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# Co-Administration of PLGA Nano-Boldine Can Reduce Cisplatin-Induced Toxicity in Normal Tissue of Cancer Mice Model: A Commentary on Our Published Research

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**Commentary**

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**Abbreviations:** PLGA: Poly Lactide-Co-Glycolide; DNA: Deoxyribose Nucleic Acid; RNA: Ribo Nucleic Acid; ROS: Reactive Oxygen Species; FDA: Food and Drug Administration; EMA: European Medicines Agency; DLS: Dynamic Light Scattering; FTIR: Fourier Transform Infrared Spectroscopy; TEM: Transmission Electron Microscopic; IP: Intraperitoneally; PI: Propidium Iodite; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction.

## Commentary

The greatest problem of using some potent anti-cancer drugs in cancer patients is its cytotoxicity to normal tissue when the cancer tissue is targeted for annihilation, often producing unwanted side-effects, and thereby restricting its effective and prolonged use in cancer patients. Therefore, one solution for such a problem could be to try to potentially reduce if not totally eliminate such side-effects often resulting from damage to normal healthy tissue. In this commentary, an attempt will be made to focus on the salient results obtained in our earlier representative study [1] primarily aimed at examining if co-administration of poly (lactide-co-glycolide) (PLGA)-nanoparticles loaded Boldine, an antioxidant ingredient of ethanolic extract of Boldo plant (*Peumus boldus*) could reduce unwanted Cisplatin-(a potent chemotherapeutic drug)-induced toxicity in normal tissue of cancer mice model, *Mus musculus*, which could be extrapolated in human cases of cancer.

Cisplatin [cis-diamminedichloroplatinum (II)] is an alkylating agent which is considered to be an efficient chemotherapy drug against cancer. This drug is used quite widely to treat different types of cancers including testicular, cervical, head, neck, bladder and lung cancer [1]. The basic principle on which its chemotherapeutic action is based is that when Cisplatin is transported into cells, the chloride ions dissociate from the positively charged platinum ion, and bind to cellular deoxyribose nucleic acid (DNA), ribo nucleic acid (RNA) and proteins [2], and the interaction causes inhibition of replication, transcription, translation and obstructs DNA-repairing [3], thereby preventing cancer growth. But despite its efficacy as a potent anti-cancer agent, unfortunately its use often has to be cut short for its concomitant production of strong side-effects on various organs like kidney, liver, brain and gastrointestinal tracts [4]. Inhibition of antioxidant enzymes by Cisplatin is another cause of inducing major side effects like nephrotoxicity and hepatotoxicity [1]. Nitric oxide plays an important role in Cisplatin-induced nephrotoxicity along with other reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide [5]. Another main reason for Cisplatin-induced toxicity possibly could be due to depletion of reduced glutathione (GSH). It has also been reported that both p53 dependent expression of caspases-cascade and p53-independent activation of caspases through Bax/Bcl2 mediated release of cytochrome C contribute to Cisplatin induced cellular death [6]. Patients treated for cancer with platinum-based compounds frequently develop cognitive impairment and structural abnormalities in the brain. Therefore, one of the major objectives of this study was to examine if co-administration of Boldine (Bol) or nano-Boldine (NBol) with Cisplatin therapy could have some protective effect against Cisplatin-induced toxicity in normal cells but without having such protective effect against Cisplatin-induced cytotoxicity in cancer cells. This study was done in the mammalian mice model (*Mus musculus*), having more than 90% genomic similarities with that of human being, and a model often used for extrapolating results applicable to human beings to a considerable extent.

Boldo (Bol), the major leaf and bark alkaloid of the Chilean boldo tree (Peumus boldus), chemically known as (S)-2, 9-Dihydroxy-1, 10- dimethoxy-aporphine, has been shown to behave as a potent antioxidant. The ethanolic crude extract of Boldo plant is generally used as a homeopathic drug against severe liver toxicity related disorder and known particularly for its anti-hepatotoxic effects. The major biologically active ingredient, Bol, has also been reported to have pharmacological activities like cyto-protective, anti-tumour and protective effect against neuronal damage [7]. Since the major side-effect of Cisplatin is noted in its production of hepatotoxicity, we became interested to examine if Boldo could counter the hepato-toxic effects and reduce hepato-toxicity.

In recent years nanoparticles of biodegradable non-toxic polymers, harmless to target organism, are preferred as carriers because of their high drug-loading capacity, controlled drug release and occasional lack of requirement of surgical intervention for removal of depleted drug [8]. Poly (lactide-co-glycolide) (PLGA)-based nanoparticles delivery has many advantages like non-degradable and sustained release of the therapeutic agent. Moreover, due to their smaller size, nanoparticles can penetrate specific tissues via receptors over-expressed by target cells or can cross the blood brain barrier. Another major advantage of PLGA over other polymers is that it can improve pharmacokinetic and pharmacodynamic profiles and is approved by the food and drug administration (FDA) and European Medicines Agency (EMA) in various drug delivery systems.

Keeping all the above-mentioned facts in mind, the detailed study was conducted on Swiss albino mice, *Mus musculus*. Hepato-cellular carcinoma was developed in the mice by oral administration of Bezo[a]pyrene (BaP) (50 mg/kg bw) suspended in olive oil, twice a week to normal healthy mice for one month and then they were kept on a normal diet for three more months for onset and development of hepato-cellular carcinoma. All suitable controls were properly maintained. PLGA-encapsulated NBol were prepared using a one-step procedure of nanoprecipitation, also known as the solvent displacement method [1]. Nanparticles of NBol were duly characterized for their size, zeta potential, % of yield, encapsulation efficiency and polydispersity index, as per standard procedure of dynamic light scattering (DLS) and also by deploying UV-Vis spectrophotometry, fluorimetry, structural integrity assessment done by fourier transform infrared spectroscopy (FTIR) as described in [1].

Further, release kinetics of Bol from its encapsulated form and tissue distribution assay of Bol and NBol were also carried out as per standard procedure. Tissue distribution assay was done in different tissues like brain, lung, heart, liver, kidneys, spleen etc. Further, transmission electron microscopic (TEM) analysis of brain tissue was done in order to see if the Boldine-loaded nanoparticles could cross the blood brain barrier.

Cisplatin was administered intraperitoneally (IP) at a standardized dose of 5-30 mg/kg bw twice a week for one month. That gave the best protective result in mice carrying induced hepatocarcinoma. 24 mice were randomly selected and divided into 4 groups, each with 6 mice, of which 3 making the treated series and remaining one group serving as the control, for conducting further experiments. For Cytotoxicity assessment, MTT assay was done. Histopathology was studied in liver and kidney for tissue distribution of Bol and NBol particles. Biochemical parameters like LPO, GSH, SOD, AST, and ALT were studied through standard kit-based estimation. Flow cytometric analysis of early and late apoptosis was done by standard Annexin V-FITC and propidium iodite (PI) staining. Nanoscale changes in chromatin organization of all groups of mice were analysed by TEM following standard method. Determination of intracellular ROS and mitochondrial membrane depolarization was determined flow-cytometrically. RNA extraction and quantitative reverse transcriptase polymerase chain reaction (RT-PCR) analysis was done as per standard protocol. Immunoblot analysis and analysis of Cytochrome C release were studied. Interaction of NBol and DNA of calf thymus was studied through circular dichroism spectroscopy (CD), to determine if NBol could induce conformational change in the DNA.

The results obtained in respect of all these parameters of study indicated that NBol had faster cellular entry, thus proving it to be a better drug carrier, targeting the cancer cells as compared to that by Bol. Also, there was a remarkable feature noticeable; though it did not antagonize the cytotoxic effects of Cisplatin in cancer cells, it could considerably reduce Cisplatin-induced cytotoxicity in normal healthy tissue. NBol could also cross the blood-barrier, which is a medically significant finding. This study could pave the way for providing impetus towards extending research further in other animal models and cell-free systems, to see if similar encouraging results could be found that might have practical application of NBol in oncology. PLGA as drug carrier has a distinct advantage as i) it is bio-degradable and non-toxic in nature, and ii) can be prepared rather easily by a simple technology of nano-encapsulation [9,10], and iii) because only a relatively low dose NBol is required to produce these favorable results in cisplatin-induced toxicity management, permitting thereby better and longer use of Cisplatin chemotherapy.

Thus, co-administration of Bol/NBol with Cisplatin may be helpful in reducing adverse toxic side effects of Cisplatin therapy. However, more animal experiments may be necessary before recommending the use of this combined

therapy in human trials for cancer patients who need and respond well to Cisplatin therapy.

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