Therapeutic potentials of superoxide dismutase

H. Younus

Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

Address for correspondence:
H. Younus, Interdisciplinary Biotechnology Unit, Aligarh Muslim University, Aligarh - 202002, Uttar Pradesh, India. Tel.: +91 571 2720 388. Fax: +91 571 272 1776. E-mail: hinayounus@rediffmail.com

ABSTRACT

Superoxide dismutases (SODs) constitute a very important antioxidant defense against oxidative stress in the body. The enzyme acts as a good therapeutic agent against reactive oxygen species-mediated diseases. The present review describes the therapeutic effects of SOD in various physiological and pathological conditions such as cancer, inflammatory diseases, cystic fibrosis, ischemia, aging, rheumatoid arthritis, neurodegenerative diseases, and diabetes. However, the enzyme has certain limitations in clinical applications. Therefore, SOD conjugates and mimetics have been developed to increase its therapeutic efficiency. Here, an overview is provided of some in vivo therapeutic effects observed with SOD.

Keywords: Oxidative stress, superoxide dismutase, therapeutic effects

Introduction

Superoxide dismutases (SODs) are a group of metalloenzymes that are found in all kingdoms of life. SODs form the front line of defense against reactive oxygen species (ROS)-mediated injury.[1] These proteins catalyze the dismutation of superoxide anion free radical (O$_2^-$) into molecular oxygen and hydrogen peroxide (H$_2$O$_2$) [Figure 1a] and decrease O$_2^-$ level which damages the cells at excessive concentration.[2] This reaction is accompanied by alternate oxidation-reduction of metal ions present in the active site of SODs.[3,4] Based on the metal cofactors present in the active sites, SODs can be classified into four distinct groups: Copper-Zinc-SOD (Cu, Zn-SOD) [Figure 1b], Iron SOD (Fe-SOD), Manganese SOD (Mn-SOD), and Nickel SOD.[5,6] The different forms of SODs are unequally distributed throughout all biological kingdoms and are located in different subcellular compartments.

SODs constitute a very important antioxidant defense against oxidative stress in the body.[7] Several studies have been performed that reveal the therapeutic potential and physiological importance of SOD.[8] The enzyme can serve as an anti-inflammatory agent and can also prevent precancerous cell changes.[9] Natural SOD levels in the body drop as the body ages[9] and hence as one age, one becomes more prone to oxidative stress-related diseases. SOD is used in cosmetics and personal care products as an anti-aging ingredient and antioxidant due to its ability to reduce free radical damage to the skin, therefore preventing wrinkles, fine lines, and age spots, and it also helps with wound healing, softens scar tissue, protects against UV rays, and reduces other signs of aging.[10] It has been reported that SOD has an important link in several human health problems including RBC-related disorders, cystic fibrosis (CF), postcholecystectomy pain syndrome, malignant breast disease, steroid-sensitive nephrotic syndrome, amyotrophic lateral sclerosis, neuronal apoptosis, AIDS, and cancer.[8,11-16] Furthermore, a strong association between the activity of SOD and Alzheimer’s disease has been suggested by some researchers.[8] It has also been reported that treatment with SOD helps recovery from mustard gas burns.[17] In many animal models having myocardial ischemia-reperfusion injury, inflammation, and cerebral ischemia-reperfusion injury, etc., SOD enzymes are found to be very effective.[18] SOD mimetics (small molecule catalytic antioxidants) offer a potential for treating diseases resulting from oxidative stress. SOD mimetics are synthetic compounds that mimic the native SOD by effectively converting O$_2^-$ into water by catalase. They are of prime interest in therapeutic treatment of oxidative stress because of their smaller size, longer half-life, and similarity in function to the native enzyme. Several attempts have been made to use SOD as a therapeutic agent against the ROS-mediated diseases. The present review describes the various therapeutic potentials of SOD.

Therapeutic Potentials of SOD

SOD and cancer

SOD, being a key cellular antioxidant, is highly responsible for the elimination of O$_2^-$.[8] Many studies have revealed the critical role of oxidative stress in carcinogenesis.[19,20] Indeed, there are several clear evidences indicating that ROS work as endogenous class of carcinogens by inducing mutations in the cells.[21-23] Diminished activity of Cu, Zn-SOD, and Mn-SOD has been reported in cancer cells.[24,25] Normalization of SOD level contributes to part of the cancer cell phenotype reversion.[24] It has been suggested that SOD may regulate cancer progression and, hence, can be used as a novel target for cancer treatment.[26-29] Furthermore, it has been shown that...
SOD and inflammatory diseases

Neutrophils play a central and essential role in the pathogenesis of inflammation. Activated neutrophils adhere to vascular endothelium and transmigrate to the extravascular space, release ROS, protease enzymes, and large amounts of chemokines. ROS and proteases damage normal tissue and extracellular matrix proteins. O$_2^-$ serves to activate endothelial cells and enhance neutrophil infiltration. Studies performed in transgenic mice overexpressing extracellular SOD and SOD mimetic have shown that inhibition of O$_2^-$ can prevent the infiltration of neutrophils at the site of damage. Neutrophil apoptosis may also be an important step in the resolution of inflammation. In individuals with Down syndrome, neutrophil apoptosis increases and Cu, Zn-SOD is overexpressed. Exogenous H$_2$O$_2$ together with SOD, increase the number of apoptotic neutrophils. SOD may serve as an inhibitory agent of neutrophil-mediated inflammation and may stand for a novel therapeutic approach for the ROS-dependent tissue damage induced by neutrophils through several mechanisms. Preclinical studies with bovine Cu, Zn-SOD showed encouraging results for its use as a human therapeutic agent in acute and chronic inflammatory conditions, including dermatosis due to burn and wound injury. Extracellular SOD, Mn-SOD and Cu, Zn-SOD have been described as potential inhibitor of inflammation by various reporters.

SOD and CF

CF is characterized by the chronic inflammation and the recruitment of activated neutrophils. In the plasma of patients with CF, SOD activity was significantly lower as compared with the healthy individuals. Furthermore, in mononuclear, polymorphonuclear, and red cells of CF patients, reduced Cu, Zn-SOD activity was observed. It has been found that the antifibrotic action of Cu, Zn-SOD is mediated by TGF-β1 repression followed by phenotypic reversion of myofibroblasts. Radiation-induced fibrosis of breast was significantly reduced by Cu, Zn-SOD. Proapoptotic agents induced apoptosis in CF but not in control cells that were reduced by treatment with SOD mimetic. These findings indicate new therapeutic possibilities targeting antioxidant pathways including SOD, so that oxidative stress and apoptosis can be reduced in CF cells, and proinflammatory response can be limited.

SOD and ischemia

ROS including O$_2^-$ and its reaction product peroxynitrite has a significant role in endothelial and tissue injury associated with ischemia and reperfusion. Overexpression of Cu, Zn-SOD reduces ischemic damage resulting from ischemia/reperfusion. Mn-SOD targeted deletion deteriorates the outcome from both temporary and permanent middle cerebral artery occlusions. The removal of O$_2^-$ and peroxynitrite by SOD mimetic helps in the prevention of cellular energetic failure and tissue damage related with ischemia and perfusion and has a beneficial effect in this situation.

SOD and aging

SOD is considered to be an anti-aging enzyme. The free radical theory of aging was proposed by Derham Harman. It postulated that oxygen free radicals generated in metabolic pathways result in age-related deterioration through oxidative damage to biomolecules, with mitochondria being the main target of attack. Accumulation of oxidative damage is considered to be one of the key mechanisms of aging. Drosophila flies having 75% reduction in SOD activity, showed accelerated loss of olfactory behavior on ageing. It has been suggested that novel SOD mimetics may be useful in attenuating aging-induced cognitive impairments and other aspects of physiological decline with aging.

SOD and rheumatoid arthritis

Rheumatoid arthritis is a systemic disease and is characterized by a chronic inflammation reaction in the synovium of...
joints, leading to degeneration of cartilage and erosion of juxta-articular bone. Increased oxidative stress or deficient antioxidant status is critical in the pathogenesis of rheumatoid arthritis. Some antioxidants including SOD and Vitamin E have an anti-inflammatory role in experimentally induced arthritis. It was found that SOD activity is low in patients suffering from rheumatoid arthritis and the administration of SOD through liposomes had a positive effect in the treatment of experimental arthritis.

SOD and neurodegenerative diseases

Oxidative stress has been shown to be involved in the pathophysiology of several neurodegenerative diseases. The affected regions of patients having Alzheimer’s disease (AD) have reduced activity of antioxidant enzymes such as SOD, catalase, and glutathione peroxidase. Familial amyotrophic lateral sclerosis (FALS) is a fatal neurodegenerative disease that leads to the selective loss of motor neurons. Several mutations in Cu, Zn-SOD gene are found to be associated with FALS. In addition, Cu, Zn-SOD is one of the prime victims of oxidative damage to the brain in AD and Parkinson’s disease. It has been experimentally demonstrated that overexpression of SOD-2 reduces hippocampal superoxide and hence prevents memory deficits in a mouse model of AD. SOD supplementation showed improvement in mice model of AD. SOD/catalase mimetic EUK-207 exhibited protection against and interruption of progression of amyloid and tau pathology and cognitive decline in a mouse model of AD.

SOD and diabetes

Increased oxidative stress plays a major role in the etiology of diabetes and its complications. Hyperglycemia stimulates the production of ROS from various sources. As a result, diabetes usually leads to increased formation of ROS and weakened antioxidant defenses. SOD catalyzes the conversion of O$_2^-$ into H$_2$O$_2$. Under hyperglycemic conditions, endothelial cells produce elevated levels of O$_2^-$. Overproduction of O$_2^-$ can inhibit glyceraldehyde-3-phosphate dehydrogenase which is an important enzyme of the glycolytic pathway. This leads to the accumulation of glucose and other intermediate metabolites of this pathway and shifts to other alternative pathways of glucose metabolism along with increased production of advanced glycation end products.

Treatment with SOD has experimentally been shown to reduce liver oxidative stress in diabetic animals. SOD mimetic (Mn[II][pyane] C12) has successfully been used to treat diabetes in diabetic rats. Chemically modified SOD (carboxymethylcellulose-SOD and poly methyl vinyl ether-co-maleic anhydride-SOD) was effective in treating diabetes and offers a therapeutic advantage in clinical use. It has been demonstrated that extracellular SOD can act as a therapeutic agent to protect the progression of diabetic nephropathy.

Current limitations of SODs for therapeutic applications

Due to the instability, high immunogenicity, low cellular uptake, and lesser circulation in vivo half-life of SOD, their clinical applications as therapeutic agents are very limited. For this reason, a wide variety of SOD conjugates have been developed with longer circulation half-lives, high stability, and lesser immunogenicity. These SOD conjugates have exhibited marked effects in vivo. The administration of SOD in free form has some disadvantages, most importantly, the low accumulation of SOD in inflamed areas due to its reduced half-life in the bloodstream and its rapid renal excretion. To overcome this, SOD can be incorporated either in highly loaded conventional liposomes or long-circulating liposomes (PEG-liposomes). Many SOD mimetics have been synthesized that can be used as pharmaceutical agents in a large number of diseases in which the native SOD is ineffective. Potent SOD mimetics such as metalloporphyrins, Mn cyclic polyamines, Mn-salen derivatives, and nitroxides have been developed for treating various diseases resulting from increased oxidative stress.

Future perspectives

Diets high in vegetables and fruits, which are good sources of antioxidants, have been found to be healthy. Traditional antioxidants such as selenium, carotenoids, and Vitamins E and C are safer products. However, research has not shown these antioxidant supplements to be beneficial in preventing diseases. The reasons may be: The effects of the large doses of antioxidants used in supplementation studies may be different from those of the smaller amounts of antioxidants consumed in foods. Differences in the chemical composition of antioxidants in foods versus those in supplements may influence their effects. For some diseases, specific antioxidants might be more effective than the ones that have been tested.

Current research reveals the potential therapeutic applications of SOD in the prevention/control of various diseases. Future approaches in this field are expected to include gene therapy to produce more antioxidants in the body, increasing the level of antioxidants in plant products by genetic modifications, synthetic antioxidant enzymes (SOD mimetics). Among the most critical antioxidants that ameliorate the effects of oxidative stress within cells are enzymes such as the SODs. Due to their importance, the SODs have received much attention in efforts to minimize oxygen radical-induced damage to normal tissues. Since the administration of exogenous SODs themselves has often proven to be problematic, a variety of innovative approaches are currently being explored in conjunction with radiotherapy. Among these SOD mimetics, the future holds great promise for the development of superior products that will serve to ameliorate the damaging effects of radiation on normal cells and tissues.
Table 1: Some diseases in which SOD has been shown to exhibit significant therapeutic action/potential in humans/animals

| Disease                     | Formulation          | Reference |
|-----------------------------|----------------------|-----------|
| Cancer                      | SOD mimic            | [33,34]   |
| Inflammatory diseases       | SOD                  | [37,40,41]|
| CF                          | SOD                  | [49]      |
| Ischemia                    | SOD                  | [54]      |
| Rheumatoid arthritis        | SOD                  | [61]      |
| Neurodegenerative diseases  | SOD                  | [69]*     |
| Diabetes                    | SOD                  | [70]*     |
|                            | SOD mimic            | [79,82]   |
|                            | Chemically modified SOD | [81]    |

*SOD used along with other pharmacologic interventions. CF: Cystic fibrosis, SOD: Superoxide dismutase

Conclusion

SOD can be used as a pharmaceutical in treating various diseases resulting from oxidative stress [Table 1]. SOD conjugates and mimetics have improved performance and overcome some of the limitations of the free enzyme. Antioxidant-based mimetics may potentially be the future of oxidative stress targeted therapies in chemoprevention. It is important that future research on the potential use of SOD or its conjugates and mimetics in the treatment of oxidative stress-related diseases should focus on patient-oriented outcomes.

Acknowledgment

Research facilities provided by Aligarh Muslim University are gratefully acknowledged.

References

1. Kangralkar VA, Patil SD, Bandivadekar RM. Oxidative stress and diabetes: A review. Int J Pharm Appl 2010;1:38-45.
2. Yasui K, Baba A. Therapeutic potential of superoxide dismutase (SOD) for resolution of inflammation. Inflamm Res 2006;55:359-63.
3. McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem 1969;244:6049-55.
4. Tainer JA, Getzoff ED, Richardson JS, Richardson DC. Structure and mechanism of copper, zinc superoxide dismutase. Nature 1983;306:284-7.
5. Miller AF. Fe superoxide dismutase. In: Messerschmidt A, Huber R, Poulos T, Wieghart K, editors. Handbook of Metalloproteins. Chichester: John Wiley & Sons; 2001. p. 668-82.
6. Youn HD, Kim EJ, Roe JH, Hah YC, Kang SO. A novel nickel-containing superoxide dismutase from Streptomyces spp. Biochem J 1996;318:889-96.
7. Landis GN, Tower J. Superoxide dismutase evolution and life span regulation. Mech Ageing Dev 2005;126:365-79.
8. Noor R, Mittal S, Iqbal J. Superoxide dismutase – Applications and relevance to human diseases. Med Sci Monit 2002;8:RA210-5.
9. Inal ME, Kanbak G, Sunal E. Antioxidant enzyme activities and malondialdehyde levels related to aging. Clin Chim Acta 2001;305:75-80.
10. Luisa Corvo M, Jorge JC, van’t Hoof R, Cruz ME, Crommelin DJ, Storm G, et al. Superoxide dismutase entrapped in long-circulating liposomes: Formulation design and therapeutic activity in rat adjuvant arthritis. Biochim Biophys Acta 2002;1564:227-36.
11. Bravard A, Sabatier L, Hoffschir F, Ricoul M, Luccioni C, Dutrillaux B, et al. SOD2: A new type of tumor-suppressor gene? Int J Cancer 1992;51:476-80.
12. Church SL, Grant JW, Ridnour LA, Oberley LW, Swanson PE, Meltzer PS, et al. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proc Natl Acad Sci U S A 1993;90:3113-7.
13. St Clair DH, Oberley TD, Muse KE, St Clair WH. Expression of manganese superoxide dismutase promotes cellular differentiation. Free Radic Biol Med 1994;16:275-82.
14. Greenlund LJ, Deckwerth TL, Johnson EM Jr. Superoxide dismutase delays neuronal apoptosis: A role for reactive oxygen species in programmed neuronal death. Neuron 1995;14:303-15.
15. Riley DP. Functional mimics of superoxide dismutase enzymes as therapeutic agents. Chem Rev 1999;99:2573-88.
16. Troy CM, Shelanski ML. Down-regulation of copper/zinc superoxide dismutase causes apoptotic death in PC12 neuronal cells. Proc Natl Acad Sci U S A 1994;91:6384-7.
17. Eldad A, Ben Meir P, Breiterman S, Chaouat M, Shafran A, Ben-Bassat H, et al. Superoxide dismutase (SOD) for mustard gas burns. Burns 1998;24:114-9.
18. Salvemini D, Riley DP. Nonpeptidyl mimetics of superoxide dismutase in clinical therapies for diseases. Cell Mol Life Sci 2000;57:1489-92.
19. Moriya K, Nakagawa K, Santa T, Shintani Y, Fujie H, Miyoshi H, et al. Oxidative stress in the absence of inflammation in a mouse model for hepatitis C virus-associated hepatocarcinogenesis. Cancer Res 2001;61:4365-70.
20. Wiseman H, Halliwell B. Damage to DNA by reactive oxygen and nitrogen species: Role in inflammatory disease and progression to cancer. Biochem J 1996;313:17-29.
21. Feig DI, Reid TM, Loeb LA. Reactive oxygen species in tumorigenesis. Cancer Res 1994;54:1890s-1894.
22. Cerutti PA. Ox-y-radicals and cancer. Lancet 1994;344:862-3.
23. Guyton KZ, Kensler TW. Oxidative mechanisms in carcinogenesis. Br Med Bull 1993;49:523-44.
24. Bafana A, Dutt S, Kumar A, Kumar S, Ahuja PS. The basic and applied aspects of superoxide dismutase. J Mol Catal B Enzym 2011;68:275-82.
25. Oberley TD. Mitochondria, manganese superoxide dismutase, and programmed neuronal death. Neuron 1995;14:303-15.
26. Glasauer A, Sena LA, Diebold LP, Mazar AP, Chandel NS. Targeting SOD1 reduces experimental non–small-cell lung cancer. J Clin Invest 2014;124:117-28.
27. Papa L, Hahn M, Marsh EL, Evans BS, Germain D. SOD2 to SOD1 switch in breast cancer. J Biol Chem 2014;289:5412-6.
28. Papa L, Manfredi G, Germain D. SOD1, an unexpected novel target for cancer therapy. Genes Cancer 2014;5:15-21.
29. Tsang CK, Liu Y, Thomas J, Zhang Y, Zheng XF. Superoxide dismutase 1 acts as a nuclear transcription factor to regulate oxidative stress resistance. Nat Commun 2014;5:3446.
Younus: Therapeutic effects of SOD

30. Salem K, McCormick ML, Wendlandt E, Zhan F, Goel A. Copper-zinc superoxide dismutase-mediated redox regulation of bortezomib resistance in multiple myeloma. Redox Biol 2015;4:23-33.

31. Li TM, Chen GW, Su CC, Lin JG, Yeh CC, Cheng KC, et al. Ellagic acid induced p53/p21 expression, GI arrest and apoptosis in human bladder cancer T24 cells. Anticancer Res 2005;25:971-9.

32. Robbins D, Zhao Y. Manganese superoxide dismutase in cancer prevention. Antioxid Redox Signal 2014;20:1628-45.

33. Thomas R, Sharifin N. SOD mimetics: A novel class of androgen receptor inhibitors that suppresses castration-resistant growth of prostate cancer. Mol Cancer Ther 2012;11:87-97.

34. Yulyana Y, Tovmasyan A, Ho IA, Sia KC, Newman JP, Ng WH, et al. Redox-active mn porphyrin-based potent SOD mimic, mnTnBuOE-2-pyP(5+), enhances carbenoxolone-mediated TRAIL-induced apoptosis in glioblastoma multiforme. Stem Cell Rev 2016;12:140-55.

35. Masini E, Cuzzocrea S, Mazzon E, Marzocco C, Mannaioni PF, Salvemini D, et al. Protective effects of M40403, a selective superoxide dismutase mimetic, in myocardial ischaemia and reperfusion injury in vivo. Br J Pharmacol 2002;136:905-17.

36. Salvemini D, Wang QZ, Zweier JL, Samouilov A, Macearthur H, Misko TP, et al. A nonpeptidyl mimic of superoxide dismutase with therapeutic activity in rats. Science 1999;286:304-6.

37. Ghio AJ, Suliman HB, Carter JD, Abushamaa AM, Folz RJ. Overexpression of extracellular superoxide dismutase decreases lung injury after exposure to oil fly ash. Am J Physiol Lung Cell Mol Physiol 2002;283:L1211-8.

38. Yasui K, Shinozaki K, Nakazawa T, Agematsu K, Komiyama A. Presenility of granulocytes in Down syndrome individuals. Am J Med Genet 1999;84:406-12.

39. Yasui K, Kobayashi N, Yamazaki T, Agematsu K, Matsuzaki S, Ito S, et al. Superoxide dismutase (SOD) as a potential inhibitory mediator of inflammation via neutrophil apoptosis. Free Radic Res 2005;39:755-62.

40. Flohé L. Superoxide dismutase for therapeutic use: Clinical experience, dead ends and hopes. Mol Cell Biochem 1988;84:123-31.

41. Niwa Y. Lipid peroxides and superoxide dismutase (SOD) induction in skin diseases, and treatment with SOD preparations. Dermatologica 1989;179 Suppl 1:101-6.

42. Bowler RP, Nicks M, Tran K, Tanner G, Chang LY, Young SK, et al. Extracellular superoxide dismutase attenuates lipopolysaccharide-induced neutrophil inflammation. Am J Respir Crit Care Med 2004;169:432-9.

43. Joseph A, Li Y, Koo HC, Davis JM, Pollack S, Kazzaz JA, et al. Superoxide dismutase attenuates hyperoxia-induced interleukin-8 induction via AP-1. Free Radic Biol Med 2005;41:1443-9.

44. Porfiro AS, Lecuța SE, Kiss B, Loghin F, Părvu AE. Investigation into the role of cu/Zn-SOD delivery system on its antioxidant and anti-inflammatory activity in rat model of peritonitis. Pharmacol Rep 2014;66:670-6.

45. De Rose V. Mechanisms and markers of airway inflammation in cystic fibrosis. Eur Respir J 2002;19:333-40.

46. Madarasi A, Lugassi A, Greiner E, Holics K, Biró L, Mozsáry E, et al. Antioxidant status in patients with cystic fibrosis. Ann Nutr Metab 2000;44:207-11.

47. Percival SS, Bowser E, Wagner M. Reduced copper enzyme activities in blood cells of children with cystic fibrosis. Am J Clin Nutr 1995;62:633-8.

48. Vozenin-Brotons MC, Sivan V, Gault N, Renard C, Geffrotin C, Delanian S, et al. Antifibrotic action of cu/Zn SOD is mediated by TGF-beta1 repression and phenotypic reversion of my fi broblasts. Free Radic Biol Med 2001;30:30-42.

49. Campana F, Zervoudis S, Perdereau B, Gez E, Fourquet A, Badiu C, et al. Topical superoxide dismutase reduces post-irradiation breast cancer fibrosis. J Cell Mol Med 2004;8:109-16.

50. Rottner M, Tual-Chalot S, Mostefai HA, Andriantsitohaina R, Freyseninet JM, Martínez MC, et al. Increased oxidative stress induces apoptosis in human cystic fibrosis cells. PLoS One 2011;6:e24880.

51. Yang G, Chan PH, Chen J, Carlson E, Chen SF, Weinstein P, et al. Human copper-zinc superoxide dismutase transgenic mice are highly resistant to reperfusion injury after focal cerebral ischemia. Stroke 1994;25:165-70.

52. Kim GW, Kondo T, Noshita N, Chan PH. Manganese superoxide dismutase deficiency exacerbates cerebral infarction after focal cerebral ischemia/reperfusion in mice: Implications for the production and role of superoxide radicals. Stroke 2002;33:809-15.

53. Murakami K, Kondo T, Kawase M, Li Y, Sato S, Chen SF, et al. Mitochondrial susceptibility to oxidative stress exacerbates cerebral infarction that follows permanent focal cerebral ischemia in mutant mice with manganese superoxide dismutase deficiency. J Neurosci 1998;18:205-13.

54. Salvemini D, Cuzzocrea S. Superoxide, superoxide dismutase and ischemic injury. Curr Opin Investig Drugs 2002;3:886-95.

55. Harman D. Aging: A theory based on free radical and radiation chemistry. J Gerontol 1956;11:298-300.

56. Hedden S, Guarente L. Genetics and the specificity of the aging process. Science 2003;299:1351-4.

57. Longo VD, Finch CE. Evolutionary medicine: From dwarf model systems to healthy centenarians? Science 2003;299:1342-6.

58. Paul A, Belton A, Nag S, Martin I, Grotewiel MS, Duttaroy A, et al. Reduced mitochondrial SOD displays mortality characteristics reminiscent of natural aging. Mech Ageing Dev 2007;128:706-16.

59. Levin ED. Extracellular superoxide dismutase (EC-SOD) quenches free radicals and attenuates age-related cognitive decline: Opportunities for novel drug development in aging. Curr Alzheimer Res 2005;2:191-6.

60. Hutchon CA, El-Gabalawy HS. Oxidation in rheumatoid arthritis. Arthritis Res Ther 2004;6:265-78.

61. Mahajan A, Tandon VR. Antioxidants and rheumatoid arthritis. J Indian Rheumatol Assoc 2004;12:139-42.

62. Karatas F, Ozates I, Canatan H, Halifeoglu I, Karatepe M, Colakti R, et al. Antioxidant status & lipid peroxidation in patients with rheumatoid arthritis. Indian J Med Res 2003;118:178-81.

63. Ugur M, Yildirim K, Kiziltunc A, Erdal A, Karatay S, Senel K, et al. Correlation between soluble intercellular adhesion molecule 1 level and extracellular superoxide dismutase activity in rheumatoid arthritis: A possible association with disease activity. Scand J Rheumatol 2004;33:239-43.

64. Pappolla MA, Omar RA, Kim KS, Robakins NK. Immunohistochemical evidence of oxidative [corrected] stress in Alzheimer’s disease. Am J Pathol 1992;140:621-8.

65. Zemlan FP, Thienuh OJ, Bosmann HB. Superoxide dismutase activity in Alzheimer’s disease: Possible mechanism for paired helical filament formation. Brain Res 1989;476:160-2.

66. Cleveland DW, Rothstein JD. From charcot to lou gehrig: Deciphering selective motor neuron death in ALS. Nat Rev Neurosci 2001;2:806-19.

67. Choi J, Rees HD, Weintraub ST, Levey AI, Chin LS, Li L, et al. Evidence of oxidative stress and aggregation of Cu,Zn-superoxide dismutase associated with alzheimer and parkinson diseases. J Biol Chem 2005;280:11648-55.

68. Massaad CA, Washington TM, Paulier RL, Klann E. Overexpression of SOD-2 reduces hippocampal superoxide and prevents memory deficits in a mouse model of alzheimer’s disease. Proc Natl Acad Sci U S A 2009;106:13576-81.

69. Persichilli S, Gervasoni J, Di Napoli A, Fusco A, Nicolia V, Giardina B,
et al. Plasma thiols levels in alzheimer’s disease mice under diet-induced hyperhomocysteinemia: Effect of S-adenosylmethionine and superoxide-dismutase supplementation. J Alzheimers Dis 2015;44:1323-31.

70. Clausen A, Xu X, Bi X, Baudry M. Effects of the superoxide dismutase/catalase mimetic EUK-207 in a mouse model of Alzheimer’s disease: Protection against and interruption of progression of amyloid and tau pathology and cognitive decline. J Alzheimers Dis 2012;30:183-208.

71. Baynes JW. Role of oxidative stress in development of complications in diabetes. Diabetes 1991;40:405-12.

72. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: A new perspective on an old paradigm. Diabetes 1999;48:1-9.

73. Ceriello A. Oxidative stress and glycemic regulation. Metabolism 2000;49:27-9.

74. Yan LJ. Pathogenesis of Chronic hyperglycemia: From reductive stress to oxidative stress. J Diabetes Res 2014;2014:137919.

75. McLellan AC, Thornalley PJ, Benn J, Sonksen PH. Glyoxalase system in clinical diabetes mellitus and correlation with diabetic complications. Clin Sci (Lond) 1994;87:21-9.

76. Saxena AK, Srivastava P, Kale RK, Baquer NZ. Impaired antioxidant status in diabetic rat liver. Effect of vanadate. Biochem Pharmacol 1993;45:539-42.

77. Graier WF, Posch K, Fleischhaecker E, Wascher TC, Kostner GM. Increased superoxide anion formation in endothelial cells during hyperglycemia: An adaptive response or initial step of vascular dysfunction? Diabetes Res Clin Pract 1999;45:153-60.

78. Du X, Matsumura T, Edelstein D, Rossetti L, Zsengeller Z, Szabo C, et al. Inhibition of GAPDH activity by poly(ADP-ribose) polymerase activates three major pathways of hyperglycemic damage in endothelial cells. J Clin Invest 2003;112:1049-57.

79. Di Naso FC, Simões Dias A, Porawski M, Marroni NA. Exogenous superoxide dismutase: Action on liver oxidative stress in animals with streptozotocin-induced diabetes. Exp Diabetes Res 2011;2011:754132.

80. Stančić A, Otašević V, Janković A, Vučetić M, Ivanović-Burmazović I, Filipović MR, et al. Molecular basis of hippocampal energy metabolism in diabetic rats: The effects of SOD mimic. Brain Res Bull 2013;99:27-33.

81. Mansuroğlu B, Derman S, Yaba A, Kızılbey K. Protective effect of chemically modified SOD on lipid peroxidation and antioxidant status in diabetic rats. Int J Biol Macromol 2015;72:79-87.

82. Kuo CW, Shen CJ, Tung YT, Chen HL, Chen YH, Chang WH, et al. Extracellular superoxide dismutase ameliorates streptozotocin-induced rat diabetic nephropathy via inhibiting the ROS/ERK1/2 signaling. Life Sci 2015;135:77-86.

83. Kakimoto K, Kojima Y, Ishii K, Onoue K, Maeda H. The suppressive effect of gelatin-conjugated superoxide dismutase on disease development and severity of collagen-induced arthritis in mice. Clin Exp Immunol 1993;94:241-6.

84. Ogino T, Inoue M, Ando Y, Awa M, Maeda H, Morino Y, et al. Chemical modification of superoxide dismutase. Extension of plasma half-life of the enzyme through its reversible binding to the circulating albumin. Int J Pept Protein Res 1988;32:153-9.

85. Cruz ME, Manuela Gaspar M, Bábara M, Martins F, Luisa Corvo M. Liposomal superoxide dismutase’s and their use in the treatment of experimental arthritis. Methods Enzymol 2005;391:395-413.

86. Salvemini D, Riley DP, Cuzzocrea S. SOD mimetics are coming of age. Nat Rev Drug Discov 2002;1:367-74.

87. Batinič-Haberle I, Rebouças JS, Spasojević I. Superoxide dismutase mimics: Chemistry, pharmacology, and therapeutic potential. Antioxid Redox Signal 2010;13:877-918.

88. Jerome-Morais A, Diamond AM, Wright ME. Dietary supplements and human health: For better or for worse? Mol Nutr Food Res 2011;55:122-35.

89. Song Y, Cook NR, Albert CM, Van Denburgh M, Manson JE. Effects of vitamins C and E and beta-carotene on the risk of Type 2 diabetes in women at high risk of cardiovascular disease: A randomized controlled trial. Am J Clin Nutr 2009;90:429-37.