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Differential response of antioxidant defense in HepG2 cells on exposure of Livotrit®, in a concentration dependent manner

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ABSTRACT

Livotrit®, a polyherbal formulation (Zandu, India) is commonly prescribed for liver health. The present study was undertaken to elucidate possible mechanism of antioxidant potential of Livotrit®. Livotrit® exhibited concentration dependent radical scavenging activity, inhibition of lipid peroxidation as well as activation and gene expression of antioxidant enzymes. Interestingly, lower concentration of Livotrit® (0.05%) significantly increased activities and gene expression of catalase, Glutathione reductase (GR) and Gluthathione peroxidase (GPx), while higher concentration of Livotrit® (0.5%) significantly increased antioxidant enzyme Heme-oxygenase 1(HO-1) and not catalase (CAT), GR and GPx. Transcription factor, Nuclear factor erythroid 2-related factor 2 (Nrf2) required for expression of catalase, GR, GPx and HO-1 was efficiently translocated into the nucleus at both concentrations. Inspite of this, concentration dependent activation of these enzymes was found to be mediated through miRNAs involved in regulation of their gene expression.

1. Introduction

Free radicals are continuously produced as natural by-products of normal metabolism and play an important role in redox signaling.[1] To counteract an overproduction of reactive oxygen species (ROS), cells have evolved a highly regulated endogenous antioxidant defense system including antioxidant enzymes and molecules. The first line of defence is executed by antioxidant enzymes namely Superoxide dismutase (SOD), CAT and GPx. In addition, inducible HO-1 is also considered as a major contributor of antioxidant defense during stress conditions.[2] The by-products of heme metabolism, catabolised by HO-1, act as potent antioxidants, thus making HO-1 a key player of antioxidant defense. Expression of HO-1 is regulated by Nrf2 which on activation translocates in the nucleus and binds to antioxidant response element (ARE) in the *ho-1* gene promoter and upregulates its expression. Since HO-1 is induced in response to various stimuli, targeted induction of this stress response enzyme is considered as an important therapeutic strategy for protection against various inflammatory and oxidative damage conditions.

A number of natural antioxidant compounds in food and plants have been demonstrated to be effective inducers of HO-1.[3] Due to their lesser side-effects, herbal formulations containing natural antioxidant compounds are becoming increasingly important in modern medicine and lifestyle disorders and thus are used as therapeutic agents in various diseases.[4] Livotrit®, a poly-herbal formulation is recommended as a daily health supplement for protection against hepatic damage. It is manufactured by Emami Limited, Kolkata and marketed by Zandu (India). It consists of the extracts of (i) *Boerhavia diffusa* (ii) *Tinospora cordifolia* (iii) *Eclipta alba* (iv) *Andropraphis paniculata* (v) *Picrorrhiza kurrao* (vi) *Embelia ribes* (vii) *Cichorium intybus* and (viii) *Amoora rohitaka*. Though, it is in use for a long period of time data about its biological activities is not available. Present study was undertaken to check the antioxidant activity of Livotrit® and elucidate its possible mechanism. The antioxidant activity of aqueous extract of Livotrit® was carried out using standard *in vitro* antioxidant assays and ability of livotrit® to modulate intracellular antioxidant defense and HO-1 was checked using HepG2 cells as a model system. We indeed observed strong

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