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Elucidation of Glutathione-*S*-transferase Activity Induced by Pectin-Cisplatin Nano-conjugates for Optimization of New Therapeutic Strategies

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Abstract

Despite tremendous efforts to search novel drugs and treatments, cancer continues to be a major health hazard. Modulation of cellular responses to platinating agents has important clinical implications as they are still heavily prescribed against various cancers. First line chemotherapeutic drug used for treating solid tumors, displays dose limiting nephrotoxicity. Natural products are being sought in order to improve the anticancer efficacy of cisplatin. Pectin, a plant polysaccharide have reported strong anti-oxidant and anti-cancer properties. In our study, Pectin-Cisplatin nanoconjugates in size range of (200 ± 20 nm) were synthesized and assessed for their anti-cancer and renoprotective role. The cytotoxicity of Pec-cis nanoconjugates and cis *per se* was assessed and co-related with the Glutathione-*s*-transferase level in both, *in-vitro (*B-16/F-10 mouse melanoma cell line) and *in-vivo* models (C57BL6 mice) in time (24 hours, 48 hours) and dose dependent (30 µg/ml and 60 µg/ml) manner. Our findings revealed that pectin-cisplatinnanoconjugates exhibited cytotoxicity similar to the cisplatin solution at 1/10th of the cisplatin content, which indicates a possible synergism between the activity of the cisplatin and pectin. MDA and histological findings were corraborated for altered renal function in tumor bearing mice. Enhanced GST level was reported post pectin-cisplatin nanoconjugates administration which confirmed that pectin-cisplatin treatment ameliorated both functional and histopathologic damage. This was further verified by lowered MDA levels when compared to cisplatin*per se*. Therefore, our results confirmed that Pectin-cisplatin nanoconjugates exhibited anti-tumor properties and rendered partial protection against cisplatin induced nephrotoxicity thereby proving the biocompatibility of pectin-cisplatin nanoconjugates for therapeutic purposes.

Keywords: Pectin-Cisplatin nanoconjugates; Cytotoxicity; Glutathione-*S*-transferase; Oxidative stress; Nephrotoxicity

Introduction

Cisplatin (Cis), is still one of the most heavily prescribed chemotherapeutic drug for the treatment of a variety of malignancies that include ovarian, testicular and lung cancer [1] but has extremely low patient compliance owing to the induced nephrotoxicity. Acute kidney injury occurs after high-dose Cis chemotherapy in approximately 20% of patients [2] and it remains a significant cause of increased morbidity and mortality among patients, particularly in critical care units. Several therapeutic strategies are being used to prevent this condition mainly by vigorous hydration with normal saline is prevalent [3]. Inflammation and oxidative stress play a key role in Cis induced renal dysfunction [4]. Cis has been reported to enhance tumor necrosis factor-alpha (TNF-R) levels [5] superoxideanions [6], peroxynitrite anions [7], hydrogen peroxide [8], and hydroxyl radicals via mobilization of iron fromrenal cortical mitochondria [9,10].

Cell death by cis is primarily initiated through the formation of intrastrand crosslinks, the majority of which involve neighbouring purine bases [11]. Accumulation of these adducts can inhibit DNA replication and transcription, triggering cell cycle arrest and apoptosis [12-14]. The severity of toxicity associated with this drug potentiates the development of newer approaches to combat cancer. Various studies demonstrated the protective effect of anti-inflammatory agents and antioxidants against Cis-induced inflammation and oxidative stress in experimental nephrotoxicity [15,16]. Cis-induced nephrotoxicity is closely associated with an increase of lipid peroxidation in the kidney tissues [17-19]. Furthermore, Cis induced glutathione depletion is a determinant step in oxidative stress in kidney tissue that leads to nephrotoxicity [20]. Cis chemotherapy induces a fall in plasma antioxidant levels, which may reflect a failure of the antioxidant defense mechanism against oxidative damage induced by commonly used antitumor drugs [21]. Renewed interest has been observed in recent years on the multiple activities of natural molecules. A large number of natural products and dietary components have been evaluated as potential chemoprotective agents. Natural compounds represent an important source of new "leads" with potent chemotherapeutic or chemopreventive activity [22].

Pectins (Pec) are complex plant polysaccharides present primarily in cell walls as an intercellular cementing material. Polysaccharides are preferred due to their unique and multifunctional attributes such as non-toxic, bio-compatible, biodegradable with adherence properties [23]. Pectin has been extensively investigated as matrix tablets for oral delivery to target the colon [24] and as microspheres [25-27].

Pectin *per se* (pec) and pH or heat-modified pectin have demonstrated chemopreventive and antitumoral activities against some aggressive and recurrent cancers [22]. It has been reported that polysaccharides in general have strong antioxidant activities and can be explored as novel potential antioxidants [28]. Due to their antioxidant activity, polysaccharides extracted from fungal, bacterial and plant sources have been proposed as therapeutic agents [29]. It has been recently reported that pectins and pectic acids have antioxidant activity that may be related to free radical scavenging activity of these molecules [30,31]. We have earlier communicated in depth physical

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