Meta-analysis of dragon’s blood resin extract as radio-protective agent

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ABSTRACT

In health sciences, many efforts had been made in past years to explore the radio-protective agents from natural resources due to rapid exposure of radiations to environment such as space traveling, radiotherapy and largely growing telecommunication industry. It becomes crucial to find natural sources for radio-protection. In correspondence, dragon’s blood (DB) is a traditional Chinese medicinal plant that possesses great medicinal values due to the presence of several phenolic compounds. For a long time, DB has been used in treatment of blood stasis, inflammation, oxidative stress, immune suppression and tumors, but recently it has been extensively used as radio-protective agent. There is no comprehensive review on radio-protective characterization of DB resin extract in literature. In our review, an attempt has been made to highlight unique and inherent radio-protection in liver, brain, kidney, lung, spleen and cerebrum. This review will help people in exploring the radioactive protectants from natural resources.

1. Introduction

Radiation exposure is increasing exponentially day by day either accidentally or by therapeutic applications. World is facing natural background radiations like cosmic radiations coming from sun and stars, terrestrial radiations from earth itself as soil and rocks contain uranium and radium, air contains radon and water contains small amounts of dissolved uranium and thorium. Hot springs are also natural radiation sources; it effects radio-sensitivity on the inhabitants of these areas[1]. Radiation therapies like fluoroscopy, computed tomography and traditional radiography have potential to cause radiation burns. Some other sources include industrial radiography, atomic power plant, and travelling to space. The ionizing radiations trigger reactive oxygen species (ROS) production. ROS damage the cells by reacting with macromolecules causing cell dysfunction, mortality and ultimately tissue damage. They also interact and damage DNA, making a cell cancerous. Although some radio-protective drugs like amifostine[2,3] and genistein[4] are available, they have some unfavorable properties, for example amifostine has a short plasma lifetime, so has to administer every day[5], causes emesis[6], and wrong concentration of these drugs can increase the damage caused by ROS to the cells. Some phenolic acids (quinic acid and chlorogenic acid) have been assessed for their protective ability against radiation-induced DNA damage[7], but it’s crucial to find natural source of radio-protective compounds such as dragon’s blood (DB) and its extract to minimize radiation havocs by its phenolic compounds.

DB is a bright red resin[8] due to presence of flavlyium chromophores[9], which has ethnomedicinal properties because it contains phenolic compounds[10,11,12]. The blood-red sap of Croton lechleri was found to contain proanthocyanidins as a major constituent which accounted for up to 90% of the dried weight[12]. DB is a rare and precious traditional medicine used by different cultures[13]. It is obtained from different species of four distinct plant genera: Croton, Dracaena, Daemonorops, and Pterocarpus. The origin of DB is believed to be from Indian ocean island of Socotra but representatives of this genus have also survived in woodlands on dry margins of the Tethys tropical forest[14]. DB has some active compounds (loureirin A, loureirin B) that show medicinal activities (Figure 1).

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Such as steroidal saponin[16] and icogenin that showed cytotoxic in vitro. The present review recapitulates current knowledge concerning gastroprotective activity without causing toxicity[25]. Its effects diarrheal, immunomodulatory, anti-ulcer like.

DB resin extract constitutes flavans[18], sterols and triterpenoids[19]. It has anti-mutagenic[20,21], antitumor activity particularly leaf of D. draco[22], which is a useful cancer chemopreventive or chemotherapeutic agent for colon and kidney cancers[22], as well as anti-hemorrhagic[23], anti-oxidative, anti-inflammatory[24], anti-diarrheal, immunomodulatory, anti-ulcer like Croton urucurana which has visceral antiinociceptive property whose bark exerts gastroprotective activity without causing toxicity[25]. Its effects appear to involve sulphuridyl compounds, increasing mucus production and reducing gastric acidity[26]. DB is also popular for its wound-healing properties[27-29]. Bark of DB is potent inhibitor of chloride secretion and fluid accumulation induced by cholera toxin[30]. DB from Croton urucurana Baill. (Euphorbiaceae) bark has antifungal activity against dermatophytes[31]. Its methanolic extract shows antibacterial activity[32]. Sap and taspine from Croton lechleri inhibit cell proliferation and are possible anticancer agents[33]. Tissue distribution and effects of their active components loureirin A and loureirin B have also been investigated in liver, kidney, lung, spleen, heart and cerebrum[34].

3. Bioreducing properties

Reducing power of a compound is its ability to donate its electron to other chemical species. So, it acts as antioxidant. Some compounds in DB have been tested for their reducing power.Reducing power of any compound can be tested by utilizing it for nanoparticle synthesis. It is well-known that natural plants have potential to reduce the magnetic and metallic nanoparticles and are considered an efficient environment-friendly route to prepare nanomaterials with specific properties[35]. The clear difference before and after reaction decrease in the height from 30% to 60% of the peaks showed that these compounds are used in bioreduction process. The change in the height of peaks of abovementioned compounds indicates that these compounds are possibly involved in the formation of nanoparticles and act as capping agent as shown in Figure 3.

4. Radio-protective effect on bone marrow

Bone marrow is a spongy flexible tissue inside bones. It produces majority of blood cells and cartilage and is a most radiation sensitive organ in the body[36]. Radiations cause myelosuppression and reduce bone growth in young children. DB and dragons blood resin extract (DBE) (its 50% ethanol extracts) have potential radio-protective properties in mouse bone marrow after ⁶⁰Co γ-ray’s exposure, which supports their candidature as a potential radio-protective and anti-oxidant agent against DNA damage[10,37]. Cytogenetic studies showed that DB and DBE treatment were highly effective in decreasing both simple and complex chromosomal aberrations. Furthermore, DB and DBE could sooth the damages to erythropoiesis, in decreasing both simple and complex chromosomal aberrations in mouse bone marrow have been shown in Figure 4.

5. Radio-protective mechanism of DB against ROS

ROS are oxygen based free radicals which majorly include peroxides, superoxide, hydroxyl radicals and singlet oxygen. They are natural byproducts of cellular metabolism but stress conditions result in dramatic increase in ROS production. ROS induced by whole-body irradiation, has markedly damaging effects on nucleic acid, lipids and proteins. It attacks the plasma membrane of cells and effects lipids by inducing peroxidation. They also affect the antioxidant system that results in oxidative stress damage, also increase the level of malondialdehyde (MDA) and NO in serum. DB

**Figure 1.** Main phenolic compounds of DB (patent of BIT&GY: a DB extract and its preparation method and uses, Patent Application No. 200810182971.7)[15].

**Figure 2.** Summary of DB’s overall effects on different organs and cells.
and DBE markedly increase the glutathione (GSH) hormone levels of blood and significantly reduce MDA and NO. It also significantly increases the superoxide dismutase (SOD) and catalase which are antioxidant enzymes to increase the antioxidant activity in serum. It collectively indicates that DB and DBE increase the antioxidant defense mechanism and protect the animals from radiation-induced cellular damages[11]. The fruit of this plant also has radical scavenging efficiency and can be used as promising antioxidant[40].

It is already reported that *D. draco* leaf extract is a promising antioxidant agent which strongly protects the erythrocyte membrane from hemolysis[41] as demonstrated in Figure 5.

6. Radio-protective effect on megakaryocyte cell

Megakaryocytes are bone marrow cells with large nucleus and are responsible for the production of platelets that are necessary...
for hemostasis. Hematopoietic cells give rise to myeloid cells (megakaryocytes). Ionizing radiations decrease the CFU-S proportion in bone marrow. The $^{60}$Co $\gamma$-irradiation reported to cause significant decrease in peripheral blood and reduction of hematopoietic cells in bone marrow. But treatment with DBE significantly accelerated the recovery of peripheral blood cells and particularly platelet after irradiation exposure. DBE increases the number of hematopoietic cells and reduces apoptosis. The effect of DBE on Mo7e cells survival and proliferation is likely associated with the activation of extracellular signal-regulated kinase[42]. Morphological changes in bone marrow of different test groups have been shown in Figure 6.

**Figure 6.** Bone marrow histology on Day 23 exposed to irradiation in various groups. The pathological section of the sternum medulla in the control group (A), irradiation group (B), GCSF group (C), DBE group (D). Both GCSF and DBE significantly improved the morphology of bone marrow histology[42].

### 7. Anti-thrombin activity on lungs and cerebrum

Thrombin converts fibrinogen into fibrin and helps fibrin in clot formation. In lungs, it causes inflammation by induction of adhesion molecules that lead to injury[43]. Neuroinflammation and apoptosis also occur due to increased level of prothrombin[44]. Exposure to radiations chance to develop thrombosis[45] can lead to tissue damage, stroke or in severe case even death.

DBE has shown to have antithrombotic activity as it effects platelet aggregation and anticoagulation activities. Mice treated with ethanol extract A (EA) fraction of DB had less thrombus in lungs and cerebrums; EA had antithrombotic activity[15]. The primary effect was inhibition of platelet aggregation, by decreasing fibrinogen levels, increasing prothrombin time and activated partial thromboplastin time[46] (Figure 7).

### 8. Radio-protective effect on liver

Liver is a vital organ, which plays an important role in metabolism, detoxification and hormonal production. It is a well-known fact that radiations produce ROS. Liver disorders like inflammation, metabolic disorder and proliferative liver diseases are majorly associated with ROS production[47]. It effects hepatocytes, proteins, lipids and DNA, which causes cell killing and tissue damage of organs[48]. As reported by Ran et al., DBE had considerable protective properties against ROS damage. As a result, liver histology of the irradiation-only group, showed hepatocyte edema, inflammatory cell infiltration and necrosis. The liver histology of mice treated with DB and DBES together with gamma irradiation exposure showed better cellular architecture than that of the irradiation-only group[11]. Draconis resina ethyl acetate extract inhibits inflammatory responses via the suppression of ROS production[49]. Effect of DB on liver histology is shown in Figure 8.
9. Radio-protective effect on spleen

Spleen plays an important role in removal of old erythrocytes and in providing immunity. The ROS produced by irradiation, cause cell killing and tissue damage of organs[50]. Exposure to radiations led to extramedullary hematopoiesis and decreases lymphocytes in the white pulp, but spleen histology after DB and DBE treatment showed very less radiation-induced damage and improved tissue morphology[11] in Figure 9.

Figure 9. Increase of dragon's blood in extramedullary haematopoiesis and decrease in the lymphocytes in the white pulp[11]. A: Irradiation-only group, showing an increase in extramedullary hematopoiesis and a decrease in the lymphocytes in the white pulp; B: DB group[11].

10. Radio-protective effect on brain

Brain is an organ having extensive metabolism[51] and also is not well equipped with antioxidant defenses, so ROS, released by inflammatory cells, threaten tissue viability in zone of ischemic core[52]. Lipid peroxidation caused by free radicals is the important pathogenesis of ischemic brain damage as large amount of free radicals are being produced in this process[53]. Cerebral edema is one of the basic pathological change of ischemic cerebrovascular disease in which cerebral water content and cerebral index increase. Different studies showed positive influence of DB on brain tissues. DB decreases cerebral index and alleviates cerebral edema significantly, also improves the antioxidant activity and decreases lipid peroxidation[54]. So, DB has radioprotective effects in radiation-induced neural injury, also can reduce the cerebral infarction. DB is a potential therapeutic agent for neurodegenerative diseases[55] (Figure 10).
11. DB effect on neurons

Neurons transmit information via electrical or chemical signals and are core component of central nervous system. Neurons are non-proliferative cells so they were thought to be resistant to radiations[56] but radiations induce neural hypofunction that can lead to brain dysfunction[57]. Neuronal degeneration is the loss of structure and function of neurons. It involves many other incurable diseases like Alzheimer’s[58] and Parkinson’s disease, mainly caused by excessive ROS production[59]. The focus of researchers is the antioxidants to cure neural degeneration because of their ability to fight ROS. Medicinal herbs are catching attention as a major source of antioxidants[60]. DB is traditional Chinese medicinal plant. Bioactivities and phytochemical studies showed some effective constituents of Chinese DB that were found to have potential therapeutic properties for neurodegenerative diseases[55]. DB has analgesic effect. It silences pain signaling pathways due to the inhibition of capsaicin-induced transient receptor potential vanilloid 1 (TRPV1) receptor currents in dorsal root ganglion neurons. Wei et al. studied the effects of DB and its components (cochinchinenin A, cochinchinenin B, loureririn B) on capsaicin-induced TRPV1 receptor currents in acutely dissociated dorsal root ganglion neurons. The results indicated that the concentration dependently and synergistically reduced capsaicin-induced TRPV1 receptor currents and increased the IC50 value of capsaicin[61]. Louririn B found to be effective in modulating sodium currents in trigeminal ganglion neurons[62]. DB dropping pills could improve the neurological function significantly and reduce cerebral infarct volume of focal cerebral ischemia[54].

12. Future prospectives

Dracaena cinnabari occupies only 5% of its current potential habitat. This potential habitat expected to reduce with 45% by 2080 because of a predicted increased aridity. Thereby, increasing permanent settlements and grazing pressure, should also be discouraged[63,64]. More insights are required on the formation mechanism of DB which enables its production in a sustainable way without destroying the endangered trees and environment[65]. 70%–80% of the stroke incidence accounts for ischemic stroke so its prevention and treatment are necessary without delay. Therefore, more focused theoretical research and practical applications on complicated mechanisms and effective drugs study of ischemic cerebral vascular disease are needed. The precise molecular mechanisms of these antithrombotic compounds that prevent platelet aggregation, extrinsic and intrinsic coagulation pathways, need to be determined in future studies. There is a need to screen active components of DB to explore maximum efficacy in humans for radioprotection. The exact role of DB in wound healing regarding its effect on mediator’s synthesis stimulation or inhibition is still missing so further studies are required. We need to investigate therapeutic potential of purified compounds of DB as compared to its crude extract.

Conflict of interest statement

We declare that we have no conflict of interest.

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