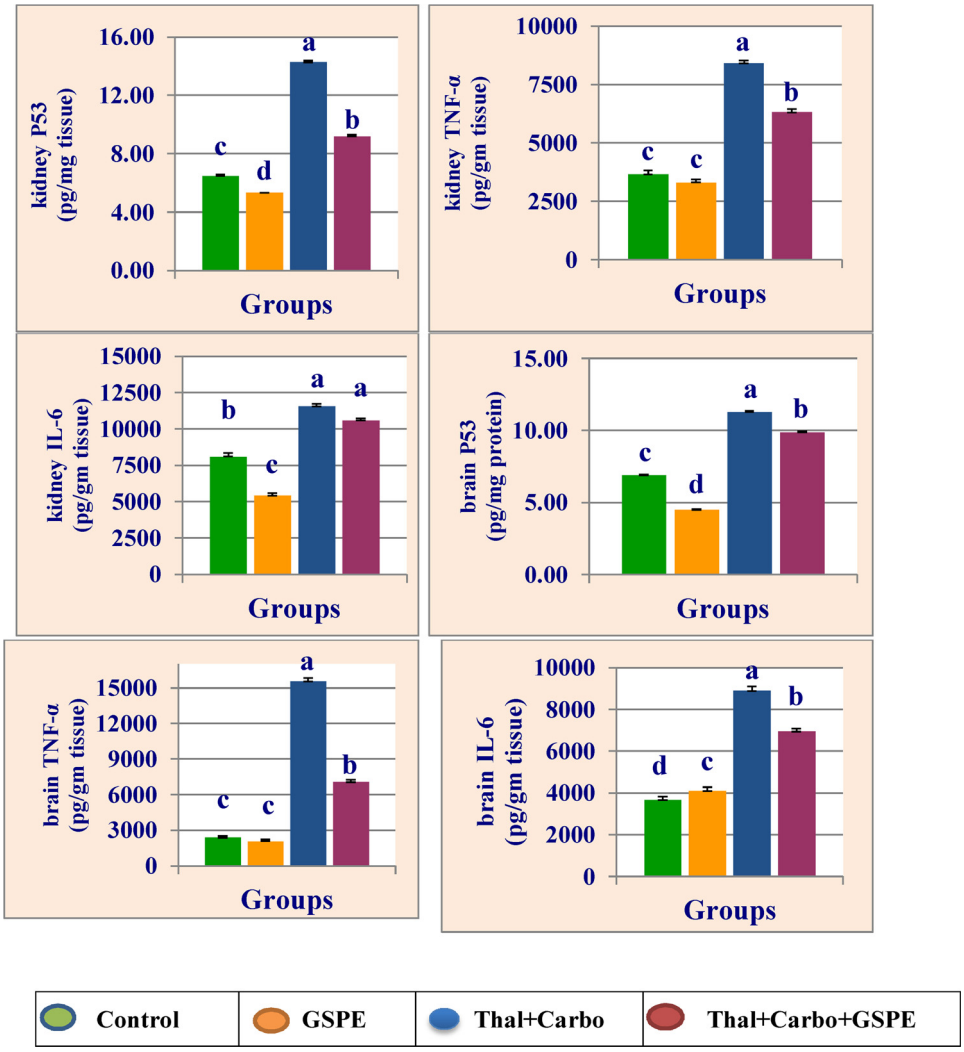

Fig. 1. Mean values ± SE of kidney and brain levels of tumor suppressor P53 (P53), tumor necrosis factor-α (TNF-α) interleukin 6 (IL-6) of male rats treated with grape seed proanthocyanidin extract (GSPE), thalidomide (Thal.), carboplatin (Carbo.) and their combination.
Mean values not sharing a common superscript letters (a–d) were significantly different, $p < 0.05$.

caspase activity. These effects would also diminish the efficacy of the treatment. The use of antioxidants during chemotherapy may enhance therapy by reducing the generation of oxidative stress-induced aldehydes [6].

Oxidative damage represents a major mechanism of cytotoxicity to normal cells by most chemotherapeutic agents since the drugs of many classes of antineoplastic agents are known to generate a high level of oxidative stress in biological systems. A good deal of evidence suggests that reactive oxygen species (ROS) have an important role in certain chemotherapy-induced side effects. Examples include doxorubicin-induced cardiotoxicity, bleomycin-induced pulmonary fibrosis, and cisplatin-induced nephrotoxicity, ototoxicity and neurotoxicity [6].

Antioxidants are potent scavengers of free radicals and serve as inhibitors of neoplastic processes. A large number of synthetic and natural antioxidants have been demonstrated to induce beneficial effects on human health and disease prevention [7]. A broad spectrum of pharmacological and therapeutic benefits of grape seed proanthocyanidin extract (GSPE) against oxidative stress and degenerative diseases, including cardiovascular dysfunctions, acute and chronic stress, gastrointestinal distress, neurological disorders, pancreatitis, various stages of neoplastic processes and carcinogenesis including detoxification of carcinogenic metabolites, have been reported [8].

GSPE is a superior scavenger as compared to vitamins C, E and carotene and prevents hepatic and brain lipid peroxidation and DNA damage in animals. Besides antioxidant activity, GSPE has been described as anti- microbial, anti-cancer, anti-inflammatory and anti-fatigue agent [9]. GSPE protects against structurally diverse drug and chemical-induced multi-organ toxicity, induces selective cytotoxicity toward human breast, lung, gastric and pancreatic cancer cells while maintaining growth and viability of normal cells [8]. Our previous studies showed that GSPE is capable of alleviating cisplatin-induced damage in kidney genomic DNA, nephrotoxicity and oxidative stress in male rats [10,11]. The aim of the present study was to investigate the chemo-protective effect of GSPE against neurotoxicity and nephrotoxicity induced by thalidomide and carboplatin *via* reactive oxygen species, nitric oxide, total antioxidant capacity, antioxidant enzymes, neurotransmitters, cytokines (tumor necrosis factor and interleukin-6), tumor suppressor gene P53, biochemical parameters and histopathological changes in male rats.

2. Materials and methods

2.1. Tested compounds and doses

Thalidomide ($C_{13}H_{10}N_2O_4$) was purchased from Sigma Chemical Company (St. Louis, MO, USA). Carboplatin ($C_6H_{14}N_2O_4Pt$) obtained from Vitafor additives and pharmaceuticals, Germany (www.vitafor.com). A dried, powdered grape seed proanthocyanidin extract (GSPE)