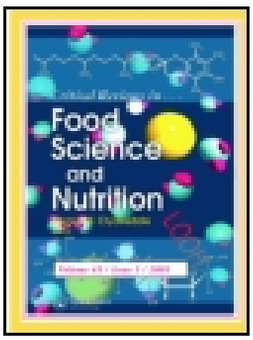

Critical Reviews in Food Science and Nutrition

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/bfsn20

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To cite this article: Mohammad Nazmul Islam, Abdur Rauf, Fowzul Islam Fahad, Talha Bin Emran, Saikat Mitra, Ahmed Olatunde, Mohammad Ali Shariati, Maksim Rebezov, Kannan R. R. Rengasamy & Mohammad S. Mubarak (2021): Superoxide dismutase: an updated review on its health benefits and industrial applications, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2021.1913400

To link to this article: https://doi.org/10.1080/10408398.2021.1913400

Published online: 27 Apr 2021.

CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
https://doi.org/10.1080/10408398.2021.1913400

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REVIEW

Superoxide dismutase: an updated review on its health benefits and industrial applications

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ABSTRACT

Many short-lived and highly reactive oxygen species, such as superoxide anion (O_2^-) and hydrogen peroxide (H_2O_2), are toxic or can create oxidative stress in cells, a response involved in the pathogenesis of numerous diseases depending on their concentration, location, and cellular conditions. Superoxide dismutase (SOD) activities as an endogenous and exogenous cell defense mechanism include the potential use in treating various diseases, improving the potential use in treating various diseases, and improving food-stuffs preparation dietary supplements human nutrition. Published work indicates that SOD regulates oxidative stress, lipid metabolism, inflammation, and oxidation in cells. It can prevent lipid peroxidation, the oxidation of low-density lipoprotein in macrophages, lipid droplets' formation, and the adhesion of inflammatory cells into endothelial monolayers. It also expresses antioxidant effects in numerous cancer-related processes. Additionally, different forms of SOD may also augment food processing and pharmaceutical applications, exhibit anticancer, antioxidant, and anti-inflammatory effects, and prevent arterial problems by protecting the proliferation of vascular smooth muscle cells. Many investigations in this review have reported the therapeutic ability and physiological importance of SOD. Because of their antioxidative effects, SODs are of great potential in the medicinal, cosmetic, food, farming and chemical industries. This review discusses the findings of human and animal studies that support the advantages of SOD enzyme regulations to reduce the formation of oxidative stress in various ways.

KEYWORDS

Antioxidant; cancer; dietary supplement; food science; human nutrition; superoxide dismutase

Introduction

Reactive oxygen species (ROS) such as H_2O_2, O_2^-, hydroxyl radical ($^{\bullet}OH$), and singlet oxygen can lead to oxidative stress in the body during normal aerobic metabolism processes (Collin 2019). ROS can be formed enzymatically, chemically, phytochemically, or through food processing. They are also formed by decomposition and inter-reactions (Choe and Min 2006). Oxidative stress may damage biomolecules, including proteins, lipids, and DNA, and could cause a wide range of disorders (Pashkow 2011; Simonian and Coyle 1996). Several antioxidant supplements are the degradation of oxidative stress, thus reducing ROS-related diseases. Besides, aerobic organisms' formation can survive in oxygen-rich environments, which provides an effective system to defend against reactant ROSs (Flohe 1984; Miao and Clair 2009). The aerobic organisms are beneficial for the physiological response involved in signaling cells in various pathways and inhibit invading pathogenic agents. An unbalanced high ROS concentration can help develop various diseases such as cancer, high blood pressure and diabetes, atherosclerosis, and inflammatory disease (Prasad et al. 2018; Zelko, Mariani, and Folz 2002). ROS can also cause oxidative stress by interacting and damaging intracellular targets such as proteins, lipids, DNA. Interestingly, McCord and Fridovich first introduced one crucial antioxidant enzyme of the defense system, superoxide dismutase (SOD). They observed that the enzymatic action converts superoxide anions into H_2O_2 and oxygen (O_2) whereas other enzymes such as peroxidases and catalase convert H_2O_2 into water (McCord and Fridovich 1969).

$$2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2$$

A group of metalloenzymes that are present in plants and animals are superoxide dismutases (SODs). These enzymes

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are the most crucial antioxidants against superoxide anion radicals in which four distinct types of metal centers (Copper/zinc, manganese, nickel, and iron ion) have been detected (Younus 2018). At present, isoforms of SODs have been identified in diverse locations in mammals and other organisms. A homo-dimeric form known as Cu/Zn SOD is localized in either the intracellular cytoplasmic region (Cu/Zn-SOD or SOD1) or extracellular region (EC-SOD or SOD3) (Okado-Matsumoto and Fridovich 2001). Besides, SOD1 commonly found in the chloroplast of plants, periplasm of bacteria (SOD-C) and plenty of regions of the cell such as lysosome, nucleus, and cytosol, among others, and SOD3 enzymes exist as a homotetramer, maintain extracellular localization with a strong affinity for heparin, which was detected in human plasma, cerebrospinal fluids, ascites, and lymph. It has been reported that plants have multiple forms of Cu/Zn -SODs enzymes that cluster into subgroups of cytosolic and chloroplastic SODs. Antioxidant enzymes such as glutathione peroxidase (GPx), SOD, and catalase (CAT) are part of defense mechanisms against oxidative stress and can rapidly inhibit ROS. Besides, Cu/Zn SODs play a crucial role in the bacterial and fungal stationary survival and aerobic growth stages. SOD1 diverges from SOD3 during evolution in animals and in the molecular weight that can make them distinct. It is essential to know that O_2^- is membrane-impermeable because of the localization of SOD in a diverse region. Hence, these superoxide radicals must be detoxified in the place where they are formed (Chang et al. 1988; Crapo et al. 1992; Culotta, Yang, and O'Halloran 2006; Fink and Scandalios 2002; Keller et al. 1991; Owsiak, Bartosz, and Bilinski 2010).

Iron and manganese metal centers SODs are typically homodimers or homotetramers that most possibly evolved from a common predecessor. They frequently bind with Fe and Mn due to their essential structural and sequence preservation but achieve significant activity with the permitted cofactor. However, few changes in SODs will fulfill their purpose for both Fe and Mn ions. Mn-SOD is generally found in prokaryotes (sodA) and mitochondria of the eucaryotes, while Fe-SOD occurs in chloroplast and prokaryotes (SOD-B). On the other hand, Mn-SOD enzymes are indispensable for life because it is present in the mitochondria. This may be due to the release of a significant superoxide ion level, which needs to scavenge immediately (Paul et al. 2007; Wolfe-Simon et al. 2005). Nickel centered superoxide dismutase (Ni-SOD) enzymes are recognized only in cyanobacteria and *streptomyces*; hence, there is not much work related to its activity (Palenik et al. 2003). Additionally, the liver SOD capacity exhibited inhibition of 2 mM KCN (28%) and cyanide (50%) poisoning by pyrogallol autoxidation in mitochondria. In this respect, Cu/Zn-SOD was inhibited by approximately 60% by 2 mM KCN in the liver cytosolic fraction (Nam et al. 2011; Okado-Matsumoto and Fridovich 2001).

SODs have great potential in the medical, cosmetic, food, agriculture, and chemicals industries because of their antioxidative effects. These enzymes are obtained commercially from marine phytoplankton, bovine liver, bacteria, cantaloupe, and horseradish. Considerable clinical experiments have shown, for instance, that SODs can prevent oncogenesis and reduce cytotoxicity (Cullen et al. 2003; Liu et al. 2004). SODs have recently been identified for preventing numerous different illnesses, such as cancer, cardiovascular, diabetes, asthma, infertility, neurological conditions, and transplant rejection (Marklund, Holme, and Hellner 1982; Nelson et al. 2003). In cosmetics, SODs were used for skin protection and acted as vital antioxidant enzymes. They are also applied in animal husbandry to reduce oxidative stress and improve the quality of animal products like meat, egg, milk, and wheat that may improve therapeutic activity (Sola-Penna and Meyer-Fernandes 1998; Xueshan, Xiaopu, and Wenli 2011). Additionally, SOD can inhibit 2 mM KCN (28%) and cyanide (50%) poisoning by pyrogallol autoxidation in mitochondria. Pyrogallol autoxidation is effective in assessing the activity of SOD in the mitochondria and cytosolic fraction of the rat liver (Nam et al. 2011; Okado-Matsumoto and Fridovich 2001). Based on the above discussion and the broad interest in these SODs, the present review summarizes the most recent literature relevant to the therapeutic, nutritional, and other uses of SODs.

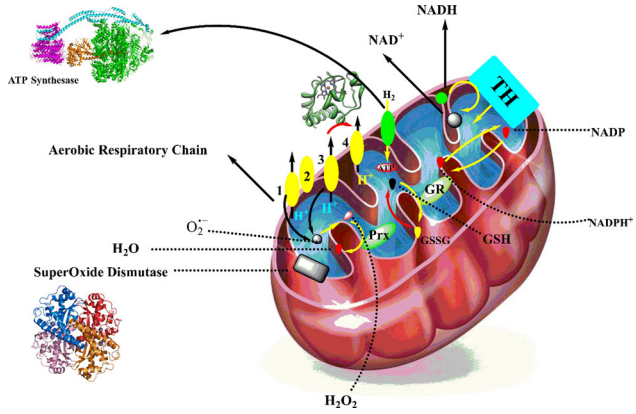

Figure 1. Possible Mechanism of SOD in suppressing various superoxide radicals, oxidative stress, and ROS. ROS: Reactive oxygen species; GPx: Glutathione peroxidase.

Mechanism of action of SOD in food systems

Superoxide dismutase, which is part of the endogenous antioxidant defense system, plays a role in preventing and alleviating oxidative stress. Besides, SOD and other endogenous antioxidants such as CAT, GPx, glutathione reductase (GR), and thioredoxin reductase (TrxR), among others, use various mechanistic actions to ameliorate oxidative injury induced by reactive free radicals. In SOD, the enzyme catalyzes the production of H_2O_2 from superoxide radicals, which is converted to water by CAT, GPx, and Fenton reaction. In short, two harmful substances are converted into harmless species (Pandey and Rizvi 2010). Depicted in Figure 1 is a sketch showing a possible mechanism of SOD in suppressing various superoxide radicals, oxidative stress, and ROS. ROS: Reactive oxygen species; GPx: Glutathione peroxidase.

Functionality and biological activity of SOD

In plants, ecological adversity such as drought, high or low temperatures, flooding, the presence of heavy metals, and macronutrient deficiency often leads to increased production of reduced oxygen and ROS. In this respect, SOD is proposed to play a vital role in the tolerance of plant stress (Stephenie et al. 2020). Blocking different signaling pathways that damage protein via peroxidation by SOD leads to maintaining food quality and reduce premature ageing of tissues and different diseases such as cancer, cardiovascular problems, diabetes, neurodegenerative disorders, and chronic inflammation (Lu et al. 2018).

The role of SOD in the food system; physiochemical properties

SODs are metal-containing proteins that can induce the reactive superoxide anion to less reactive hydrogen peroxide and oxygen. GPx and CAT then act on the peroxide and convert it to water and oxygen (Fernandez et al. 1985; Vitale et al. 2000). Moreover, research findings indicated that large quantities of antioxidants found in food augment the antioxidant defense system present in the body by preventing oxidative stress and several human disorders (Manal Azat Aziz, Diab, and Mohammed 2019).

Production of SOD, from initial techniques to last achievements

Nowadays, SOD has become a crucial topic in the enzyme industry because of its wide range of applications. This has resulted in numerous patents and research papers dealing with the various applications of SODs. In the last 40 years, more than thirty thousand research papers have been published in PubMed indexed journal. Thus, the rate of SODs-related innovations is gaining attention by the scientific and industrial communities.

Earlier, SOD was widely extracted from animal sources such as the serum and liver of pig, chicken, and cattle, employing biochemical methods. Besides, it was obtained from plant sources, including vegetables, seeds, fruits, and cereals. For commercial utilization, low content and efficiency of extraction became the bottleneck, and thus the focus has shifted to methods leading to large scale production development (Bafana et al. 2011). Reducing oxidative stress, SOD could be induced in microbial organisms. For instance, this type of technique was reported by Lopes et al. (2009), where induction of SOD production in *Yarrowia lipolytical* yeast batch culture was achieved by increasing air pressure from 1 to 6 bar (Lopes et al. 2009). However, research on process optimization on SOD production is still under development due to the absence of systematic reports concerning the effect of several oxidative stress conditions on SOD yield.

Consequently, researchers have directed their attention to SOD production through bacterial sources. Several bacteria have been utilized in bioreactors with microfiltration, such as *Escherichia Coli*, *Pseudomonas* and *Brucella*, which contribute to the constant decrease of the inhibitory metabolites and recycling cells to the bioreactor. In a bioreactor, a fed-batch culture of *Streptococcus lactis* generates 4.3-fold higher production of SOD in comparison with other common batch culture (Benov et al. 1996; Taniguchi et al. 1989).

Proteus mirabilis expresses three SOD activities, which depended on soluble iron and oxygen in the culture medium. It also applied to reduce cadmium and lead production of SOD in liquid culture and solid medium. Additionally, SOD activity can be affected in extracts from cells grown in the presence of cadmium, which supports the assumption of interaction between toxic metal ions and iron. Thus, supplements containing Fe could counteract the effect of heavy metal ions such as Cd and Pb, which compete with Fe (Eickhoff et al. 1995). Besides, a *Lactobacillus fermentum* ME-3 strain has been employed to manage GIT and urogenital infections and oxidative stress because of high SOD activity compared with other familiar antimicrobial properties (Mikelsaar et al. 2007). The recent progress in understanding the mechanisms of copper, zinc-superoxide dismutation, with a significance for amyotrophic lateral sclerosis and a focus on evolutionary biology, is regulated through the CCS-dependent and CCS-dependent pathways (Kirby et al. 2008; Leitch, Yick, and Culotta 2009).

Post and novel sources of extraction

Multicellular eukaryotes like algae and filamentous fungi are suitable sources for SOD production due to their intensive respiration and abundant mycelium. Several researchers have reported on SOD production from these organisms. In Cu/Zn SOD production from *Humicola lutea* 103 strain was investigated, where a 1.7-fold increase in SOD activity was achieved by exposure to a 20% of dissolved O_2 (DO). Besides, researchers used a fractional acetone precipitation method for purifying the enzyme by gel filtration chromatography. Moreover, high Mn-SOD instead of Cu/Zn SOD was isolated from a mutant *H. lutea* 110 strain (Angelova et al. 2001; Angelova et al. 1996; Bognar et al. 2006). Similarly, a process for thermostatic Mn-SOD production was developed by Heliosynthese (present name Thallia Pharmaceuticals, France), where thermophilic cyanobacteria were used to isolate Mn-SOD by growing them at 40-80 °C photo-reactors. Here, various cell lysis methods, ultrafiltration, protein precipitation, and chromatography were applied (Gudin and Trezzy 1996).

In the era of recombinant biotechnology development, Hartman et al. (1986) reported that production of SOD enzyme was accomplished in *E. coli* using a vector containing a thermo-inducible lambda PL promoter and beta-lactamase-derived ribosomal binding site. Interestingly, this recombinant human Mn-SOD production is 10% higher than the total bacterial protein. Salt preparation, chromatography, and gel filtration techniques were employed to purify these enzymes (Beck et al. 1988). In Cu/Zn SOD production, *E. coli* was insufficient to saturate the overexpressed SOD due to intracellular concentration of Cu^{2+}. However, the

situation was improved by adding supplementary metal salt in the growth medium (Hartman et al. 1986).

Hence, Beck et al. (1988) proposed using heat shock-inducible λ-based expression technique resulted in 25% higher-level human Mn-SOD (hMnSOD) expression in *E. coli* as compared with the total bacterial protein by Mn^{2+} supplementation. The combination of ion-exchange chromatography and heat treatment methods were used to purify this recombinant enzyme (Beck et al. 1988; Hartman et al. 1986). Another method used metal delivery systems of *E. coli*, which generates SOD proteins. The active site binding required for in vitro re-metallization process of the apo-enzymes production. However, this process is time-consuming and high temperature-dependent (Whittaker and Whittaker 1999). Interestingly, Ahl, Lindberg, and Tibell (2004) described using an *Escherichia coli*-based expression system for the overproduction of human intracellular wild type CuZn-SOD. This is based on the coexpression of SOD variants with yeast copper chaperone yCCS during growth in a medium supplemented with Cu^{2+} and Zn^{2+}. The recombinant SOD enzymes represented 30–50% of the total bacterial protein. These enzymes were purified to homogeneity, and active enzymes were obtained in high yield (Ahl, Lindberg, and Tibell 2004). In another method, site-directed mutagenesis was used to convert low-usage codons to high-usage codons for the same amino acid in the Mycobacterium tuberculosis genes for antigens 85 A and 85B and SOD. This Codon replacement in the genes encoding antigen 85 A and SODe led to four- to six-fold increases in recombinant protein production, suggesting that this strategy may generally apply to overexpression of mycobacterial genes in *E. coli* (Lakey et al. 2000). Eukaryotic hosts (e.g., yeast) were also used for SOD production since eukaryotic proteins were not glycosylated properly in bacteria. In yeast, N-acetylated human SOD expressed a higher level by utilizing yeast glyceraldehyde phosphate dehydrogenase promoter (Hallewell et al. 1987). For overexpression of Mn-SOD, Yue et al. (2008) used a system named the bacmid (baculovirus shuttle vector), which allowed insects like *Bombyx mori* as bioreactors for protein production (Yue et al. 2008). Additionally, human liposarcoma (LSA) cells cultures system were also applied for the production of Mn-SOD. This protein production was carried out by ion-exchange chromatography on Q-sepharose, gel filtration on superdex-75, whereas immune-affinity chromatography was used in this antibody for purification (Mancini 2018).

Human SOD3 (EC-SOD) was isolated and characterized by a complementary DNA clone from the human placenta. The plasmid expression was transfected into Chinese hamster ovary cells, which secreted human EC-SOD to the culture medium. Later, it was placed into the transgenic rabbits to express regulatory sequences for recombinant gene and secreted biologically active SOD. The recombinant protein was fully active (tetrameric form) and showed heparin affinity to reduce coagulation. As a result, production at equivalent levels in transgenic farm animals would yield sufficient extracellular SOD for therapeutic purposes (Hansson et al. 1994; Strömqvist et al. 1997; Tibell et al. 1987).

Similarly, PPL Therapeutics (Pharming, the Netherland), which develops human proteins for therapeutic and nutritional use, has developed a technique for SOD3 production from transgenic lambs. In this respect, He et al. (2002) indicated that 26% of the total cellular protein was obtained using *E. coli* as a host, which could be needed to denature and refold for active enzymes production. Additionally, a good yield of recombinant SOD3 in the *B. mori* system was reported by other researchers (He et al. 2002). Similarly, methylotrophic yeast *Pichia pastoris* was used for the production of SOD. Here, alcohol oxidase-1 gene (AOX1) promotor and yeast-matting factor signal peptide was subjected to construct a synthetic secretion cassette. EC-SOD was exported into the culture medium (440 mg/L concentration) after 36 h of methanol induction, which was suitable for more excellent production of EC-SOD (Chen et al. 2006). A list of effective endogenous, exogenous and various SOD models with their supplementation and disease management therapy for several diseases is shown in Table 1.

Biocatalyst improvements

Though superoxide dismutase enzymes (SODs) have potential antioxidant activity, numerous techniques and methods are applied to improve its physicochemical properties. Cu, Zn-SOD protects against oxidative damage by converting the reactive superoxide radical (O_2^-) to molecular oxygen and H_2O_2 at the active site in a rate-limited reaction by diffusion and enhanced by electrostatic guidance. Getzoff et al. (1992) described a method to improve SOD by enhancing the positive charge or its accessibility at the active site, where the amino-acid site chains that are implicated in electrostatic guidance are Glu 132, Glu 133, and Lys 136 form a hydrogen-bonding network. According to this method, the site-specific mutants that increase local positive charge while maintaining this orienting network (Glu–>Gin) have faster reaction rates and increased ionic-strength dependence. Thus, electrostatically facilitated diffusion rates can be increased while the active-site electrostatic network's structural integrity is maintained. Another study was described by Chockalimgam et al. (2006), where researchers applied mutagenesis on specific amino acids to enhance the activity of SOD (Chockalingam et al. 2006; Getzoff et al. 1992).

Several factors such as pharmacokinetics, biocatalytic activity, stability, efficient targeting, and antigenicity, among others, were considered during the improvement of SODs activity. In this regard, methods including mutation, strain breeding, genetic engineering, and others have been applied to lower the production and activity of SODs. For instance, Veronese et al. (2002) described a method where a conjugation of polyethylene glycol (PEG) with SOD demonstrated more excellent resistance to oxidative stress, improved endothelium relaxation, and inhibited lipid oxidation. Accordingly, the construction of these complex conjugates could help treat disorders related to the heart and lung (Veronese et al. 2002).

Besides, catalase and SOD (CAT-SOD) conjugation may improve the dismutation of superoxide ions (O_2^-).

Table 1. SOD studies and effects based on their various experimental models.

Field of Study	Doses	Subjects	Assay	Outcomes	References
Dietary	SOD UI/gHb (1092–1817)	Human	HPC, clinical enzymology, LC, fluorometry	GliSODin® production and application of GliSODin (500UI-NBT SOD/day)	(Cloarec et al. 2007)
	Melon juice extract (0.7, 2.8 or 5.6 mg/d)	Hamster	Atherogenic diet, HF	Extramel® (Melon juice) containing high SOD to prevent atherosclerosis, liver steatosis, decreases aortic fatty streak (49–85%), cardiac (45%) and liver (67%)	(Décordé et al. 2010)
	alpha-TA (200mg/kg), rosemary (5.7 g/kg)	Broiler chick	TBA, MDA	Improves body weight, feed consumption	(Yesilbag et al. 2011)
	TA (0, 100 and 600 mg/kg)	Shrimp	Na+/K+-ATPase	Reduces acute salinity changes ($P < 0.05$), maintain osmotic balance	(Liu et al. 2007)
	Fish oil (0.4 g/kg)	Male rat	Plasma TBARS, NO, XO, GSH-PX	Remarkably improves SOD activity, reduces TBARS in plasma, decreases FR attack, LP	(Erdogan et al. 2004)
	Cu (13.2 mg/ kg), Se (0.07 mg/ kg), vitamin E group (70mg DL-alpha-TA / kg), vitamin C (200 mg/ kg), vitamin A group (240 mg RA/ kg), vitamin C group (500 mg ascorbic acid / kg) diet	Chicken	n.m.	Remarkably increases (75, 40, 12, 12%) antioxidant activity by CuZnSOD, reduces LPO levels	(Öztürk-Ürek, Bozkaya, and Tarhan 2001)
	B. subtilis (0.0, 0.42×107, 1.35×107 cfu/g)	Fish	SGR, FER	Improves growth, survival capacity, disease management of *Larimichthys crocea* (yellow croaker)	(Ai et al. 2011)
	Sesame seed (5%, 10% dose)	Rats	HC assay	Remarkably decreases HTP, TC, PLDL, improves HD, richest HMG-CoA reductase activity	(Visavadiya and Narasimhacharya 2008)
	Protandim (1 μl/ml), TPA (5 nM)	Mice	JB6 (P+, CL41), JB6 (P-, CL30-7b), WBA	Dietary supplements suppress DMBA/TPA, p53 apoptosis	(Robbins et al. 2010; Stephenie et al. 2020)
Treatment of cancer	NBT (1 mg/mL)	Syngeneic mice	Cell line (BMT-11, BMT-11 cl-9), NBT	Suppresses tumor progression by active SOD derivative of oxykine (41%)	(Okada et al. 2006; Stephenie et al. 2020)
	PC-SOD 40, 80 mg	Human	Clinical trial	Improves UC	(Stephenie et al. 2020; Suzuki et al. 2008)
	EGCG	Human phase I study	Cisplatin, etoposide radiation	Protection from stage III NSCLC increases tissue protection	(Stephenie et al. 2020; Zhao et al. 2014)
	n.m.	U118-9 HMGC	Transfection of cDNA	Mimetic plasmid recombinant production increases activity CuZnSOD (1.5-, 2.0-, 2.6-, and 3.5-fold), decreases tumor growth cell (42%)	(Stephenie et al. 2020; Zhang et al. 2002)
	Protandim (1 μL/mL), TPA (5 nM)	Mice	JB6 (P+, CL41), JB6 (P-, CL30-7b), WBA	Skin cancer (Protandim, dietary supplements), suppresses DMBA/TPA, p53 apoptosis	(Robbins et al. 2010; Stephenie et al. 2020)
	n.m.	Gene (AdMnSOD, AdCuZnSOD)	Cell line (MCF 10A, MDA-MB231, and MCF-7)	Inhibits HBCCG in vitro and in vivo xenograft	(Stephenie et al. 2020; Weydert et al. 2006)
	n.m.	Transgenic mice	IL-10, NF-κB, HIF-1α	Novel therapeutic response for the treatment of angiogenesis and psoriasis.	(Kim et al. 2011; Stephenie et al. 2020)
			n.m.		(Stone et al. 1992)

(*continued*)

Table 1. Continued.

Field of Study	Doses	Subjects	Assay	Outcomes	References
Anti-inflammatory activity	SOD (1,000 IU/kg), PEG-SOD (1,000 IU/kg; U74006F, 3 mg/kg or U78715G. 3 mg/kg)	Sprague-Dawley rat		PEG encapsulation via SOD to reduce inflammation	
	n.m.	Rodent	Pleurisy, carrageenan paw edema	Liposome encapsulation by SOD	(Regnault et al. 1995)
	1, 4, or 13 mg/kg/day	Rat	MPO, lipid peroxidation, Endothelial VCAM-1 assay	Improves Ontosein formulation, suppresses IBS, treatment of colitis	(Seguí et al. 2004)
Drought stress management	n.m.	Plant	NBT-RF	Highest level of SOD activity (304.47–553.53 U/mg protein) from grapevine	(Ju et al. 2018)
Transgenic potato plants production	s.d.	Bacterial codA gene	MVTTA, SSTTA, DSTTA, WBA, RT-PCR assay	Abiotic stress management and synergistic effects	(Ahmad et al. 2010)
Genetic engineering	n.m.	*Escherichia coil*	Recombinant assay	bGH, hGH or SOD analogs production	(Aviv et al. 1997)
Treatment of aging	1×10^9, $(2–3) \times 10^7$, 5×10^5 cells/ml	Yeast	Enzyme activity assay	Reduces SOD-1-deficient strain, successive augmentation of cell viability	(Owsiak, Bartosz, and Bilinski 2010)
	n.m.	Flies and mice	MAA, Sod2 mutants assay	Elevates olfactory behavior (75%), SOD2 inhibiting from aging	(Paul et al. 2007)
	Age (14–22) month	Mice	Novel EC-SOD mimetics, neural signaling pathway	Reduces neurobehavioral damage that accumulates of aging process, lowers AD	(Levin 2005)
Novel enzyme (glycosylated Cu/Zn SOD) production	Bioreactor (3 L)	*Humicola lutea* 103 fungal strain	Ultra-Turrax-IKA-Werk homogenizer, IEC, HPLC	Purification and 1.7-fold augmented SOD production 300×103 U (kg wet biomass)$^{-1}$	(Angelova et al. 2001; Bafana et al. 2011)
Antiviral activity	0.1 ml saline (500 U per mouse/day, IV)	Mice	PI, MST assay	Maximum protection effect from influenza virus	(Angelova et al. 2001)
Recombinant SOD production	n.m.	Bacteria	Yeast-copper chaperone yCCS	Improves total bacterial protein (30–50%)	(Ahl, Lindberg, and Tibell 2004)
Antibacterial activity	s.d.	Planktonic bacteria (*Proteus mirabilis*)	1X and 1Y (Resistant variants), MIC	Natural resistance developing and increases antioxidant defense activity by SOD	(Aiassa, Barnes, and Albesa 2010; Bafana et al. 2011; Eickhoff et al. 1995)
Human MnSOD production	n.m.	*Escherichia coil*	IEC, P_L promoter, Recombinant hMnSOD assay	Enhances enzymatic activity	(Beck et al. 1988)
GIT and urogenital infections	s.d.	Bacteria	*L. fermentum* ME-3 strain	Management OS, ROS, infections	(Mikelsaar et al. 2007)
Biomass production	n.m.	*Humicola lutea* 110	Fermentation, shake-flask cultures	Intensifies O_2^- generation, maximum protein SOD effect (84.1 and 120.8 U/mg)	(Angelova et al. 1996)
Treatment of TMJ dysfunction	i.i.	Human	30 joints in 29 patients	Orgotein production, SOD effective (83%) for 25 joints	(Lin, Pape, and Friedrich 1994)
Treatment of Myeloid Graffi tumor	*H. lutea* SOD (65 U, 125 U)	Hamsters	MST, PS assay	Latent elongation time of tumor appearance reduces early stage of tumor growth progression rate (73–75%, 10 days), and increases mean survival time (5.2 days)	(Angelova et al. 2001)
Antioxidant activity	s.d.	Plant seed	Enzymatic cofactor, UVA	Food, cosmetics, pharmaceuticals compositions and enhanced temperature stabilization	(Bafana et al. 2011; Bresson-Rival et al. 1999)

(*continued*)

Table 1. Continued.

Field of Study	Doses	Subjects	Assay	Outcomes	References
	n.m.	Rat	Sertoli cell cultures SOD_{EX}	Regulating germ cell and male fertility	(Mruk et al. 2002)
	n.m.	Human	Lung mechanics (elastance), FVC, Sp_{o2}	Cures the IPF, PC-SOD impedes lung fibrosis	(Tanaka et al. 2012)
	TA (0, 100 and 600 mg/kg)	Shrimp	Na+/K+-ATPase	Reduces acute salinity changes ($P < 0.05$), maintains osmotic balance	(Liu et al. 2007)
	Fish oil (0.4 g/kg)	Male rat	Plasma TBARS, NO, XO, GSH-PX	Decreases FR attack, LP and to manage numerous disease	(Erdogan et al. 2004)
	Cu (13.2 mg/ kg), Se (0.07 mg/ kg), vitamin E group (70 mg DL-alpha-TA / kg), vitamin C (200 mg/ kg), vitamin A group (240 mg RA/ kg), vitamin C group (500 mg ascorbic acid / kg) diet	Chicken	n.m.	Remarkably increased (75, 40, 12, 12%) antioxidant activity by CuZnSOD, reduces LPO levels	(Öztürk-Ürek, Bozkaya, and Tarhan 2001)
	B. subtilis (0.0, 0.42 × 107, 1.35 × 107 cfu/g)	Fish	SGR, FER	Improves growth, survival capacity, disease management of *Larimichthys crocea* (yellow croaker)	(Ai et al. 2011)
Anti-diabetic activity	Sesame seed (5%, 10% dose)	Rats	HC assay	Remarkably decreases HTP, TC, PLDL, improves HD, richest HMG-CoA reductase activity	(Visavadiya and Narasimhacharya 2008)
	n.m.	Rat	n.m.	Glisodin® production to manage Type 2 diabetes	(Trea et al. 2013)
Treatment of Respiratory disease	rhMnSOD 3mg/kg/day, 1–10 mg/ kg/day MnSOD,	Baboon	Hemodynamics, respiratory variables (Pa_{o2})	Reduces HPD, PSF, maintain arterial oxygen supply	(Simonson et al. 1997; Welty-Wolf et al. 1997)
	PC-SOD 500 mg/kg, PBS (1 mL/kg)	Human	TUNEL, RT-PCR assay	Decreases IPF, PC-SOD impedes lung fibrosis	(Tanaka et al. 2010)
	n.m.	Human	Lung mechanics (elastance), FVC, Sp_{o2}	Cures the IPF, PC-SOD, impedes lung fibrosis	(Tanaka et al. 2012)
Treatment of Cardiovascular disease	SOD 100 IU /mg, catalase 10 IU /mg and GPx 1 IU /mg	Pig	TUNEL, immunoassay	melon extract/gliadin SOD after aortic cross-clamping to decreases DNA damage, to decrease oxidative cell injury	(Kick et al. 2007)
	n.m.	Hamster	n.m.	Extramel® juice prevent atherosclerosis, liver steatosis, decreases aortic fatty streak	(Décordé et al. 2010)
Soil stress treatment	n.m.	Plant	NBT-RF	Reduces soil flooding by Fe-SOD (55%), improves AOS	(Yordanova, Christov, and Popova 2004)

n.m.: Not mentioned; s.d.: Several doses; SODEX: SOD expression; NBT-RF: Nitrobue Tetrozolium/Riboflavin; X-XOD: xanthine/xanthine oxidase; GR: glutadione reductase; APX: ascorbate peroxidase; POD: peroxidase; o.a.: Oral administration; i.i: Intraarticular injection; TMJ: Temporomandibular joint; IBS: Inflammatory bowel disease; VCAM-1: Vascular cell adhesion molecule 1; PEG: Polyethylene glycol; HPC: HP chromatography; LC: Liquid chromatography; HMGC: Human malignant glioma cells; HBCCG: Human breast cancer cell growth; WBA: Western blot analysis; IL: Interleukin; PKC: Protein kinase C; VEGF: Vascular endothelial growth factor; MMP: Matrix metalloproteinase; TIMP; Tissue inhibitor of metalloproteinase; NSCLC: non-small-cell lung cancer; EGCG: Epigallocatechin-3-gallate; NBT: Nitroblue tetrazolium; UC: Ulcerative colitis; HPD: Hyperoxic pulmonary distress, PSF: Pulmonary shunt fraction; IPF: Idiopathic pulmonary fibrosis; TA: Tocopherol acetate; TBARS: Thiobarbituric acid reactive substances; NO: Nitric oxide; XO: Xanthine oxidase; GSH-PX: Glutathione peroxidase; FR: Free radical; LP: Lipid peroxidation; RA: Retinol acetate; SGR: Specific growth rate; FER: Feed efficiency ratio; HTTP: Hepatic total lipid; TC: Total cholesterol; PLDL: Plasma LDL-cholesterol; HC: Hypercholesteraemia; MAA: Mitochondrial aconitase activity; AD: Alzheimer's disease

Maksimenko (2005) and Maksimenko et al. (2010) suggested a method that involves a superoxide dismutase-chondroitin sulfate conjugation, which significantly reduced the thrombus mass by improving the bio-catalytic activity of this enzyme (Maksimenko et al. 2010; Maksimenko 2005). Similarly, Eremin, Litvinchuk, and Metelitsa (1996) showed that CAT conjugation to aldehyde dextran's and SOD in microemulsions enhances both enzymes' stabilities (Eremin, Litvinchuk, and Metelitsa 1996). Moreover, researchers genetically engineered a hybrid chimeric SOD called SOD2/3 with greatly improved pharmacological properties. Rosenbaugh and colleagues developed a non-viral delivery

system in which CuZnSOD protein is electrostatically bound to a synthetic poly(ethyleneimine)-poly(ethyleneglycol) (PEI-PEG) polymer to form a polyion complex (CuZnSOD nanozyme). Results showed that CuZnSOD nanozyme inhibits AngII intra-neuronal signaling in vitro and in vivo. Route of administration also became a crucial factor for SOD activity in the human body. Within this context, Kaipel and coworkers investigated methods to improve the biological half-life of recombinant human Cu/Zn SOD (rhSOD) within systemic circulation by liposomal encapsulation and aerosolization into the lungs. This was accomplished using a "needle-free" route of drug administration via the lungs combined with the sustained release effect of liposomes in an experimental pig model. These researchers showed that biologic half-life within systemic circulation was substantially prolonged in aerosol-treated animals compared to intravenously administered liposomal rhSOD (Kaipel et al. 2008).

Pharmaceutical applications of SOD

Superoxide dismutase (SOD), one of the most efficacious antioxidants in nature, can be given as a supplement to prevent or reverse several disorders' chronicity. The enzyme elevates cellular repair and rejuvenation by inhibiting the injury induced by reactive free radicals (Manal Azat Aziz, Diab, and Mohammed 2019).

SOD in cancer management

Several studies have revealed the importance of oxidative stress in carcinogenesis and the induction of mutation caused by ROS, which is regarded as an endogenous carcinogen (Cerutti and Amstad 1993; Guyton and Kensler 1993; Oberley 2004). Studies showed reduced activities of CuZn-SOD and Mn-SOD in cancer cells and amelioration of SOD level, which promotes cancer cell phenotype reversion (Guyton and Kensler 1993; Oberley 2004). These findings also indicated that the endogenous antioxidant enzyme could control the progression of cancer, and thus can serve as a novel target in the treatment of cancer (Glasauer et al. 2014; Papa, Hahn, et al. 2014; Papa, Manfredi, et al. 2014; Tsang et al. 2014). Besides, CuZn-SOD could play a vital role in managing multiple myeloma (Salem et al. 2015). On the other hand, Li et al. (2005) proposed that SOD contributes to the migratory and invasive actions of pancreatic (bladder) cancer via stimulation of H_2O_2/extracellular signal-regulated kinase/nuclear factor-kappa B axis (Li et al. 2005).

Research findings indicated that SOD liposome and mimetics are promising and effective in cancer prevention animal models. These liposomes are safe as per early phase clinical trials. Hence, dietary supplement-based SOD cancer prevention highlights the importance of antioxidant-based cancer prevention. Besides, SOD inhibits oncogenic activity and subsequent metabolic shifts during early tumorigenesis (Robbins and Zhao 2014). Interestingly, published research showed that SOD mimetics effectively manage castration-resistant prostate cancer where the expression of SOD-2 is highly reduced (Thomas and Sharifi 2012). Moreover, Yulyana and coworkers described an efficacious SOD mimetic called MnTnBuOE-2-PyP(5+), which stimulates tumor necrosis factor-related apoptosis-inducing ligand that is mediated by carbenoxolone in brain tumor (Hina Younus 2018; Yulyana et al. 2016).

SOD in skin management

SOD is required to produce specific quantities of skin building cells to manage fibroblasts and play a role in inhibiting amyotrophic lateral sclerosis. This condition can lead to mortality when nerves in the brain and spinal cord are affected. However, the presence of SOD can alleviate this condition and thereby prevent brain and spinal cord nerve injury. Furthermore, SOD can be used to manage inflammatory disorders, prostate impairments, arthritis, corneal ulcer, and burn injuries and can ameliorate and suppress the smoke and radiation exposure (Manal Azat Aziz, Diab, and Mohammed 2019; Carillon et al. 2013).

Hence, SOD can be used as a pharmaceutical product to attenuate the aforementioned abnormal conditions. Published work indicated that SOD could block the formation of wrinkles. It can also promote the healing of wounds, scars reduction, and lightens pigmentation of the skin induced by ultra violet radiations. Therefore, lotions and other pharmaceuticals containing SOD could exhibit these ameliorative properties. Furthermore, SOD promotes the movement of nitric oxide into follicles of hair. This action of SOD is vital for individuals with genetic predisposition or free radicals for hair loss impairment. The enzyme exhibits this action by abrogating reactive free radicals from nitric oxide-relaxed into blood vessels resulting in alleviation or prevention of hair loss. In this respect, intakes of dietary supplements containing SOD can sustain the total health and well-being and prevent the production of free reactive radical production (Manal A Aziz et al. 2016). Figure 2 depicts protecting mechanism of SOD.

SOD in aging attenuation

SOD is regarded as an anti-ageing enzyme, and the involvement of free radicals in aging is documented (Harman 1991). In this regard, oxygen-free radicals produced in metabolic cascades lead to age-associated deterioration via oxidative damage to biological molecules involving mitochondria as the actual organ of attack. Oxidative stress injury accumulation is also regarded as ageing's main mechanistic actions (Harman 1992; Hekimi and Guarente 2003; Longo and Finch 2003). It is also known that elevated SOD activity can be used to protect against oxidative stress-induced neurotoxicity, where acutely increased extracellular-SOD (EC-SOD) activity protects against neurobehavioral impairment caused by acute ischemia. Furthermore, chronically increased EC-SOD activity might help against chronic oxidative stress-induced neurobehavioral damage, which accumulates during the aging process. In this respect, mice with

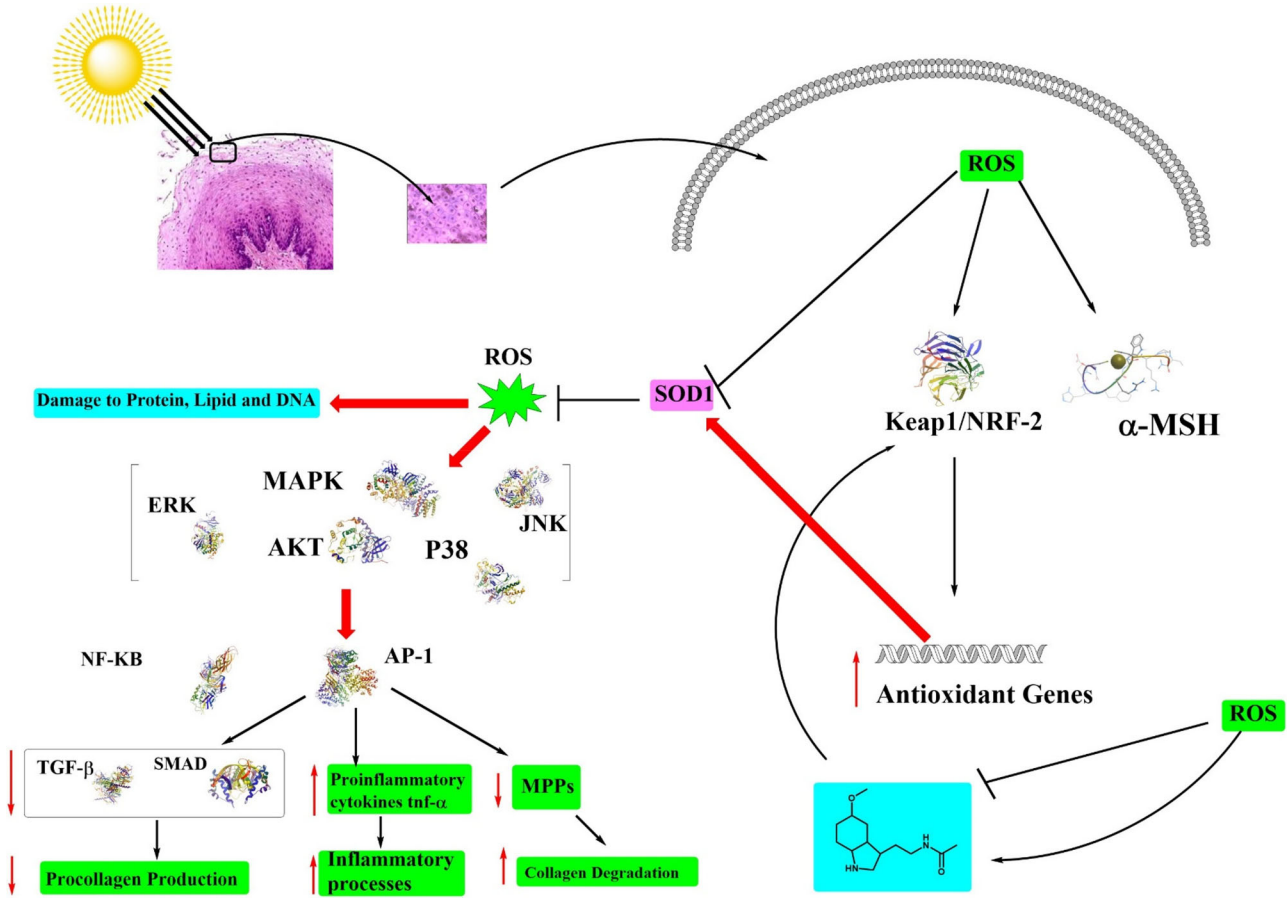

Figure 2. Schematic of SOD protecting mechanisms in skin therapy.

genetic overexpression of EC-SOD do not show the ageing-induced decline in learning and memory. This implies that EC-SOD mimetics may help attenuate ageing-induced cognitive impairments and other physiological decline aspects with aging. Similar findings by Paul and coworkers highlighted Mn-SOD's role in protecting animals from aging and age-associated pathology. This was established by generating a collection of Drosophila mutants that progressively reduce SOD2 expression and function. Results suggest that new SOD mimetics may be vital in ameliorating cognitive impairments induced by aging and other areas of physiological abnormality with aging (Levin 2005; Paul et al. 2007).

SOD in management of cystic fibrosis

Management of cystic fibrosis is another area where SOD could be employed. The disease is characterized by stimulated neutrophils and chronic inflammation (De Rose 2002). Madarasi et al. (2000) reported that the level of SOD in the plasma of patients with cystic fibrosis is low compared to that of healthy persons (Madarasi et al. 2000). Also, individuals with cystic fibrosis showed decreased activities of Cu/Zn-SOD in polymorphonuclear, mononuclear, and red blood cells. It was observed that the anti-fibrotic action of Cu/Zn-SOD is controlled by repression of the transforming growth factor-beta 1 (TGF-β1) followed by phenotypic reversion of myo-fibroblasts. Similarly, breast fibrosis induced by radiation was remarkably decreased by Cu/Zn-SOD. (Vozenin-Brotons et al. 2001).

Besides, Rottner et al. (2011) showed evidence that high oxidative stress is associated with increased apoptosis in cystic fibrosis transmembrane conductance regulator (CFTR)-mutated cells. Furthermore, these researchers found, at least partly by lowered EC-SOD activity and controlling Cu/Zn-SOD and Mn-SOD expressions, a reduced protection mechanism for anti-oxidant. These results reveal novel therapeutic potential targeting antioxidant cascade involving SOD; thus, apoptosis and oxidative stress can be alleviated in cells with cystic fibrosis, and pro-inflammatory stimulus can be reduced (Rottner et al. 2011).

SOD in diabetes management

Elevated oxidative stress plays a vital role in the pathogenesis of diabetes and related complications (Baynes 1991; Baynes and Thorpe 1999; Ceriello 2000). During diabetes, prolonged hyperglycemia activates ROS production from different sources, resulting in an impaired antioxidant defense system. Furthermore, there is an elevated production of superoxide anion radical from endothelial cells in diabetes. Du et al. (2003) concluded that the produced superoxide anion radicals abrogate the glyceraldehyde-3-phosphate dehydrogenase (GAPDH) effect, a vital enzyme found in glycolysis (Du et al. 2003). This results in the accumulation of glucose and other intermediate compounds of

this metabolic pathway and moves to other shunt pathways of sugar metabolism with elevated glycated end products' production.

In diabetic animals, SOD treatment decreases oxidative stress in the liver, and the enzyme mimetic was known as Mn-II (pyane) C12, was efficacious in the management of diabetes (Di Naso et al. 2011; Stančić et al. 2013). Similarly, Kuo et al. (2015) showed that chemically altered SODs, such as poly (methyl vinyl ether-co-maleic anhydride)-SOD carboxymethylcellulose-SOD were efficacious in treating diabetes and give a therapeutic edge in human use. Besides, it was shown that EC-SOD could serve as a therapeutic agent to inhibit the ROS/ERK1/2 signaling pathway. Thus, inactivate the diabetic nephropathy progression in the rat model (Kuo et al. 2015).

SOD in treatment of inflammatory disorders

Cell neutrophils are involved in the inflammation of pathogenesis. SOD acts as an endogenous cellular defense system to degrade the superoxide ion into oxygen and hydrogen peroxide under oxidative stress. Hence, SOD can act as a therapeutic agent for the treatment of inflammatory disorders. A mechanism that involves the regulation of neutrophil apoptosis may contribute to the efficacy of SOD. In this activated neutrophils must be removed by apoptosis, where neutrophil apoptosis has been suggested as a possible target for controlling neutrophil-mediated tissue injury. It has been suggested that added SOD induces neutrophil apoptosis, and hydrogen peroxide has been proposed as a possible primary mediator of ROS-induced neutrophil apoptosis. Furthermore, SOD may be helpful as an inhibitory mediator of neutrophil-mediated inflammation (Yasui and Baba 2006). Moreover, superoxide anion radical induces stimulation of endothelial cells and activates neutrophils' infiltration for providing protective effects in myocardial ischemia (M40403) (Masini et al. 2002; Yasui and Baba 2006).

Published research reported that treatment with SOD inhibits superoxide anion radical and neutrophil infiltration in transgenic mice, with overexpressed extracellular SOD, decreases lung injury (Ghio et al. 2002). Besides, apoptosis of neutrophil is vital in inflammation resolution, and in patients with Down syndrome (DS), apoptosis of neutrophil elevates the expression of CuZn-SOD. Furthermore, accelerated apoptosis of granulocytes may be a factor to prevent chronic airway inflammation and bronchial asthma in DS individuals (Kozo Yasui et al. 1999). Similarly, researchers indicated that SOD could be used as an inhibitory agent for inflammation-mediated by neutrophil and can serve as a new therapeutic strategy for the ROS-dependent tissue impairment through different mechanistic actions (K Yasui and Baba 2006). Additionally, preclinical studies involving bovine CuZn-SOD revealed promising results for its use as a human therapeutic agent in chronic and acute inflammation. Furthermore, SOD based CuZn-SOD, Mn-SOD of extracellular sources could serve as promising remedies to attenuating inflammations such as lipopolysaccharide-induced neutrophilic inflammation in a various animal model (Bowler et al. 2004; Joseph et al. 2008; Porfire et al. 2014).

SOD in the management of ischemia

Superoxide anion radical and its reaction products such as peroxynitrite as well as other ROS contribute to tissue and endothelial injuries linked with reperfusion and cerebral ischemia and play a significant role in the pathogenesis of cerebral infarction in reperfusion injury after a focal stroke (Bognar et al. 2006; Ye et al. 2011). On the other hand, research findings showed that CuZn-SOD overexpression decreases ischemic injury caused by reperfusion in transgenic mice (Yang et al. 1994). However, SOD mimetic treatment helps remove peroxynitrite and superoxide anion radicals and prevents failure of cellular energies and tissue injury linked to ischemia (Salvemini and Cuzzocrea 2002).

SOD in neurodegenerative diseases management

Oxidative stress plays a major role in the pathogenesis of numerous neurodegenerative disorders. Researchers demonstrated that the activity of SOD and other antioxidant enzymes such as GPx and CAT decreases in individuals with Alzheimer's disease and suggested a potential mechanism for combining helical filament development (Pappolla et al. 1992; Zemlan, Thienhaus, and Bosmann 1989). However, familial amyotrophic lateral sclerosis, a chronic neurodegenerative disorder that causes selective loss of motor nerve cells, has been associated with many mutations in CuZn-SOD (Cleveland and Rothstein 2001). Similarly, brain Cu/Zn-SOD is the main affected enzyme to manage oxidative stress in Parkinson's and Alzheimer's diseases (Choi et al. 2005). Consequently, supplementation with SOD caused an amelioration effect in experimental mice for Alzheimer's disease by enhancing plasma thiols concentration levels (Persichilli et al. 2015). Meanwhile, CAT/SOD mimetic (EUK-207) exerted an inhibitory effect against amyloid and tau protein secretion for cognitive impairment in experimental mouse (Clausen et al. 2012).

SOD in rheumatoid arthritis management

Rheumatoid arthritis, a systemic disorder characterized by severe inflammation in the synovium of joints, induces degeneration of cartilage and juxta-articular bone erosion. Impaired antioxidant state or elevated oxidative stress are involved in rheumatoid pathogenesis (Mahajan and Tandon 2004). SOD and other antioxidants such as vitamin E showed anti-inflammatory action in experimental animals with arthritis. Besides, the activity of SOD reduced rheumatoid arthritis formation via lipid peroxidation in mitochondria, which was reported in several case studies (Karatas et al. 2003). In this regard, SOD administration via liposome was also an effective medication in experimental animals against arthritis development (Ugur et al. 2004). Figure 4 depicted in overall therapeutic activity of SOD.

Industrial application

Dairy industry

Enzymes are proteins that are precise in their action and catalyze specific reactions. Enzymes are widely used in the dairy industry to generate better dairy products and for future dairy technology. Significant nutritional dairy products were obtained to overcome malnutrition and obesity and shift toward low fat and healthy foods. After inventing different techniques that employ SODs, the dairy industry focuses on development by adding SOD to dairy products (Mir Khan and Selamoglu 2020; Wengui 1994). Similarly, reported that SODs are used as effective antioxidants in packaged dairy foods, which are more effective when combined with CAT. Several manufacturers worldwide, including Nestle, SmithKline Beechem, and Amul, among others, have made milk products and used enzymes for biotechnological development (Zaheer and Gupta 2019). On the other hand, Neelakantan, Mohanty, and Kaushik (1999) indicated that microbial enzymes, including SOD, are used in milk products in the dairy industry (Neelakantan, Mohanty, and Kaushik 1999).

Ghasemian and colleagues evaluated the activities of erythrocyte superoxide dismutase (e-SOD) and its functional components, Cu and Zn, in cows with

subclinical mastitis and normal cows. Results revealed that optimum antioxidant intake in the feed might enhance the resistance against subclinical mastitis. This implies that erythrocyte superoxide dismutase (e-SOD) plays a vital role to overcome these obstacles and that the dairy industry provides supplements for cattle and cows (Ghasemian et al. 2011). Besides, several investigators have indicated that SOD is present in milk, and its presence lowers the oxidation of homogenized milk in the absence of light (Hicks 1980; Hicks, Koryckadahl, and Richardson 1975). In the dairy industry, the gram-positive bacterium *Lactococcus lactis* is of paramount importance due to its conversion of lactose to lactic acid, which causes acidification of milk. Other researchers investigated that proteins are induced when *L. lactis* is subjected to exposure by gel electrophoresis and exposed to low p^H. These researchers identified SOD as one of these proteins and that it plays a role in processing milk products, which could lead to dairy industrial development (Frees, Vogensen, and Ingmer 2003; Kimoto-Nira et al. 2014).

Production of protein hydrolysates

Protein hydrolysates are the complex mixture of peptides, free amino acids, and oligopeptides produced by extensive or partial hydrolysis. These hydrolysates could provide nutritional support to patients with plenty of needs and used for managing food allergy, phenylketonuria, and chronic failure in the liver (Clemente 2000). According to Culotta, Yang, and O'Halloran (2006), the human SOD3 is an extracellular homotetramer that maintains its location because of its strong affinity to heparin found on cell surfaces. Researchers determined the active SOD through soluble protein and soluble sugar content of *Camellia sinensis* leaves under low-temperature stress; soluble protein and sugar content increase with cold stress (Zhu et al. 2011). Furthermore, the proteolysis process can be used to remove the heparin-binding domain to control its mobility in tissues (Culotta, Yang, and O'Halloran 2006). These findings demonstrate that antioxidants are part of the diet. However, their bioavailability through dietary supplementation depends on several factors such as poor solubility, inefficient permeability, instability due to storage of food, and degradation in the gastrointestinal tract first-pass effect and GI degradation (Ratnam et al. 2006).

Taniguchi and colleagues developed a microfiltration bioreactor for the production of SOD by *Streptococcus lactis*, which involves the continuous removal and cell recycling of inhibitory metabolites from the bioreactor (Taniguchi et al. 1989). Research findings showed that an increasing number of proteins overexpressed in heterologous hosts as recombinant biotechnology being developed. Another study reported that SODs derived from recombinant production systems were found in their metal cofactor (Beck et al. 1988; Hartman et al. 1986). Besides, the effect on Angiotensin II (Ang II) by up-regulating levels of SOD and hemo-oxygenase-1 (HO-1), and by down-regulating the levels of xanthine-oxidase-1 (XO-1) was strong; this results in an antioxidant effect to inhibit the production of ROS in endothelial human umbilical vein cells (HUVECs). Thus, peptides isolated from protein hydrolysates of SOD may be used in the food and drug industries as potential antioxidants.

Baking industry

Superoxide dismutase enzymes have a wide range of application in the baking industry (Arora 2020; Singh et al. 2016). In this respect, SODs have been employed to regulate the intensity of processing free radical in living tissues for making wheat flour biochemical composition (Kaprelyants, Fedosov, and Zhygunov 2013). Besides, yeasts are widely applied in bakery products. Interestingly, Cu/Zn SOD enhanced the activity of stress resistance of yeast by scavenging superoxide radical (Qiu et al. 2019; Randez-Gil, Corcoles-Saez, and Prieto 2013). In the baking industry, people commonly use potassium bromate as leaven in flour dough. However, it should be avoided. In this process, Cu/Zn SOD showed significant activity in reducing oxidative response (Nwonuma et al. 2015). In short, wheat grains play a vital role in the baking industry due to the production of SOD, which mitigates oxidative stress. Various phytochemicals in wheat grains, such as polyphenol, enhance the activity of SOD (Arshad et al. 2017).

Brewing and wine industry

In the global wine technology, Cu/Zn SODs were used for detoxifying the products (Vivier and Pretorius 2002). In this regard, Gamero-Sandemetrio, Gómez-Pastor, and Matallana (2013) indicated that SOD and catalase zymogram profiles increase the high fermentative capacity and stress tolerance

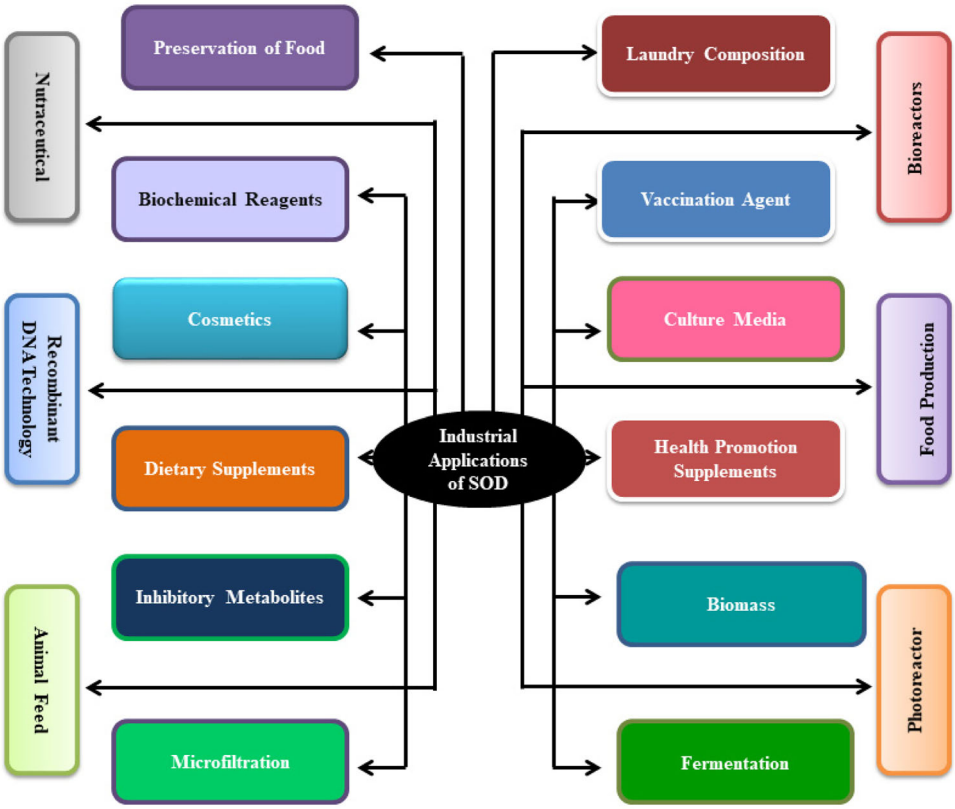

Figure 3. Industrial applications of SOD.

of yeasts in the wine industry (Gamero-Sandemetrio, Gómez-Pastor, and Matallana 2013; Landolfo et al. 2008). In yeasts, SOD mutants reveal both cytosolic SOD1 and SOD2, which are used as pro-oxidants for sterilization of wine vessels and preserved the wine products (Piper 1999). In this context, grapes were frequently used in the wine industry, whereas industrial waste such as grape seed meal (GSM) increase the activity of SOD in the duodenum and reduce lipid peroxidation, which was a notable development in the wine industry (Pistol et al. 2019). In addition, researchers have developed SOD biosensors to evaluate the antioxidant capacity of several red and white wines. This method is based on comparing the response of these biosensors to increasing concentration of the superoxide radicals produced in solution by the xanthine/xanthine oxidase system, both in the presence and absence of the test sample; results were compared with those traditional spectrophotometric and spectro-fluorometric methods (Campanella et al. 2004). Similarly, research findings showed that SOD has significant potential to reduce the rancid ability of original malt juice and stabilize the flavor of beer during the fermentation process in the wine industry (Yu-Lan 2011).

Animal feed

Yesilbag and coworkers evaluated the effects of dietary supplementation with vitamin E, dried rosemary leaves and volatile rosemary oil on the performance, meat quality, and serum SOD activity in broilers fed on maize-soybean meal-based diets. These researchers demonstrated that dietary supplementation with rosemary and its volatile oil improved broiler meat quality. Besides, results showed that rosemary volatile oil supplementations positively affect these broilers' growth performance (Yesilbag et al. 2011). Furthermore, the same dietary supplementation significantly reduced *E. coli* counts in meat samples from experimental groups. On the other hand, an investigation by Rui, Nie, and Tong (1990) revealed that cultivars with high initial and stress-induced SOD activities are more tolerant of photo-inhibition than those with low initial and stress-induced SOD activities.

Moreover, these researchers indicated that in 5 drought-resistant cultivars, SOD activity and water stress resistance are positively correlated (Rui, Nie, and Tong 1990). Oxidative stress relief was also reported for the carcinogenic hosts of the protein-bound polysaccharide *Coriolus versicolor* QUEL (PS-K), which expresses the mimetic activity of SOD. Findings indicated that oxidative stress decreases to the normal level one day after the initial administration of PS-K3.0 g/day in human cancer patients (Kobayashi et al. 1994). Figure 3 is a general industrial application of SOD, where the enzyme is a priority for large-scale production for pharmaceutical and industrial purposes.

Conclusions and future trends

A common consensus has been recognized on antioxidant therapy and its preventive role against various diseases, including cancer. The inhibitory actions of antioxidants present in food items such as vegetables, fruits, and phytochemicals derived from these against numerous diseases have

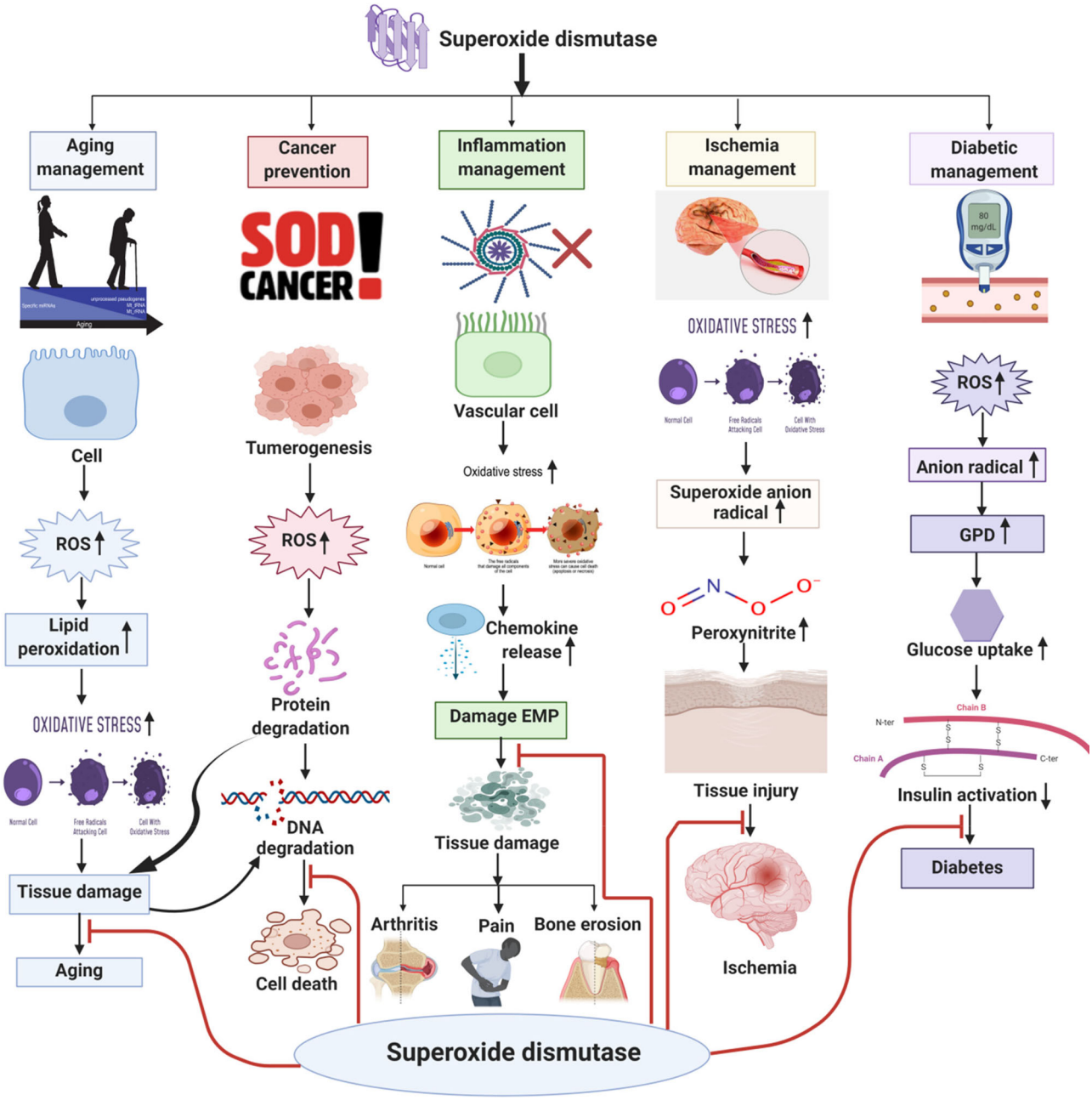

Figure 4. The mechanistic illustration of the therapeutic potential of SOD.

opened new avenues to explore their ameliorative perspectives and reparative characteristics. Investigations and findings discussed in the present work indicated the multifaceted activities of SODs, which support their use as food ingredients. These SODs exhibit high antioxidant activity and are involved in a variety of diseases as preventive agents. They regulate oxidative stress, lipid metabolism, inflammation, and oxidation in cells. In addition, SODs exert antioxidant effects, augment food processing and pharmaceutical applications, exhibit anticancer, antioxidant, and anti-inflammatory effects, as well as prevent arterial problems by protecting the proliferation of vascular smooth muscle cells by acting against superoxide anion radicals.

In the present review, a wide range of pharmacological, medicinal, and industrial values for SODs were discussed, as they mitigate possible oxidative injuries by scavenging free radicals, counteract aging, reduce free skin damage to fibrosis as a result of breast cancer radiation, strongly support treating oxidative stress-related diseases, and emerged as a promising alternative for the prevention and treatment of diseases.

Scale-up production and optimization remain an unending field of research related to anti-oxidants, including enzymes, and phytochemicals, which play a synergistic role with SODs. In short, articles provided in this review highlight the health benefits of SODs, which may be used to develop new dietary supplements and drugs that will improve the recovery, reproducibility, and stability of products. Besides, nanotechnologies and colloidal dispersions are used to formulate an effective food system, which can be employed to encapsulate and provide usable SODs to defend against oxidation and oxidative stress problems, one area of

research worth exploring. Over the decades, the enzyme in reactive oxygen biology has set several benchmarks. This review has provided updated details pertaining to the growing interest of SODs in food, medical, and industrial applications.

Acknowledgements

Authors are thankful to the higher education commission of Pakistan. The authors are also grateful to the Department of Pharmacy, International Islamic University Chittagong, Bangladesh for their supports.

Funding

This research received no external funding.

Conflicts of interest

The authors declare no conflict of interest.

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