Journal of Coastal Life Medicine

journal homepage: www.jclmm.com

Review article https://doi.org/10.12980/jclm.5.2017J7-75

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

Subaika Mahmood[1], Toseef Fatima[1], Hina Zulfaqar[1], Romana Saher[1], Muhammad Rafiq[1], Abdul Rehman[1], Rongji Dai[2*], Muhammad Ashfaq[1], Murtaza Hasan[1*]

[1]*Department of Biochemistry & Biotechnology (Baghdad-ul-Jadeed Campus), the Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan*

[2]*School of life Sciences, Beijing Institute of Technology, Beijing, 100081, People's Republic of China*

ARTICLE INFO

Article history:
Received 27 Apr 2017
Received in revised form 26 May, 2nd revised form 13 Jun 2017
Accepted 15 Jul 2017
Available online 30 Aug 2017

Keywords:
Dragon's blood
Bioreduction
Radioprotection
Oxidative stress
Immune suppression

ABSTRACT

In health sciences, much 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 accidently 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 flavylium chromophores[9], which has ethnomedicinal properties because it contains phenolic compounds[10,11]. 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).

*Corresponding author: Murtaza Hasan, Department of Biochemistry & Biotechnology (Baghdad-ul-Jadeed Campus), the Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan.
Tel/Fax: +92-062-9255574
E-mail: murtazapirachaiub@gmail.com
Rongji Dai, School of life Sciences, Beijing Institute of Technology, Beijing, 100081, People's Republic of China.
E-mail: dairongji@bit.edu.cn
The journal implements double-blind peer review practiced by specially invited international editorial board members.

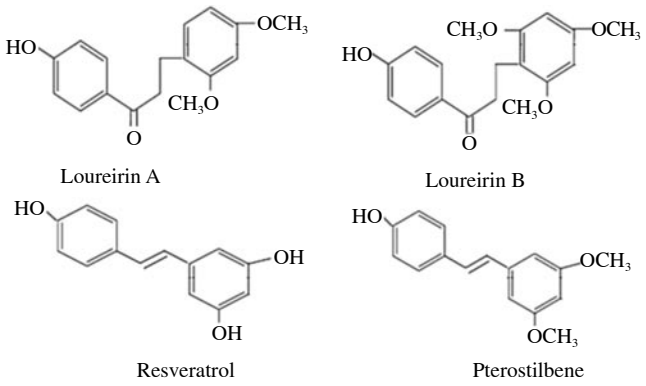


Figure 1. Main phenolic compounds of DB (patent of BIT&GY: a DB extract and its preparation method and uses, Patent Application No. 200810182971.7)[15].

But there are some components of *Dracaena draco* (*D. draco*) such as steroidal saponin[16] and icogenin that showed cytotoxic effects. Icogenin was found to be a cytotoxic compound with growth inhibition activity by causing the induction of apoptosis[17].

The present review recapitulates current knowledge concerning *in vitro* and *in vivo* radio-protective characterization before clinical applications of this resinous medicine derived from *Dalbergia cochinchinensis*. The overall sketch of radio-protective potential of DB resin extract has been shown in Figure 2.

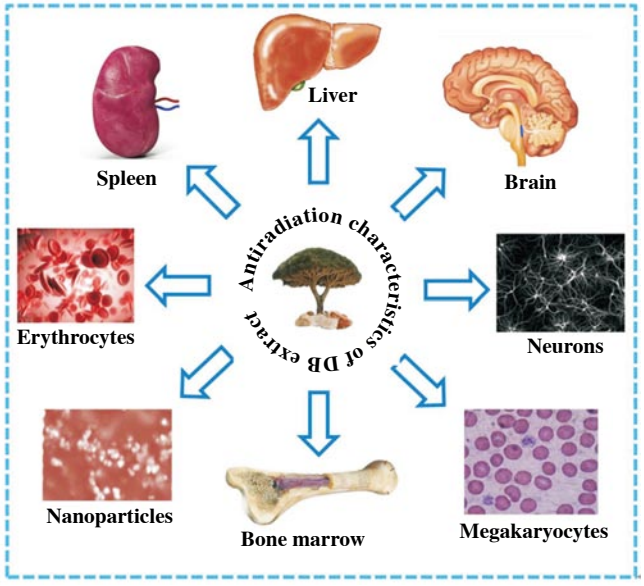


Figure 2. Summary of DB's overall effects on different organs and cells.

2. Ethno-medicinal properties

DB resin extract constitutes flavans[18], sterols and triterpenoids[19]. It has anti-mutagenic[20,21], antitumor activity particularly leaf of *D. draco*, 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 antinociceptive property whose bark exerts gastroprotective activity without causing toxicity[25]. Its effects appear to involve sulphydryl 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 ^{60}Co 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, minimize radiation induced genomic instability of bone marrow cells, enhance recovery and improve survival from severe radiation-induced myelosuppression like recombinant human granulocyte colony-stimulating factor (GCSF), by decreasing the frequency of micronuclei[38], potentially providing a protection for living body exposed with ionizing irradiation. Radiation-induced 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

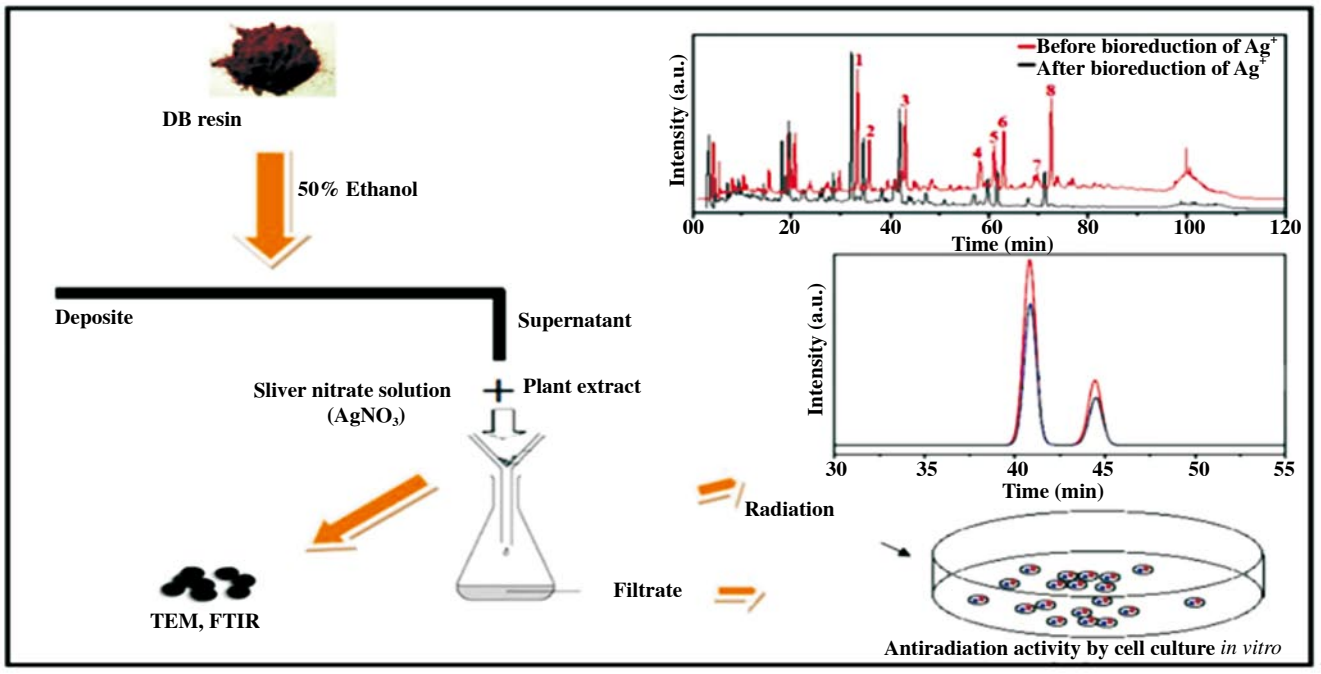
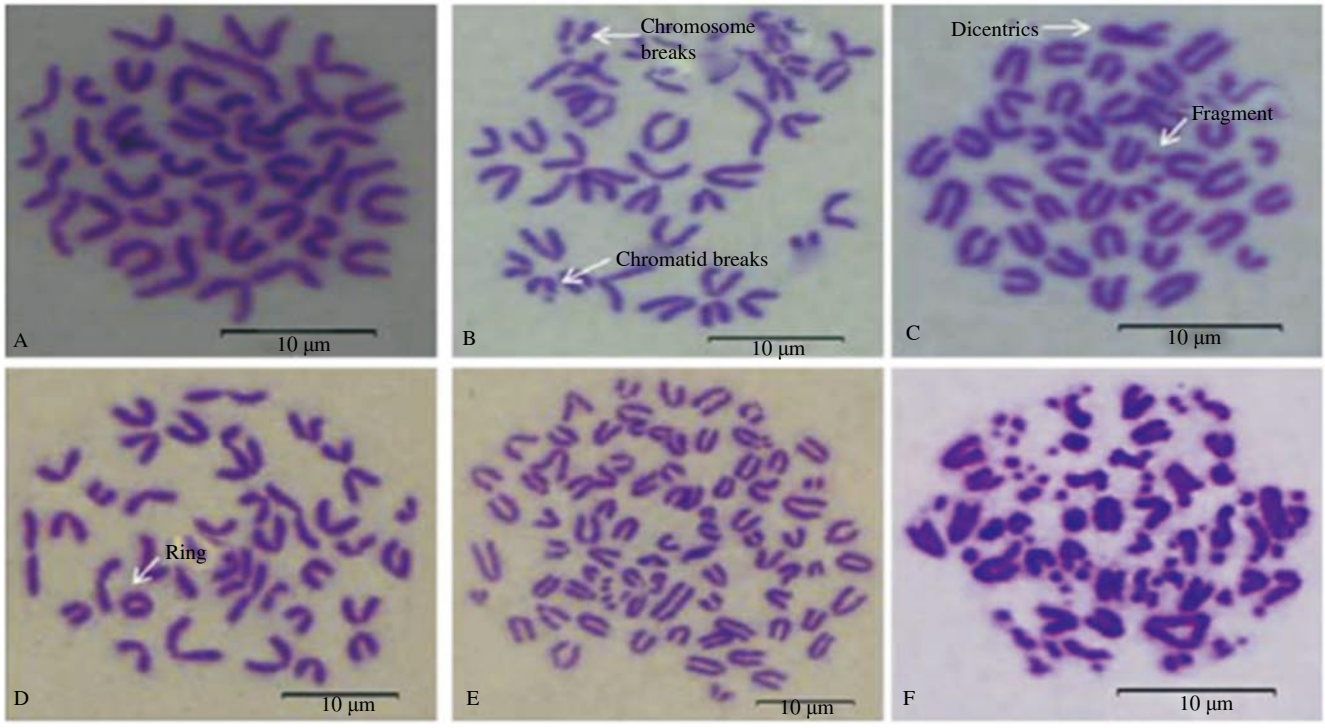


Figure 3. Schematic representation procedure of nanoparticles synthesis and antiradiation activity of DB resin extract.
Inset chromatographic profiles of DB extracts before and after bioreduction of silver ions by plant extract and bioreduction of silver ions by loureirin A and loureirin B before and after reaction[35]. FTIR: Fourier-transform infrared spectroscopy.

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



Figue 4. Radiation-induced chromosomal aberrations in mouse bone marrow.
A: Normal chromosome; B: Breaking of chromatid and chromosome (arrow); C: Dicentrics and fragmentation (arrow); D: Ring formation in chromosomes (arrow); E: Polyploidy in chromosomes; F: Severely damaged chromosomes in cells[39].

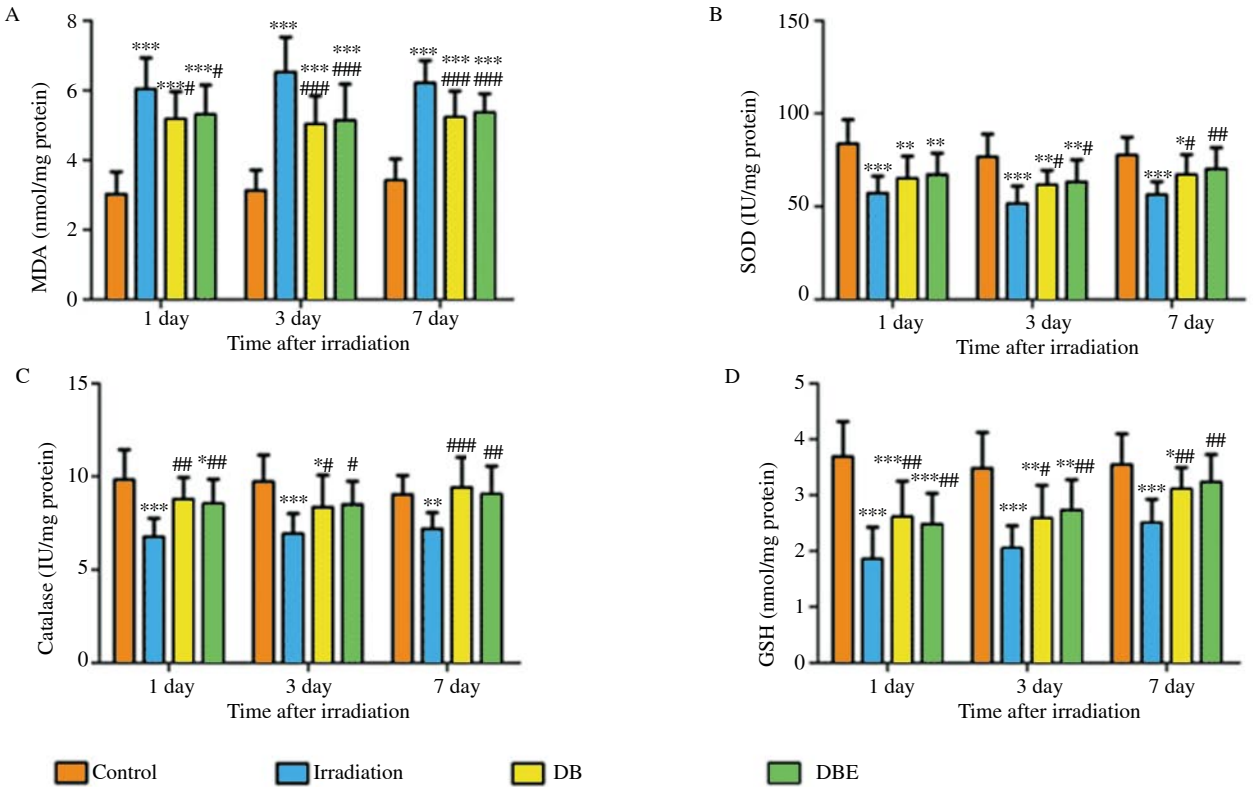


Figure 5. Effects of DB and DBE on the liver antioxidant status of irradiated mice.
The bars represent standard deviation. DB and DBE-treated groups showed significantly lower levels of MDA (A), higher activity of catalase (C), and even higher levels of GSH (D) in the liver on Days 1, 3, 7 after irradiation. They also revealed markedly higher activity of SOD (B) on Days 3 and 7[11].

for hemostasis. Hematopoietic cells give rise to myeloid cells (megakaryocytes). Ionizing radiations decrease the CFU-S proportion in bone marrow. The ^{60}Co γ-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.

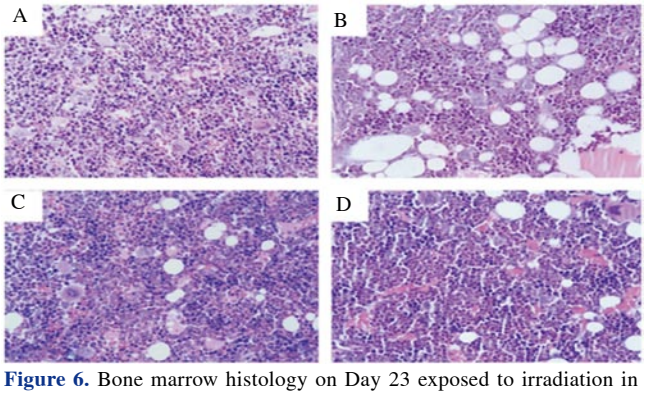


Figure 6. Bone marrow histology on Day 23 exposed to irradiation in various groups.
The pathological section of the sternum medulla in the control group (A), irradiation group (B), GCSF group (C), DBE group (D). Both GCSF and DBE significantly improved the morphology of bone marrow histology[42].

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.

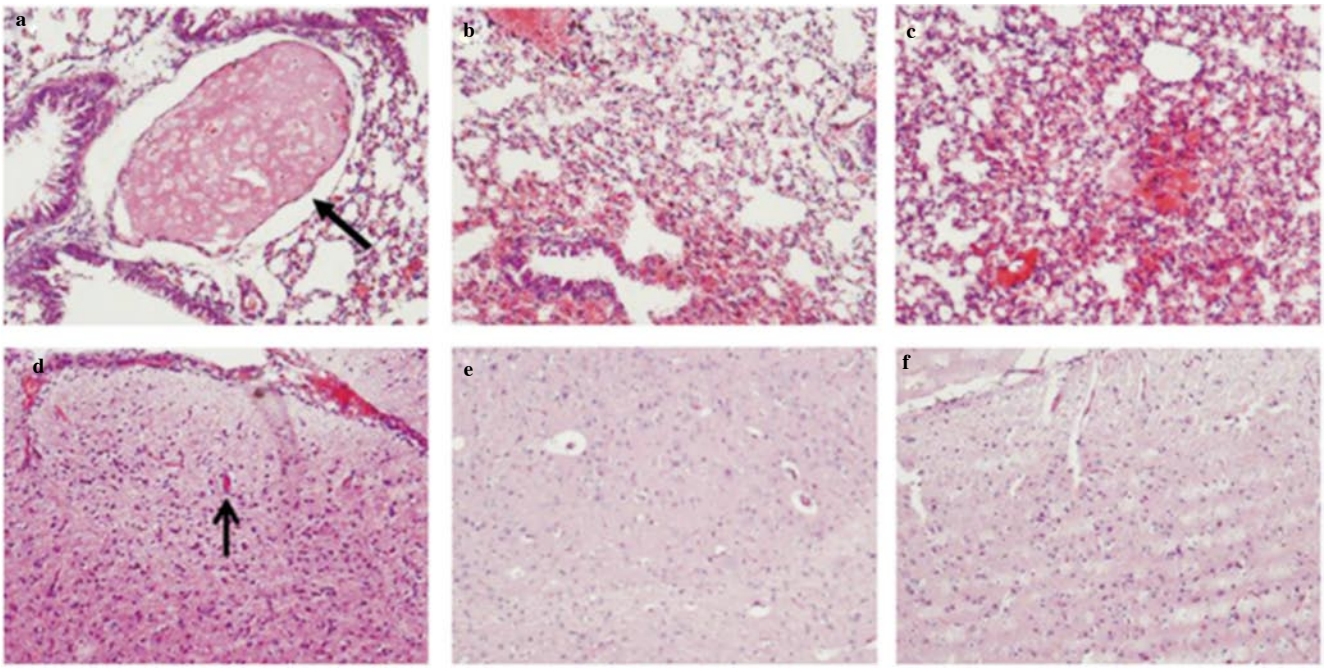


Figure 7. Effect of dragons blood on pathological changes, blood hemorrhage, thrombotic and blood stasis in mice lungs[15].
Effect of EA and precipitate B in pathological photomicrograph of mice lung and cerebrum (a and d), mice treated with EA had less thrombus in lungs and cerebrums (b and e), mice treated with precipitate B showed serious pathological changes of hemorrhage and blood stasis in lungs (c and f) indicating that EA had positive antithrombotic effects *in vivo*[15].

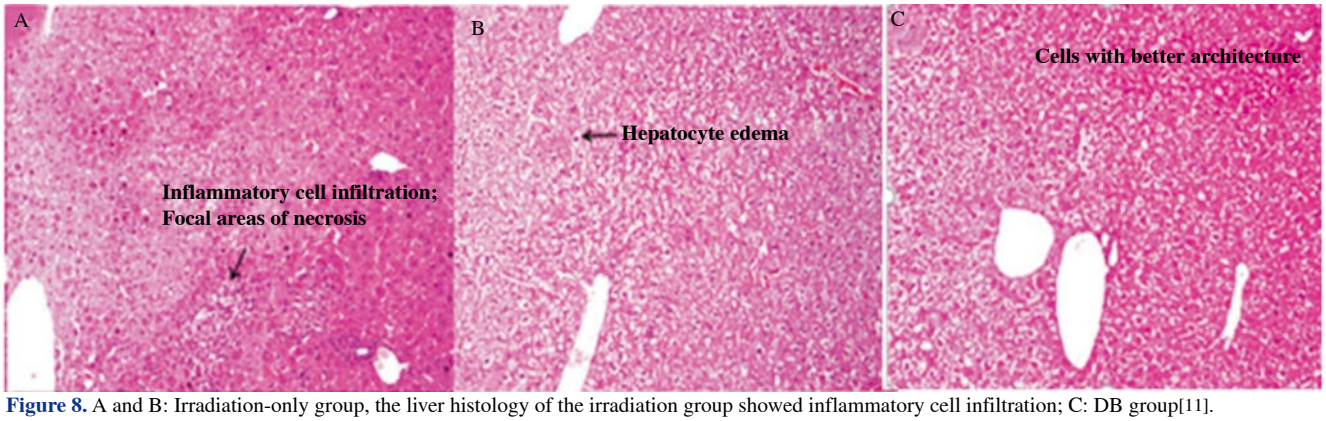


Figure 8. A and B: Irradiation-only group, the liver histology of the irradiation group showed inflammatory cell infiltration; C: DB group[11].

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.

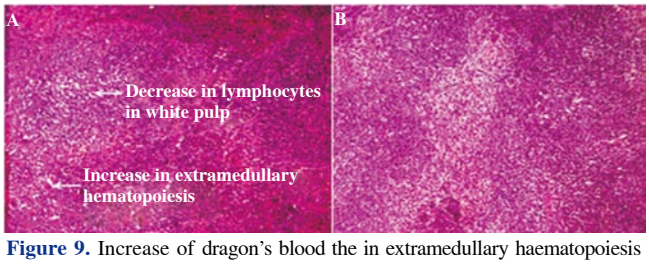


Figure 9. Increase of dragon's blood the in extramedullary haematopoiesis and decrease in the lymphocytes in the white pulp[11]. A: Irradiation-only group, showing an increase in extramedullary hematopoiesis and a decrease in the lymphocytes in the white pulp; B: DB group[11].

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).

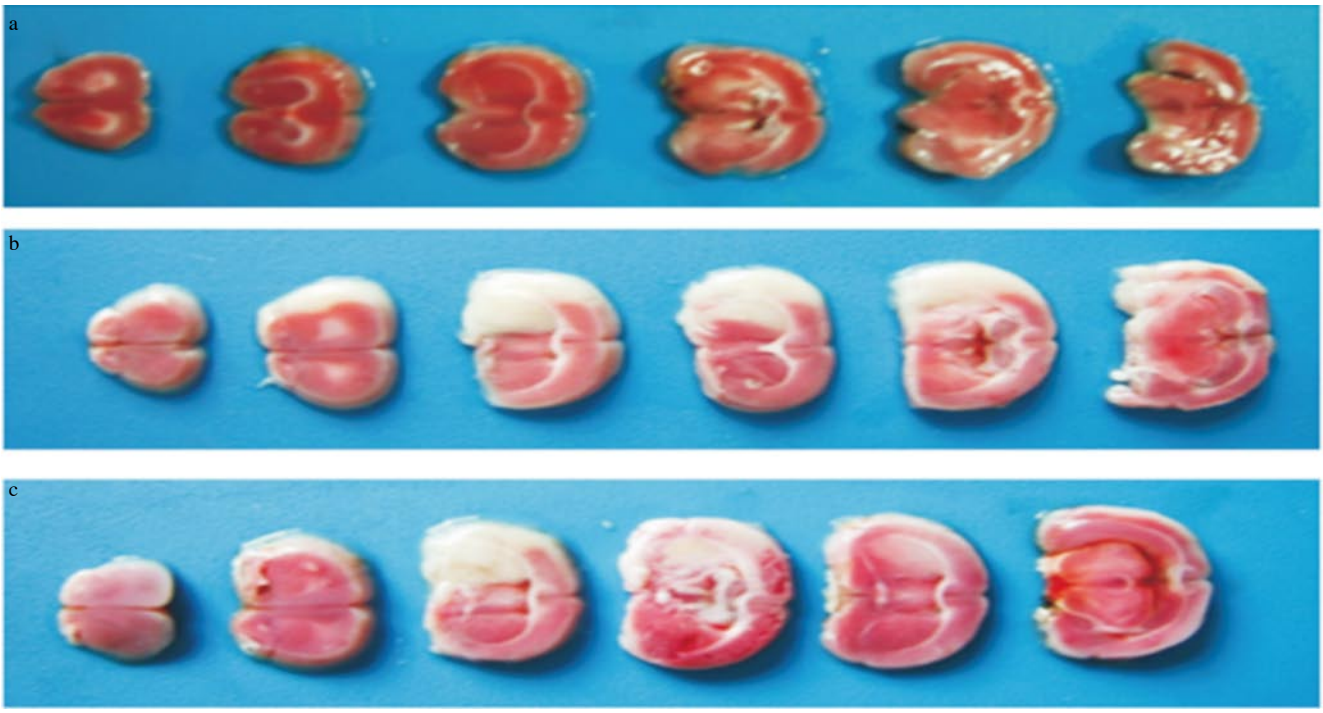


Figure 10. Effect of DB dropping pills on cerebral infarction size in middle cerebral artery occlusion rats model.
a: Sham operation group; b: Model group; c: DB dropping pills high group[54].

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, loureirin 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 IC_{50} value of capsaicin[61]. Loureirin 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.

Acknowledgments

We are thankful to Professor Yulin Deng for providing information on antiradiation characteristics of DB resin extract.

References

[1] Masoomi JR, Mohammadi S, Amini M, Ghiassi-Nejad M. High

background radiation areas of Ramsar in Iran: evaluation of DNA damage by alkaline single cell gel electrophoresis (SCGE). *J Environ Radioact* 2006; **86**: 176-86.

[2] Vesna J, Danica J, Kamil K, Viktorija DS, Silva D, Sanja T, et al. Effects of fullerenol nanoparticles and amifostine on radiation-induced tissue damages: histopathological analysis. *J Appl Biomed* 2016; **14**: 285-97.

[3] Yang X, Ding Y, Ji T, Zhao X, Wang H, Zhao X, et al. Improvement of the *in vitro* safety profile and cytoprotective efficacy of amifostine against chemotherapy by PEGylation strategy. *Biochem Pharmacol* 2016; **108**: 11-21.

[4] Song L, Ma L, Cong F, Shen X, Jing P, Ying X, et al. Radioprotective effects of genistein on HL-7702 cells via the inhibition of apoptosis and DNA damage. *Cancer Lett* 2015; **366**: 100-11.

[5] Asna N, Lewy H, Ashkenazi IE, Deutsch V, Peretz H, Inbar M, et al. Time dependent protection of amifostine from renal and hematopoietic cisplatin induced toxicity. *Life Sci* 2005; **76**: 1825-34.

[6] Kleinsasser N. Amifostine is an effective radioprotector for people with head and neck cancer but has nausea and emesis side-effects. *Evidence-based Oncol* 2001; **2**: 107-8.

[7] Cinkilic N, Cetintas SK, Zorlu T, Vatan O, Yilmaz D, Cavas T, et al. Radioprotection by two phenolic compounds: Chlorogenic and quinic acid, on X-ray induced DNA damage in human blood lymphocytes *in vitro*. *Food Chem Toxicol* 2013; **53**: 359-63.

[8] Edward HGM, de Oliveira LFC, Quye A. Raman spectroscopy of coloured resins used in antiquity: dragon's blood and related substances. *Spectrochim Acta A Mol Biomol Spectrosc* 2001; **57**: 2831-42.

[9] Sousa MM, Melo MJ, Parola AJ, Seixas de Melo JS, Catarino F, Pina F, et al. Flavylium chromophores as species markers for dragon's blood resins from *Dracaena* and *Daemonorops* trees. *J Chromatogr A* 2008; **1209**: 153-61.

[10] Xin N, Li YJ, Li X, Wang X, Li Y, Zhang X, et al. Dragon's blood may have radioprotective effects in radiation-induced rat brain injury. *Radiat Res* 2012; **178**: 75-85.

[11] Ran Y, Wang R, Gao Q, Jia Q, Hasan M, Awan MUF, et al. Dragon's blood and its extracts attenuate radiation-induced oxidative stress in mice. *J Radiat Res* 2014; **55**: 699-706.

[12] Cai Y, Evans FJ, Roberts MF, Phillipson JD, Zenk MH, Gleba YY. Polyphenolic compounds from *Croton lechleri*. *Phytochemistry* 1991; **30**: 2033-40.

[13] Cui JL, Wang CL, Guo SX, Xiao PG, Wang ML. Stimulation of dragon's blood accumulation in *Dracaena cambodiana* via fungal inoculation. *Fitoterapia* 2013; **87**: 31-6.

[14] Habrova H, Cermak Z, Pavlis J. Dragon's blood tree – threatened by overmaturity, not by extinction: dynamics of a *Dracaena cinnabari* woodland in the mountains of Soqotra. *Biol Conserv* 2009; **142**: 772-8.

[15] Xin N, Li YJ, Li Y, Dai RJ, Meng WW, Chen Y, et al. Dragon's blood extract has antithrombotic properties, affecting platelet aggregation functions and anticoagulation activities. *J Ethnopharmacol* 2011; **135**: 510-4.

[16] Mimaki Y, Kuroda M, Ide A, Kameyama A, Yokosuka A, Sashida Y. Steroidal saponins from the aerial parts of *Dracaena draco* and their cytostatic activity on HL-60 cells. *Phytochemistry* 1999; **50**: 805-13.

[17] Hernández JC, León F, Quintana J, Estévez F, Bermejo J. Icogenin, a new cytotoxic steroidal saponin isolated from *Dracaena draco*. *Bioorg Med Chem* 2004; **12**: 4423-9.

[18] González AG, León F, Hernández JC, Padrón JI, Sánchez-Pinto L, Barrera JB. Flavans of dragon's blood from *Dracaena draco* and *Dracaena tamaranae*. *Biochem Sys Ecol* 2004; **32**: 179-84.

[19] Masaoud M, Schmidt J, Adam G. Sterols and triterpenoids from *Dracaena cinnabari*. *Phytochemistry* 1995; **38**: 795-6.

[20] Rossi D, Guerrini A, Maietti S, Bruni R, Paganetto G, Poli F, et al. Chemical fingerprinting and bioactivity of Amazonian Ecuador *Croton lechleri* Müll. Arg. (Euphorbiaceae) stem bark essential oil: a new functional food ingredient? *Food Chem* 2011; **126**: 837-48.

[21] Rossi D, Guerrini A, Paganetto G, Bernacchia G, Conforti F, Statti G, et al. *Croton lechleri* Müll. Arg. (Euphorbiaceae) stem bark essential oil as possible mutagen-protective food ingredient against heterocyclic amines from cooked food. *Food Chem* 2013; **139**: 439-47.

[22] Valente MJ, de Pinho PG, Henrique R, Pereira JA, Carvalho M. Further insights into chemical characterization through GC–MS and evaluation for anticancer potential of *Dracaena draco* leaf and fruit extracts. *Food Chem Toxicol* 2012; **50**: 3847-52.

[23] Esmeraldino LE, Souza AM, Sampaio SV. Evaluation of the effect of aqueous extract of *Croton urucurana* Baillon (Euphorbiaceae) on the hemorrhagic activity induced by the venom of *Bothrops jararaca*, using new techniques to quantify hemorrhagic activity in rat skin. *Phytomedicine* 2005; **12**: 570-6.

[24] Choy CS, Hu CM, Chiu WT, Lam CSK, Ting Y, Tsai SH, et al. Suppression of lipopolysaccharide-induced of inducible nitric oxide synthase and cyclooxygenase-2 by Sanguis Draconis, a dragon's blood resin, in RAW 264.7 cells. *J Ethnopharmacol* 2008; **115**: 455-62.

[25] Rao VS, Gurgel LA, Lima-Júnior RCP, Martins DTO, Cechinel-Filho V, Santos FA. Dragon's blood from *Croton urucurana* (Baill.) attenuates visceral nociception in mice. *J Ethnopharmacol* 2007; **113**: 357-60.

[26] Wolff Cordeiro K, Aparecida Pinto L, Nazari Formagio AS, Faloni de Andrade S, Leite Kassuya CA, de Cássia Freitas K. Antiulcerogenic effect of *Croton urucurana* Baillon bark. *J Ethnopharmacol* 2012; **143**: 331-7.

[27] Gupta D, Bleakley B, Gupta RK. Dragon's blood: botany, chemistry and therapeutic uses. *J Ethnopharmacol* 2008; **115**: 361-80.

[28] Pieters L, De Bruyne T, Van Poel B, Vingerhoets R, Totté J, Vanden Berghe D, et al. *In vivo* wound healing activity of dragon's blood (*Croton* spp.), a traditional South American drug, and its constituents. *Phytomedicine* 1995; **2**: 17-22.

[29] Rossi D, Bruni R, Bianchi N, Chiarabelli C, Gambari R, Medici A, et al. Evaluation of the mutagenic, antimutagenic and antiproliferative potential of *Croton lechleri* (Muell. Arg.) latex. *Phytomedicine* 2003; **10**: 139-44.

[30] Fischer H, Machen TE, Widdicombe JH, Carlson TJS, King SR, Chow JWS, et al. A novel extract SB-300 from the stem bark latex of *Croton lechleri* inhibits CFTR-mediated chloride secretion in human colonic epithelial cells. *J Ethnopharmacol* 2004; **93**: 351-7.

[31] Gurgel LA, Sidrim JJC, Martins DT, Filho VC, Rao VS. *In vitro* antifungal activity of dragon's blood from*Croton urucurana* against dermatophytes. *J Ethnopharmacol* 2005; **97**: 409-12.

[32] Peres MTL, Monache FD, Cruz AB, Pizzolatti MG, Yunes RA. Chemical composition and antimicrobial activity of *Croton urucurana* Baillon (Euphorbiaceae). *J Ethnopharmacol* 1997; **56**: 223-6.

[33] Montopoli M, Bertin R, Chen Z, Bolcato J, Caparrotta L, Froldi G. *Croton lechleri* sap and isolated alkaloid taspine exhibit inhibition

against human melanoma SK23 and colon cancer HT29 cell lines. *J Ethnopharmaco* 2012; **144**: 747-53.

[34] Zhao H, Chen Z. An HPLC-ESI-MS method for analysis of loureirin A and B in dragon's blood and application in pharmacokinetics and tissue distribution in rats. *Fitoterapia* 2013; **86**: 149-58.

[35] Hasan M, Iqbal J, Awan U, Saeed Y, Ranran Y, Liang Y, et al. Mechanistic study of silver nanoparticle's synthesis by dragon's blood resin ethanol extract and antiradiation activity. *J Nanosci Nanotechnol* 2015; **15**: 1320-6.

[36] Farese AM, Cohen MV, MacVittie TJ. Recombinant human G-CSF enhances recovery and improves survival from severe radiation-induced myelosuppression. In: Molineux G, Foote M, Arvedson T, editors. *Twenty years of G-CSF: clinical and nonclinical discoveries*. Basel: Springer; 2012.

[37] Sgambato A, Ardito R, Faraglia B, Boninsegna A, Wolf FI, Cittadini A. Resveratrol, a natural phenolic compound, inhibits cell proliferation and prevents oxidative DNA damage. *Mutat Res Genet Toxicol Environ Mutagen* 2001; **496**: 171-80.

[38] Rjiba-Touati K, Ayed-Boussema I, Skhiri H, Belarbia A, Zellema D, Achour A, et al. Induction of DNA fragmentation, chromosome aberrations and micronuclei by cisplatin in rat bone-marrow cells: protective effect of recombinant human erythropoietin. *Mutat Res Genet Toxicol Environ Mutagen* 2012; **747**: 202-6.

[39] Ran Y, Wang R, Lin F, Hasan M, Jia Q, Tang B, et al. Radioprotective effects of dragon's blood and its extract against gamma irradiation in mouse bone marrow cells. *Phys Med* 2014; **30**: 427-31.

[40] Silva BM, Santos RP, Mendes LS, de Pinho PG, Valentão P, Andrade PB, et al. *Dracaena draco* L. fruit: phytochemical and antioxidant activity assessment. *Food Res Int* 2011; **44**: 2182-9.

[41] Santos RP, Mendes LS, Silva BM, de Pinho PG, Valentão P, Andrade PB, et al. Phytochemical profiles and inhibitory effect on free radical-induced human erythrocyte damage of *Dracaena draco* leaf: a potential novel antioxidant agent. *Food Chem* 2011; **124**: 927-34.

[42] Ran Y, Xu B, Wang R, Gao Q, Jia Q, Hasan M, et al. Dragon's blood extracts reduce radiation-induced peripheral blood injury and protects human megakaryocyte cells from GM-CSF withdraw-induced apoptosis. *Phys Med* 2016; **32**: 84-93.

[43] Cheng SE, Lee IT, Lin CC, Hsiao LD, Yang CM. Thrombin induces ICAM-1 expression in human lung epithelial cells via c-Src/PDGFR/PI3K/Akt-dependent NF-kappaB/p300 activation. *Clin Sci* 2014; **127**: 171-83.

[44] Krenzlin H, Lorenz V, Danckwardt S, Kempski O, Alessandri B. The importance of thrombin in cerebral injury and disease. *Int J Mol Sci* 2016; **17**: 84.

[45] Abdel-Razeq HN, Mansour AH, Ismael YM. Incidental pulmonary embolism in cancer patients: clinical characteristics and outcome – a comprehensive cancer center experience. *Vasc Health Risk Manag* 2011; **7**: 153-8.

[46] Gibbs A, Green C, Doctor VM. Isolation and anticoagulant properties of polysaccharides of *Typha augustata* and *Daemonorops* species. *Thromb Res* 1983; **32**: 97-108.

[47] Cichoż-Lach H, Michalak A. Oxidative stress as a crucial factor in liver diseases. *World J Gastroenterol* 2014; **20**: 8082-91.

[48] Sinha M, Das DK, Bhattacharjee S, Majumdar S, Dey S. Leaf extract of *Moringa oleifera* prevents ionizing radiation-induced oxidative stress in mice. *J Med Food* 2011; **14**: 1167-72.

[49] Heo SK, Yi HS, Yun HJ, Ko CH, Choi JW, Park SD. Ethylacetate extract from draconis resina inhibits LPS-induced inflammatory responses in vascular smooth muscle cells and macrophages via suppression of ROS production. *Food Chem Toxicol* 2010; **48**: 1129-36.

[50] Sharma S, Haldar C. Melatonin prevents X-ray irradiation induced oxidative damagein peripheral blood and spleen of the seasonally breeding rodent, *Funambulus pennanti* during reproductively active phase. *Int J Radiat Biol* 2006; **82**: 411-9.

[51] Kalogeris T, Bao Y, Korthuis RJ. Mitochondrial reactive oxygen species: a double edged sword in ischemia/reperfusion vs preconditioning. *Redox Biol* 2014; **2**: 702-14.

[52] Lakhan SE, Kirchgessner A, Hofer M. Inflammatory mechanisms in ischemic stroke: therapeutic approaches. *J Transl Med* 2009; **7**: 97.

[53] Cuzzocrea S, Riley DP, Caputi AP, Salvemini D. Antioxidant therapy: a new pharmacological approach in shock, inflammation, and ischemia/reperfusion injury. *Pharmacol Rev* 2001; **53**: 135-59.

[54] Xin N, Yang FJ, Li Y, Li YJ, Dai RJ, Meng WW, et al. Dragon's blood dropping pills have protective effects on focal cerebral ischemia rats model. *Phytomedicine* 2013; **21**: 68-74.

[55] Li N, Ma Z, Li M, Xing Y, Hou Y. Natural potential therapeutic agents of neurodegenerative diseases from the traditional herbal medicine Chinese dragon's blood. *J Ethnopharmacol* 2014; **152**: 508-21.

[56] Gauger GE, Tobias CA, Yang T, Whitney M. The effect of space radiation of the nervous system. *Adv Space Res* 1986; **6**: 243-9.

[57] Wu PH, Coultrap S, Pinnix C, Davies KD, Tailor R, Ang KK, et al. Radiation induces acute alterations in neuronal function. *PLoS One* 2012; **7**: e37677.

[58] Vickers JC, Dickson TC, Adlard PA, Saunders HL, King CE, McCormack G. The cause of neuronal degeneration in Alzheimer's disease. *Prog Neurobiol* 2000; **60**: 139-65.

[59] Schon EA, Manfredi G. Neuronal degeneration and mitochondrial dysfunction. *J Clin Invest* 2003; **111**: 303-12.

[60] Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. *Curr Neuropharmacol* 2009; **7**: 65-74.

[61] Wei LS, Chen S, Huang XJ, Yao J, Liu XM. Material basis for inhibition of dragon's blood on capsaicin-induced TRPV1 receptor currents in rat dorsal root ganglion neurons. *Eur J Pharmacol* 2013; **702**: 275-84.

[62] Liu X, Yin S, Chen S, Ma Q. Loureirin B: an effective component in dragon's blood modulating sodium currents in TG neurons. *Conf Proc IEEE Eng Med Biol Soc* 2005; 5: 4962-5.

[63] Attorre F, Francesconi F, Taleb N, Scholte P, Saed A, Alfo M, et al. Will dragonblood survive the next period of climate change? Current and future potential distribution of *Dracaena cinnabari* (Socotra, Yemen). *Biol Conserv* 2007; **138**: 430-9.

[64] Scholte P, De Geest P. The climate of Socotra Island (Yemen): a first-time assessment of the timing of the monsoon wind reversal and its influence on precipitation and vegetation patterns. *J Arid Environ* 2010; **74**: 1507-15.

[65] Wang XH, Zhang C, Yang LL, Gomes-Laranjo J. Production of dragon's blood in *Dracaena cochinchinensis* plants by inoculation of *Fusarium proliferatum*. *Plant Sci* 2011; **180**: 292-9.