Biological Trace Element Research
https://doi.org/10.1007/s12011-019-01683-w

Disulfiram and Its Copper Chelate Attenuate Cisplatin-Induced Acute Nephrotoxicity in Rats Via Reduction of Oxidative Stress and Inflammation

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Received: 22 September 2018 / Accepted: 19 February 2019

Abstract

The use of cisplatin (CP) in chemotherapy of resistant cancers is limited due to its dose-dependent nephrotoxicity. Disulfiram (DSF), the aversion therapy for alcoholism, has recently emerged as an anticancer and chemopreventive agent. Its anticancer activity is potentiated in the presence of copper. However, such use of copper leads to several adverse effects. In the present study, the protective effect of DSF and its copper chelate (Cu-DEDC) against CP-induced nephrotoxicity in rats was evaluated. Nephrotoxicity was induced by a single intraperitoneal injection of CP (5 mg/kg). The treatment groups included control (vehicle treated), CP (CP-treated), CP + DSF (CP followed by DSF), CP + DSF + Cu (CP followed by DSF and $CuCl_2$), CP + Cu-DEDC (CP followed by Cu-DEDC), and CP + AMF (amifostine pre-treated and CP-treated). The DSF, Cu-DEDC, and $CuCl_2$ were administered orally at 50 mM/kg/day dose for 5 days post CP injection. AMF served as a standard chemo protectant, administered intravenously 30 min prior to CP. The markers of oxidative stress, inflammation, and kidney function estimated on the 6th day revealed that both DSF and Cu-DEDC significantly attenuated the CP-induced rise in the serum/urine creatinine and blood urea nitrogen (BUN). The CP-induced rise in serum alkaline phosphatase (ALPase) was reversed by these drugs. Both drugs reduced the levels of malondialdehyde and nitric oxide (NO) in kidney tissues. These drugs reversed CP-induced depletion of SOD, catalase, and GSH in the kidneys. There was a significant reduction in the CP-induced TNF-α and IL-1β production along with prevention of histological alterations. Above observations indicate that DSF and Cu-DEDC may have significance as adjuvants to protect against CP-induced nephrotoxicity.

Keywords Cisplatin · $Cucl_2$ · Cu-DEDC · Cytokines · Disulfiram · Nephrotoxicity

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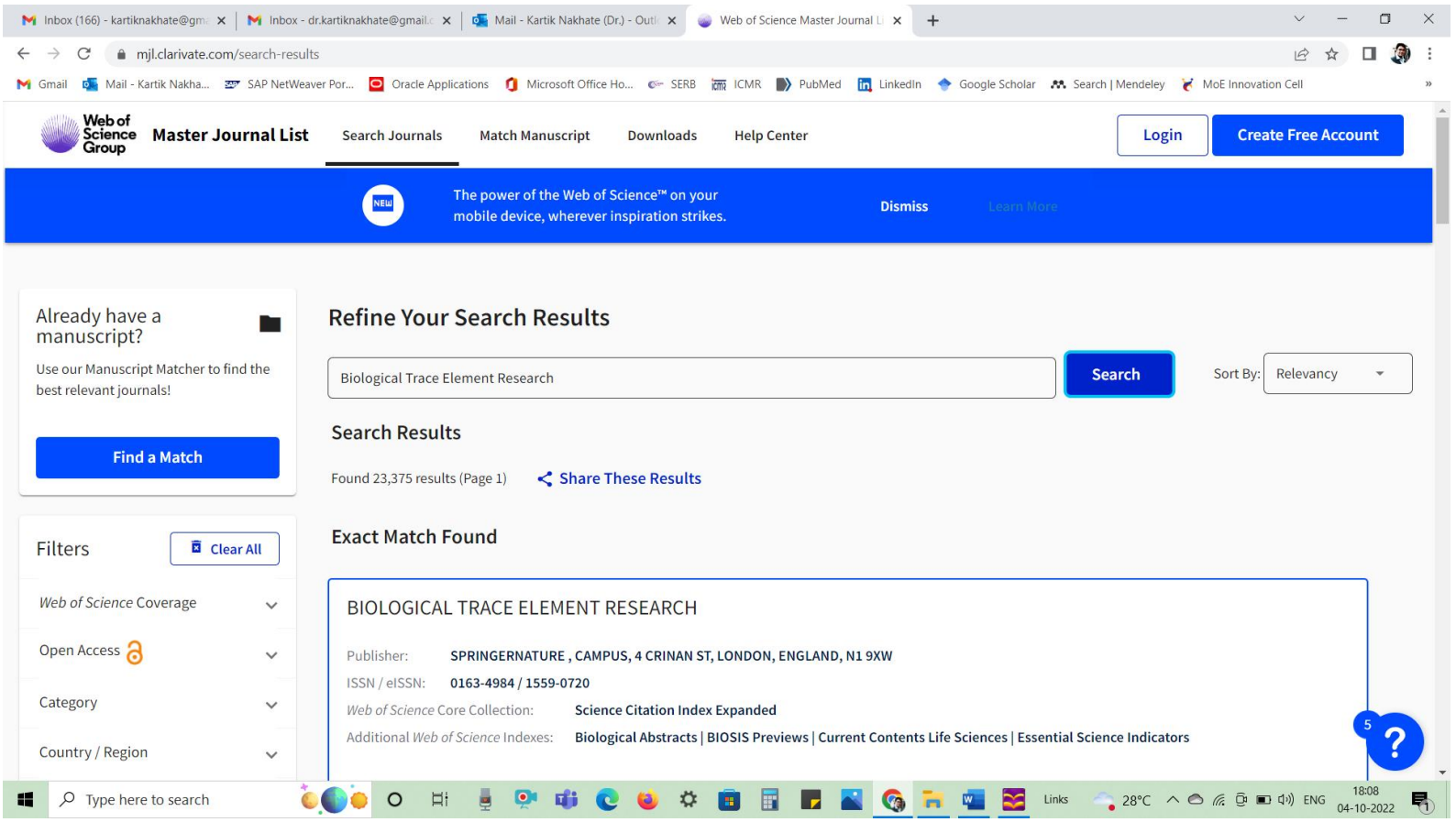
Introduction

Cisplatin (CP) is widely used as a chemotherapeutic agent in the treatment of several cancers including head, neck, testis, ovary, breast, bladder, esophageal, and cervical cancers. However, its clinical use is restricted due to its adverse effects like nephrotoxicity, ototoxicity, and neurotoxicity [1–4]. Accumulating evidences suggest a need for the development of therapeutic strategies to prevent the CP-associated organ toxicities while retaining its anticancer activity. Intravenous administration of amifostine (AMF) prior to CP injection is a currently available therapy against CP-induced nephrotoxicity. Therefore, research to identify and develop suitable nephroprotective adjuvants to chemotherapy is warranted.

Disulfiram (DSF) is in use since the last five decades as an aversion therapy for alcoholism [5]. Recently, DSF is re-emerging as an anticancer and chemopreventive agent for the treatment of various cancers [6, 7]. DSF has been reported

Published online: 01 March 2019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