Available online at www.ijpab.com

DOI: http://dx.doi.org/10.18782/2320-7051.5998

ISSN: 2320 – 7051

Int. J. Pure App. Biosci. **5 (5):** 1478-1484 (2017)

Review Article

International Journal of Pure & Applied Bioscience

OPEN ACCESS

The Interplay of Oxidants and Antioxidants: Oxidative Stress in Bovine Tropical Theileriosis

Neelam[1*], Praveen Kumar[1], Meenakshi Virmani[2], N. K. Rakha[1] and Ricky Jhambh[1]

[1]Department of Veterinary Medicine

[2]Department of Veterinary Physiology and Biochemistry

LLR University of Veterinary and Animal Sciences, Hisar – 125004, Haryana

*Corresponding Author E-mail: neelamaps2011@gmail.com

Received: 2.10.2017 | Revised: 27.10.2017 | Accepted: 29.10.2017

ABSTRACT

Oxidants are the compounds which are capable of oxidising target molecules. Oxidants are produced from various endobiotic and xenobiotic sources. Oxidants oxidises the target molecules and leads to damaging effects on various cellular components e.g. lipid, proteins and DNA. To counteract the harmful effects of oxidants, the antioxidant system plays an important role in individual. Antioxidant system comprises the non enzymatic components and a series of antioxidant enzymes. Enzymatic components mainly include glutathione, vitamin C and vitamin E. Major antioxidant enzymes include superoxide dismutase, glutathione peroxidase and catalase. Imbalance between oxidants and antioxidants in favour of oxidants leads to oxidative stress. This review aims to focus on the various aspects of the oxidative stress and the involvement of the oxidative stress in an important haemoprotozoan disease, bovine tropical theileriosis.

Key words: *Xenobiotic, Lipid, Proteins, DNA, Antioxidant*

INTRODUCTION

A vast literature is available on the oxidative stress which arises due to the imbalance between the oxidants and antioxidants at the cellular or individual level and its role in the development of various pathological conditions[1]. Oxidants refer to any endobiotic or xenobiotic that induces oxidative stress either by generation of free radicals or by inhibiting antioxidant system. It includes all reactive, free radicals containing molecules in cells or tissues. The free radicals produced in the tissues can inflict direct damage to macromolecules, such as lipids, nucleic acids and proteins[2]. Antioxidant system involves various enzymatic and non-enzymatic molecules that are usually distributed within the cytoplasm and various cell organelles. Non-enzymatic components include glutathione, selenium, vitamin C and vitamin E. The antioxidant enzymes glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase are the major enzymes which are capable of minimizing the oxidative stress in the cell organelles[3]. These enzymatic and non enzymatic antioxidant systems are necessary for sustaining life by maintaining a delicate intracellular redox balance and minimizing undesirable cellular damage caused by free radicals[4].

Cite this article: Neelam, Kumar, P., Virmani, M., Rakha, N.K. and Jhambh, R., The Interplay of Oxidants and Antioxidants: Oxidative Stress in Bovine Tropical Theileriosis, *Int. J. Pure App. Biosci.* **5(5):** 1478-1484 (2017). doi: http://dx.doi.org/10.18782/2320-7051.5998

In animals the oxidative stress has been reported in various pathological conditions which are relevant for the animal production, sufferings from such diseases results in huge economic losses. One of important disease among these is bovine tropical theileriosis (BTT). BTT is caused by the parasite *Theileria annulata*, the disease causes heavy economic losses due to extensive death losses, decreased milk and meat production and increased risk of secondary infections[5,6]. The bovine mortality rate is up to 40 per cent to 60 per cent in infected animals[7]. The infection is widespread, particularly in the Mediterranean Europe, Middle East, India, middle Asia and China[8]. This disease is characterised by the superficial lymph nodes enlargement, pallor mucous membrane and pyrexia. Atypical clinical markers are inappetance, coughing, respiratory distress, lacrymation, exophthalmia, cutaneous lesions and nervous symptoms[9]. Progressive anaemia is the main pathological feature of theileriosis. Anaemia occurs due to various factors *viz.* destruction of haematopoietic precursor cell destruction[10], activation of complement products[11] and removal of the infected and non-infected erythrocytes by phagocytosis[12]. Also there are evidence which suggest that anaemia occurs due to the damage of the erythrocytes caused by oxidative stress[13,14]. Buparvaquone is the drug of choice for the treatment of theileriosis. It has been reported that after administration of buparvaquone oxidative stress increases in the bovine tropical theileriosis. Therefore there is need of administration of antioxidants as a supportive therapy in the animals infected with bovine tropical theileriosis for fast and better recovery from bovine tropical theileriosis[15].

The aim of this review is to focus on the oxidative stress which arises through the imbalance between the oxidants and antioxidants at the cellular or individual level, and to provide an overview on the involvement of oxidative stress in theileriosis.

OXIDANTS AND THEIR EFFECTS ON CELLULAR COMPONENTS

Oxidants are the compounds which can oxidise the target molecules. The mechanism of oxidation occurs mainly through three processes: a) abstraction of a hydrogen atom b) abstraction of an electron and c) the addition of the oxygen. The oxidants can be classified on the basis that whether they contain free radicals i.e. an unpaired electron in their outer orbit or not. Due to the presence of free radical in the outer orbit these molecules are unstable. Species containing the free radicals in the outer orbit are: hydroxyl radical ($HO^{\cdot}$), nitric oxide ($NO^{\cdot}$) and superoxide (O_2^{-}). Compounds which do not contain free radical in their orbit are: peroxynitrite ($ONOO^{-}$), hydrogen peroxide (H_2O_2) and hypochlorous acid (HOCl) [16]. The free radicals are generated as a by product of normal aerobic metabolism, but under stressful conditions their levels increases beyond the optimum levels which proves to be a basic health hazard. The immune defense mechanism uses the lethal effects of oxidants in a beneficial manner and with the use of oxidants phagocytes kills the pathogens by using the enzyme nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[17,18]. This leads to the production of free radicals after an immune challenge. To respond the immune challenge phagocytes increase their oxygen uptake as much as 10–20 folds, which is called as respiratory burst. The mechanism of respiratory burst leads to the production of various highly reactive free radicals. As because these free radicals are non specific in their function, therefore along with killing of pathogens, the cytotoxic effects of free radicals also injures the host tissue[19]. Mitochondrion is the major cell organelle which is responsible for the production of free radicals[20,21]. During generation of ATP, free radicals are produced by the mitochondria due to leakage of electron from the respiratory chain when the reduction of molecular oxygen to water occurs.

The free radical causes the direct damage to macromolecules of individuals, such as lipids, nucleic acids and proteins. The poly unsaturated fatty acids are the primary oxidation targets. The free radicals, particularly superoxide anion radical ($O2^{\cdot-}$), hydroxyl radical ($OH^{\cdot-}$), and alkyl peroxyl radical ($^{\cdot}OOCR$), are potent initiators of lipid

peroxidation. The end products of lipid peroxidation, such as malondialdehyde (MDA) and F2-isoprostanes are accumulated in body. Oxidation of DNA bases can cause mutations and deletions in both nuclear and mitochondrial DNA. Mitochondrial DNA is more prone to oxidative damage because it is near to the production site of the free radicals. The oxidative change in DNA leads to functional changes in various types of proteins, which is evident by the altered physiological functions[22]. Along with it initiation of protein modification is started by hydroxyl radicals, which leads to the oxidation of side chains of amino acid, cross linkage of protein and finally fragmentation of protein[23].

ANTIOXIDANTS

To counteract the harmful effects taking place in the cell due to free radicals, the aerobic organisms system has evolved with some strategies like repair mechanism to alleviate the oxidative damages, physical protection mechanism against damage, and the final most important is the antioxidant defense mechanisms[16]. The antioxidants are synthesised *in vivo* or these can be taken in diet[24]. The antioxidants are the first line of choice to take care of the oxidants and these are very efficient in removing the free radicals, thus protecting cells from the harmful effects of the free radicals. In healthy aerobic organisms, production of free radicals is approximately balanced with antioxidant defense system[25]. The antioxidant system includes a network of antioxidant enzymatic and non enzymatic molecules which are usually distributed within the cytoplasm and various cell organelles. Enzymatic antioxidants act as primary defense mechanism whereas non enzymatic antioxidants act as secondary against defense mechanism against the oxidants. The enzymatic antioxidant system includes SOD, catalase and peroxidases (glutathione peroxidase). The SOD is first line of defense against free radicals. GPx is mainly a cytosolic selenoenzyme (selenium containing) and attack hydroperoxides with the aid of reduced glutathione (GSH) to form oxidized glutathione (GSSG) and the reduction product of the hydroperoxide [26]. Catalase decomposes the H_2O_2 to water and O_2, thus protecting the cell against oxidative stress induced by H_2O_2 or consequently formed $OH^{\bullet}$ [27]. Non-enzymatic components of antioxidant system involve vitamin E, vitamin C, selenium and glutathione. α-tocopherol (vitamin E) and ascorbic acid (vitamin C) acts as cellular antioxidant vitamins which are present in the cell membrane and plasma lipoproteins[28]. Vitamin E is a family of lipid-soluble vitamins, among which α-tocopherol is the most active form and is a powerful biological antioxidant. Vitamin E effectively minimizes oxidative stress, lipid peroxidation and toxic effects of free radicals in the biological system[29]. Main function of vitamin E is the protection of cell and cellular components against lipid peroxidation[30], and there are also evidences that suggest that α-tocopherol and ascorbic acid function together in a cyclic-type of process. The antioxidant mechanisms of ascorbic acid are based on the properties of donation of hydrogen atom to lipid radicals, quenching of singlet oxygen, and removal of molecular oxygen[31]. Selenium (Se) is component of some proteins and enzymes present in blood and tissues and acts as a potent antioxidant as well as potent immunomodulator. These protective effects of Se (as co-antioxidant) seem to be primarily associated with its presence in the seleno-enzymes, which are known to protect DNA and other cellular components from oxidative damage[32].

MARKERS OF OXIDATIVE STRESS

For measurement of oxidative stress various methods including direct and indirect measures of oxidants and antioxidants are there. But these methods often need specialized equipments and considerable experience. The action of oxidants and antioxidants can be monitored in situ by electron spin resonance, but these methods are not suitable for routine analysis. (Lykkesfeldt). The methods for measurement of oxidative stress *viz.* MDA and the natural antioxidants, metalloenzymes Cu, Zn-superoxide dismutase (Cu, Zn-SOD), and selenium dependent glutathione peroxidase (GPx), are currently

considered to be the most important, which are suitable for routine analysis[33,34]. MDA (three-carbon compound) which is an end product of lipid peroxidation, formed from peroxidized polyunsaturated fatty acids, mainly arachidonic acid is considered as an important biomarker of lipid peroxidation. It is Since MDA levels are increased in various diseases with excess of oxygen free radicals, many relationships with free radical damage were observed. Cu, Zn-SOD which is an intracellular enzyme, responsible for dismutation of extremely toxic superoxide radical into potentially less toxic hydrogen peroxide is widespread in nature, but being a metalloenzyme, its activity depends upon the free copper and zinc reserves in the tissues. GPx is an intracellular enzyme and this belongs to several proteins in mammalian cells that can metabolize hydrogen peroxide and lipid hydroperoxides[22].

OXIDATIVE STRESS IN THEILERIOSIS

Oxidative stress in the haemoprotozoan disease BTT has been studied and reported by many workers. The schizont stage of the parasite infects the leucocytes and the piroplasmic stage infects the erythrocytes. The progressive anaemia in this disease is the characteristics feature of the disease, it has been reported that erythrocytes are very prone to oxidative stress.

Grewal et al.,[35] monitored the levels of antioxidant enzymes and assayed the lipid peroxidation and osmotic fragility of erythrocytes in cattle naturally infected with *Theileria annulata* and reported the significant erythrocytic fragility and lipid peroxidation. The activities of antioxidant enzymes Glucose-6-phosphate dehydrogenase (G6PD) and GPx were significantly increased. They suggested it as that there was increase in the oxidative stress and the significant rise in the activities of antioxidant enzymes G6PD and GPx could not lower the oxidative stress. Due to the oxidative stress the lysis of erythrocytic membrane and lower values of haemoglobin occurred. The increased activities of antioxidant enzymes indicated towards the body's defence mechanism towards the oxidative stress but could not lower it. Other workers[13,14,36,37,38] reported the decreased levels of SOD and GPx, indicating the increased exposure of erythrocytes to the oxidative stress. Due to severe damage to the antioxidant system in BTT there is need of antioxidative therapy in theileriosis. But the studies on antioxidative therapy in theileriosis has not fully explored.

However there is extensive literature available on theileriosis, but scanty literature is available on the involvement of oxidative stress in bovine tropical theileriosis. Morever, it has reported that the specific drug (buparvaquone) used for theileriosis also causes the oxidative stress, perhaps it kills the parasite through formation of free radicals. McHardy, 1989 [39] reported that buparvaquone persists for a long time in plasma. Kumar et al.,[15] reported that oxidative stress in theileria infected animal increases with administration of buparvaquone (drug of choice) alone. Along with buparvaquone, the administration of vitamin C (antioxidant therapy) for three days in theileriosis revealed the significant reduction in oxidative stress level, however, when the vitamin C administration was stopped after three days, there was again increase in oxidative stress level beyond normal values, when the therapeutic evaluation was done on day fourteen. Therefore, another study for therapeutic evaluation of antioxidants as supportive therapy was done, along with the administration of specific drug i.e. buparvaquone[40]. The antioxidant therapy comprising the vitamin C was prolonged (administered of vitamin C every day for nine days, at recommended dose) and it was compared it with antioxidant therapy comprising vitamin E and selenium combination (administered on day 0, 3 and 6 at recommended dose) and the therapeutic evaluation was done on day 0, 3, 6 and 9 of therapy for the oxidative stress indices in blood. We found that the oxidative stress indices in blood showed significant improvement in antioxidants supplemented groups; however, more improvement was observed in animals which were supplemented

with vitamin E and selenium combinations as compare to the animals which were supplemented with vitamin C. Thus, our findings suggest that vitamin E and selenium combination as better adjunct antioxidant therapy as compare to vitamin C in cases of bovine tropical theileriosis.

CONCLUSION

Oxidative stress is an imbalance between oxidants and antioxidants in favour of oxidants. Various enzymatic and non enzymatic components of the antioxidant system are involved to counteract the harmful effects which arise due to the oxidation of the cellular components due to oxidants. There are strong evidences that suggest that the dynamic balance between the oxidation and the antioxidation process in theileriosis is severely damaged. Therefore, there is need of antioxidant therapy for faster and better recovery of theileria infected animals. Vitamin E and selenium preparation given three times at three days interval proved to better antioxidant therapy as compared to Vitamin C given every day for nine days.

REFERENCES

1. Hoeschen, R.J., Oxidative stress and cardiovascular disease, *Can. J. Cardiol.* **13(11):** 1021-1025 (1997).
2. Cherubini, A., Ruggiero, C., Polidori, M.C. and Mecocci, P., Potential markers of oxidative stress in stroke, *Free Radic. Biol. Med.* **39(7):** 841–852 (2005).
3. El-Bahr, S.M., Biochemistry of free radicals and oxidative stress, *Sci. Int.* **1(5):** 111-117. (2013).
4. Durackova, Z., Some current insights into oxidative stress, *Physiol. Res.* **59(4):** 459–469 (2010).
5. Zhang, Z. H., *Theileria annulata* and its control in China. Proceedings of a Workshop Held at Ilrad Nairobi (Kenya), pp: 3-9 (1990).
6. Inci, A., Ica, A., Yildirim, A., Vatansever, Z., Çakmak, A., Albasan, H., Cam, Y., Atasever, A., Sariozkan, S. and Duzlu, O., Economical impact of tropical theileriosis in the Cappadocia Region of Turkey, *Parasitol. Res.* **101(2 Suppl):** 171-174 (2007).
7. Razmi, G.R., Barati, F. and Aslani, M.R., Prevalence of *Theileria annulata* in dairy cattle in Mashhad area, Iran *J. Vet. Parasitol.* **23:** 81-83 (2009).
8. D'Oliveira, C., Weide V.M., Habela, M.A., Jacquiet, P. and Jongejan, F., Detection of *Theileria annulata* in blood samples of carrier cattle by PCR, *J. Clin. Microbiol.* **13:** 2665–2669 (1995).
9. Singh, S.K., Sudan, V., Singh A.P. and Yadav B.K., Evaluation of clinical markers for diagnosis of bovine theileriosis – A study of 21 calves, *Intas Polivet.* **15(1)**: 91-95 (2014).
10. Mbassa, G.K., Balemba, O., Maselle, R.M. and Mwaga, N.V., Severe anaemia due to haematopoietic precursor cell destruction in field cases of East Coast Fever in Tanzania, *Vet. Parasitol*. **52:** 243– 256 (1994).
11. Omer, O.H., El-Malik, K.H., Mahmoud, O.M., Haroun, E.M., Hawas, A., Sweeney and Magzoub M. Hematological profiles in pure breed cattle naturally infected with *Theileria annulata* in Saudi Arabia. *J. Vet. Parasitol.* **107:** 161-168 (2002).
12. Shiono, H., Yagi, Y., Kumar, A., Yamanaka, M. and Chikayama, Y., Accelerated binding of to red blood cells with increasing anaemia in cattle experimentally infected with *Theileria sergenti*. *J. Vet. Med*. **51:** 39–42 (2004).
13. Rezaei, A.S. and Dalir-Naghadeh, B., Evaluation of antioxidant status and oxidative stress in cattle naturally infected with *Theileria annulata*, *Vet. Parasitol.* **142**: 179–186 (2006).
14. Razavi, S.M., Nazifi, S., Batenia, M. and Rakhshandehrooa, E., Alterations of erythrocyte anti-oxidant mechanisms: Antioxidant enzymes, lipid peroxidation and serum trace elements associated with anemia in bovine tropical Theileriosis, *Vet. Parasitol.* **180**: 209– 214 (2011).
15. Kumar, A., Rakha, N.K. and Virmani, M., Enhancing clinical recovery of bovine

tropical theileriosis by use of antioxidant supportive therapy, *Ind. J. Anim. Sci.* **86 (5):** 518–524 (2016).

16. Lykkesfeldt, J. and Svendsen, O., Oxidants and antioxidants in disease: oxidative stress in farm animals, *Vet. J.* **173(3):** 502-511 (2007).
17. Hampton, M.B., Kettle, A.J. and Winterbourn, C.C., Inside the neutrophil phagosome: oxidants, myeloperoxidase, and bacterial killing, *Blood*, **92(9):** 3007-3017 (1998).
18. Babior, B.M., NADPH oxidase: an update. *Blood*, *93*(5), pp.1464-1476 (1999).
19. Rice-Evans, C.A. and Gopinathan, V., Oxygen toxicity, free radicals and antioxidants in human disease: biochemical implications in atherosclerosis and the problems of premature neonates, *Essays biochem.* **29:** 39 (1995).
20. Liu, Y., Fiskum, G. and Schubert, D., Generation of reactive oxygen species by the mitochondrial electron transport chain. *J. Neurochem.* **80(5):** 780-787 (2002).
21. Inoue, M., Sato, E.F., Nishikawa, M., Park, A.M., Kira, Y., Imada, I. and Utsumi, K., Mitochondrial generation of reactive oxygen species and its role in aerobic life. *Curr. Med.Chem.* **10(23):** 2495-2505 (2003).
22. Rahal, A., Kumar, A., Singh, V., Yadav, B., Tiwari, R., Chakraborty, S. and Dhama, K., Oxidative stress, prooxidants, and antioxidants: the interplay. *BioMed Res. Int.* (2014).
23. Berlett, B.S. and Stadtman, E.R., Protein oxidation in aging, disease, and oxidative stress. *J. Biol. Chem.* **272(33):** 20313-20316 (1997).
24. Halliwell, B., Biochemistry of oxidative stress. *Biochem. Soc. Trans*. 1147-1150. (2007).
25. Halliwell, B. and Gutteridge, J.M., *Free Radic. Biol. Med*. Oxford University Press, USA (2015).
26. Bandyopadhyay, U., Das, D. and Banerjee, R.K., Reactive oxygen species: oxidative damage and pathogenesis, *Curr. Sci.* **77:** 658-666 (1999).
27. Deisseroth, A.L.B.E.R.T. and Dounce, A.L., Catalase: Physical and chemical properties, mechanism of catalysis, and physiological role, *Physiol. Rev.* **50(3):** 319-375 (1970).
28. Bast, A., Haenen, G.R. and Doelman, C.J., Oxidants and antioxidants: State of the art, *Am. J. Med.* **9:** 2S-13S (1991).
29. Ogutcu, A., Uzunhisarcikli, M., Kalender, S., Durak, D., Bayrakdar, F. and Kalender, Y., The effects of organophosphate insecticide diazinon on malondialdehyde levels and myocardial cells in rat heart tissue and protective role of vitamin E, *Pestic. Biochem. Physiol.* **86:** 93–98 (2006).
30. Pryor, W.A., Vitamin E and heart disease: basic science to clinical intervention trials, *Free Rad. Biol. Med*. **28**:141–64 (2000).
31. Rumsey, S.C, Wang, Y. and Levine, M., Vitamin C. In: Papas AM, editor. Antioxidant status, diet, nutrition and health, Boca Raton, Fla. CRC Press, pp: 479–96 (1999).
32. Valko, M., Rhodes C.J., Moncol, J., Izakovic, M. and Mazur, M. Free radicals, metals and antioxidants in oxidative stress-induced cancer, *Chem. Biol. Interact.* **16:** 1–40 (2006).
33. Singh, K. P., Ahmad, A. H., Hore, S. K., Singh, V., Lohani, M., and Rahal, A., Effect of *Emblica officinalis* on antioxidative and haematological parameters following mercury induced toxicity, in *Proceedings of the 6th Annual conference of ISVPT*, Patna, India, November, (2006).
34. Singh, K.P., Ahmad, A.H., Singh, V., Pant, K. and Rahal, A., Effect of Emblica officinalis fruit in combating mercury-induced hepatic oxidative stress in rats. *Ind. J. Anim. Sci. (India)* (2011).
35. Grewal, A., Ahuja C.S., Singha, S.P.S. and Chaudhary, K.C., Status of lipid peroxidation, some antioxidant enzymes

and erythrocyte fragility of crossbred cattle naturally infected with *Theileria annulata*, *Vet. Res. Comm*. **29(5):** 387-394 (2005).

36. El-Deeb, W.M. and Younis, E.E. Clinical and biochemical studies on *Theileria annulata* in Egyptian buffaloes (*Bubalus bubalis*) with particular orientation to oxidative stress and ketosis relationship, *Vet. Parasitol.* **164**: 301–305 (2009).
37. Hassanpour A., Sabegh Y.G. and Sadeghi-nasab, A., Assessment of serum antioxidant enzymes activity in cattle suffering from theileriosis, *Eur. J. Exp. Biol*. **3:** 493-96. (2013).
38. Nazifi, S., Razavi, S.M., Hasanshahi, F. and Esmailnezhad, Z., Effect of the severity of *Theileria annulata* infection on some haematological parameters and antioxidant enzymes in naturally infected cattle, *Bulg. J. Vet. Med.* **12(1):** 63−71 (2009).
39. McHardy, N., Buparvaquone, the new antitheilerial: a review of its efficacy and safety. In: Dolan, T.T. (Ed.), Theileriosis in Eastern, Central and Southern Africa. Proc. Workshop on East Coast Fever Immunisation held in Lilongwe, Malawi, 20- 22 September 1988. ILRAD, Nairobi, pp. 158-165. 1989.
40. Neelam, 2016. Estimation of oxidative stress and evaluation of antioxidants as supportive therapy in bovine tropical theileriosis, *M. V. Sc. Dissertation*, LUVAS, Hisar, India.