Article

Superoxide dismutase (SOD): Physicochemical properties, pharmacokinetics, therapeutic applications, and perspectives

WenJun Zhang
School of Life Sciences, Sun Yat-sen University, Guangzhou, China
E-mail: zhwj@mail.sysu.edu.cn, wjzhang@iaees.org

Received 20 April 2026; *Accepted 29 April 2026*; *Published online 18 May 2026*; *Published 1 March 2027*

Abstract
Superoxide dismutase (SOD) constitutes the first line of defense against oxidative stress by catalyzing the dismutation of superoxide anion radicals ($O^{\bullet -}$) into molecular oxygen and hydrogen peroxide. Since its discovery in 1969, SOD has been extensively characterized across species ranging from bacteria to mammals, revealing a family of metalloenzymes with distinct metal cofactors, subcellular localizations, and regulatory mechanisms. This comprehensive review synthesizes over five decades of research on SOD, encompassing its discovery history, molecular structure and classification, physicochemical properties, extraction and purification methodologies, pharmacokinetics, and multifaceted pharmacological actions. The therapeutic potential of SOD has been investigated in numerous pathological conditions, including aging, skin photoaging, cardiovascular diseases, neurodegenerative disorders, cancer, radiation injury, diabetic complications, and organ protection. Clinical trials have demonstrated both promise and limitations, with bioavailability remaining a central challenge. Recent advances in SOD mimetics, nanozyme formulations, and targeted delivery systems have opened new avenues for therapeutic application. This review critically evaluates the current state of knowledge, identifies gaps in understanding, and proposes future research directions to harness the full therapeutic potential of SOD.

Keywords superoxide dismutase; oxidative stress; antioxidant; free radicals; SOD mimetics; nanozymes; therapeutic applications.

Network Biology
ISSN 2220-8879
URL: http://www.iaees.org/publications/journals/nb/online-version.asp
RSS: http://www.iaees.org/publications/journals/nb/rss.xml
E-mail: networkbiology@iaees.org
Editor-in-Chief: WenJun Zhang
Publisher: International Academy of Ecology and Environmental Sciences

1 Introduction

Reactive oxygen species (ROS) are continuously generated as byproducts of aerobic metabolism and play dual roles in cellular physiology: at low to moderate concentrations, they function as signaling molecules, while excessive accumulation leads to oxidative damage of lipids, proteins, and DNA (Sies, 1997; Halliwell & Gutteridge, 2015). The superoxide anion radical ($O^{\bullet -}$) represents the primary ROS generated through mitochondrial electron transport chain leakage, NADPH oxidase activity, and xanthine oxidase reactions

(Turrens, 2003; Bedard & Krause, 2007). To counteract oxidative stress, organisms have evolved a sophisticated antioxidant defense network comprising enzymatic and non-enzymatic components (Jomova et al., 2024). Superoxide dismutase (SOD, EC 1.15.1.1) stands at the forefront of this defense system, catalyzing the dismutation of superoxide radicals at diffusion-limited rates (McCord & Fridovich, 1969; Forman, 1973).

The biological significance of SOD is underscored by its ubiquitous distribution across all oxygen-metabolizing organisms, from bacteria to humans, and by the lethal consequences of its genetic ablation in model organisms (Carlioz & Touati, 1986; Li et al., 1995; Lebovitz et al., 1996). The field of free radical biology itself originated with the discovery of SOD, which provided the first compelling evidence that superoxide radicals are produced in biological systems and that organisms possess dedicated enzymatic machinery for their elimination (McCord & Fridovich, 1969; Case, 2017). Over the subsequent five decades, research on SOD has expanded dramatically, elucidating its molecular reaction mechanisms, subcellular localization patterns, tissue-specific isoform distribution, and roles in diverse physiological and pathological processes (Miller, 2012; Wang et al., 2018; Zheng et al., 2023).

The therapeutic applications of SOD have been explored in numerous disease contexts characterized by oxidative stress, including cardiovascular diseases (Ambrosio et al., 1986; Zweier et al., 1987; Altshuler et al., 2021), neurodegenerative disorders (Rosen et al., 1993; Khayatan et al., 2024), cancer (Oberley & Buettner, 1979; Hempel et al., 2011; Islam et al., 2026), diabetes mellitus and its complications (Peixoto et al., 2008; De Blasio et al., 2017; Mohammedi et al., 2014), radiation-induced tissue injury (Petkau, 1978; Lee et al., 2001; Xu et al., 2024), and inflammatory conditions (Salvemini et al., 1999; Murata et al., 2004). However, the clinical translation of SOD-based therapies has been hampered by several challenges, including limited bioavailability, rapid plasma clearance, poor cellular uptake, and immunogenicity concerns with non-human enzymes (McCord & Edeas, 2005; Carillon et al., 2013; Rosa et al., 2021).

Recent years have witnessed remarkable progress in overcoming these limitations through innovative strategies such as liposomal encapsulation, PEGylation, lecithinization, nanoparticle-based delivery systems, and the development of small-molecule SOD mimetics (Salvemini et al., 2002; Batinic-Haberle et al., 2010; Weitner et al., 2013; Altshuler et al., 2021). Furthermore, the emergence of SOD nanozymes—nanomaterials with inherent SOD-like catalytic activity—has opened a new frontier in antioxidant therapeutics (Dastmalchi et al., 2026). This review aims to provide a comprehensive, evidence-based synthesis of the current knowledge on SOD, spanning its fundamental biochemistry to its clinical applications, while identifying critical gaps and future research priorities.

2 Discovery and History

2.1 Early Identification of Copper-Containing Proteins

The history of SOD research began in 1938 when Mann and Keilin first isolated a blue copper-containing protein from bovine erythrocytes, which they termed hemocuprein (Mann & Keilin, 1938). This protein exhibited a characteristic blue-green color attributable to its copper content, but its biological function remained unknown for three decades (Mann & Keilin, 1938; McCord & Fridovich, 1969). Subsequent investigations identified similar copper-containing proteins in various tissues and organisms, including human erythrocytes (erythrocuprein), liver (hepatocuprein), and brain (cerebrocuprein), collectively referred to as cupreins (Carrico & Deutsch, 1970). Notably, a distinct green-colored manganese-containing protein was also identified in chicken liver, which would later be recognized as a different isoform of SOD (McCord & Fridovich, 1969).

2.2 The Seminal Discovery of Enzymatic Function

The breakthrough that transformed these enigmatic metalloproteins into functionally defined enzymes

occurred in 1969 when Joe M. McCord and Irwin Fridovich demonstrated that erythrocuprein catalyzes the dismutation of superoxide anion radicals (McCord & Fridovich, 1969). This discovery emerged from investigations into the mechanism of xanthine oxidase-mediated reduction of cytochrome. McCord and Fridovich observed that the blue copper protein inhibited this reduction and subsequently demonstrated its catalytic activity toward superoxide radicals (McCord & Fridovich, 1969). Based on this enzymatic function, they proposed the name "superoxide dismutase" for the enzyme (McCord & Fridovich, 1969). This landmark discovery established the existence of superoxide radicals in biological systems and the concept of dedicated enzymatic antioxidant defenses, effectively founding the field of free radical biology (Fridovich, 1995; Case, 2017).

2.3 Subsequent Isoform Discoveries

Following the characterization of the copper-zinc SOD (Cu,Zn-SOD or SOD1) from bovine erythrocytes, additional isoforms were identified. In 1973, Weisiger and Fridovich discovered a manganese-containing superoxide dismutase (Mn-SOD or SOD2) in the mitochondrial matrix of chicken liver, distinguished by its insensitivity to cyanide inhibition and its subcellular localization (Weisiger & Fridovich, 1973). The mitochondrial targeting of Mn-SOD proved to be evolutionarily significant, given that mitochondria are the primary source of superoxide production through electron transport chain activity (Weisiger & Fridovich, 1973; Slot et al., 1986).

The third mammalian isoform, extracellular superoxide dismutase (EC-SOD or SOD3), was discovered by Stefan Marklund and colleagues in 1982 (Marklund et al., 1982). EC-SOD was identified as a tetrameric, copper- and zinc-containing glycoprotein present in extracellular fluids, including plasma, lymph, and synovial fluid (Marklund et al., 1982; Marklund, 1984a). SOD3 was subsequently shown to bind to heparan sulfate proteoglycans on cell surfaces and in the extracellular matrix through its carboxy-terminal heparin-binding domain, providing spatial regulation of superoxide levels in the extracellular compartment (Sandstrom et al., 1992; Karlsson et al., 1988).

2.4 Evolutionary Perspective

The evolutionary history of SODs reflects the adaptation of life to the increasing atmospheric oxygen concentrations that accompanied the evolution of oxygenic photosynthesis (Miller, 2012; Case, 2017). Phylogenetic analyses reveal that SOD enzymes evolved independently on at least three occasions, giving rise to the structurally distinct Cu,Zn-SOD, Mn-SOD/Fe-SOD, and Ni-SOD families (Miller, 2012; Case, 2017). The Mn-SOD and Fe-SOD families share a common evolutionary origin and are structurally homologous, while Cu,Zn-SOD represents an independent evolutionary invention (Smith & Doolittle, 1992). The existence of multiple independent evolutionary origins underscores the critical selective pressure to detoxify superoxide in aerobic environments (Miller, 2012).

3 Classification, Structure, and Physicochemical Properties

3.1 Classification by Metal Cofactor

Superoxide dismutases are classified into several distinct families based on their metal cofactor requirements and structural characteristics (Fig. 1):

3.1.1 Copper-Zinc Superoxide Dismutase (Cu,Zn-SOD; SOD1)

SOD1 is a homodimeric enzyme of approximately 32 kDa, with each subunit containing one copper and one zinc ion (McCord & Fridovich, 1969; Tainer et al., 1982). The enzyme is primarily localized in the cytoplasm, although a fraction is also found in the mitochondrial intermembrane space (Okado-Matsumoto & Fridovich, 2001; Sturtz et al., 2001). The crystal structure of bovine SOD1, solved by Tainer and colleagues in 1982, revealed a Greek key beta-barrel fold with the active-site copper ion coordinated by four histidine residues

(His44, His46, His61, and His118 in the bovine sequence) in a distorted square-planar geometry (Tainer et al., 1982). The zinc ion plays a structural rather than catalytic role, stabilizing the active-site conformation (Tainer et al., 1982; Getzoff et al., 1992). Human SOD1 crystallizes as a homodimer with 153 amino acids per subunit, and the atomic-resolution crystal structure has been determined (Strange et al., 2003).

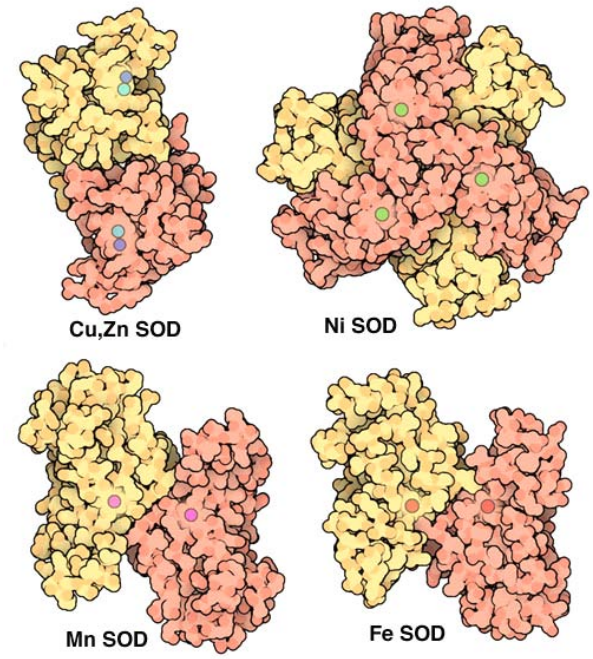

Fig. 1 Some molecular families of superoxide dismutase (PDB-101, 2026).

3.1.2 Manganese Superoxide Dismutase (Mn-SOD; SOD2)

SOD2 is a homotetrameric enzyme of approximately 88-96 kDa, with each subunit containing one manganese ion in the active site (Weisiger & Fridovich, 1973; Borgstahl et al., 1992). Unlike SOD1, SOD2 is exclusively localized in the mitochondrial matrix, where it contains an N-terminal mitochondrial targeting sequence that is cleaved after import (Wispe et al., 1989; Borgstahl et al., 1992). The crystal structure reveals an alpha-helical domain and a mixed alpha/beta domain, with the manganese ion coordinated by three histidine residues, one aspartate residue, and a solvent molecule in a trigonal bipyramidal geometry (Borgstahl et al., 1992; Wagner et al., 1993). Human SOD2 consists of 222 amino acids in the mature form, with high structural conservation across species (Borgstahl et al., 1992).

3.1.3 Extracellular Superoxide Dismutase (EC-SOD; SOD3)

SOD3 is a homotetrameric, copper- and zinc-containing glycoprotein with a molecular mass of approximately 135 kDa (Marklund et al., 1982; Marklund, 1984a). SOD3 is the predominant SOD isoform in extracellular fluids and is distinguished from SOD1 by its N-terminal signal peptide for secretion, its tetrameric quaternary structure, and its C-terminal heparin-binding domain that mediates association with extracellular matrix components (Hjalmarsson et al., 1987; Sandstrom et al., 1992; Karlsson et al., 1988). The mature human SOD3 subunit contains 222 amino acids and displays approximately 50% amino acid sequence homology with the SOD1 subunit within the catalytic domain (Hjalmarsson et al., 1987).

3.1.4 Iron Superoxide Dismutase (Fe-SOD)

Fe-SOD is primarily found in prokaryotes, plants, and some protozoa, but is absent in mammals (Yost & Fridovich, 1973; Stalling et al., 1984). Fe-SOD is structurally homologous to Mn-SOD, and the two enzymes

share a common evolutionary origin (Stalling et al., 1984; Parker & Blake, 1988). The enzyme is typically dimeric or tetrameric and contains iron in the active site (Yost & Fridovich, 1973).

3.1.5 Nickel Superoxide Dismutase (Ni-SOD)

Ni-SOD represents the most recently discovered SOD family, first identified in Streptomycesspecies (Youn et al., 1996). Unlike other SOD families, Ni-SOD contains nickel in its active site coordinated by a unique "nickel hook" motif involving the N-terminal amine, a cysteine thiolate, and two additional cysteine residues (Barondeau et al., 2004; Wuerges et al., 2004). The structure reveals a hexameric assembly with a novel fold unrelated to other SOD families, representing an independent evolutionary origin (Barondeau et al., 2004).

3.2 Structural Features and Catalytic Mechanism

The catalytic mechanism of SOD involves a two-step "ping-pong" reaction in which the metal ion at the active site alternately reduces and oxidizes superoxide radicals (McCord & Fridovich, 1969; Klug-Roth et al., 1973; Fielden et al., 1974):

Step 1: $M^{(n+1)+}$-SOD + $O_2^{\bullet -} \rightarrow M^{n+}$-SOD + O_2

Step 2: M^{n+}-SOD + $O_2^{\bullet -}$ + $2H^+ \rightarrow M^{(n+1)+}$-SOD + H_2O_2

where M represents the catalytic metal (Cu, Mn, Fe, or Ni). The overall reaction is:

$$2O_2^{\bullet -} + 2H^+ \rightarrow O_2 + H_2O_2$$

The reaction proceeds at near diffusion-limited rates, with rate constants on the order of 10^9 $M^{-1}s^{-1}$, making SOD one of the most catalytically efficient enzymes known (Klug-Roth et al., 1973; Fielden et al., 1974; Rotilio et al., 1972). The catalytic efficiency is attributed to the electrostatic guidance provided by charged amino acid residues surrounding the active-site channel, which direct the superoxide anion toward the catalytic metal center (Getzoff et al., 1983; Getzoff et al., 1992; Sines et al., 1990).

For Cu,Zn-SOD, the catalytic copper ion cycles between Cu^{2} and Cu^{+} oxidation states, whil e the zinc ion maintains structural integrity (Tainer et al., 1982; Getzoff et al., 1992). The active-site channel is formed at the dimer interface, with Arg141 (bovine numbering) playing a critical role in electrostatic guidance of the substrate (Getzoff et al., 1983; Fisher et al., 1994). In Mn-SOD, the manganese ion cycles between Mn^{3} and Mn^{2+} states, and the active site is located within each monomer rather than at subunit interfaces (Borgstahl et al., 1992; Edwards et al., 1998).

3.3 Physicochemical Properties

The physicochemical properties of SOD isoforms have been extensively characterized. The thermal stability of SOD varies considerably among isoforms and source organisms. Table 1 shows the key physicochemical and structural properties of human superoxide dismutase isoforms.

Bovine Cu,Zn-SOD exhibits remarkable thermostability, retaining activity after heating to 70°C, a property exploited in purification protocols (McCord & Fridovich, 1969). Hyperthermophilic archaeal SODs display extreme thermostability, with the Fe-SOD from *Sulfolobus solfataricus* retaining activity at temperatures exceeding 100°C (Ursby et al., 1999). The pH optimum for most SOD isoforms ranges from pH 7.0 to 10.0, with catalytic activity declining at acidic pH (Klug-Roth et al., 1973; Argese et al., 1993). The isoelectric points of SOD isoforms range from approximately 4.5 to 6.5, reflecting differences in amino acid composition and post-translational modifications (Marklund, 1980; Marklund, 1984b).

Table 1 Key physicochemical and structural properties of human superoxide dismutase isoforms.

Property	Cu,Zn-SOD (SOD1)	Mn-SOD (SOD2)	EC-SOD (SOD3)
Gene symbol	SOD1	SOD2	SOD3
Metal cofactor(s)	1 $Cu^{2+/+}$ (catalytic), 1 Zn^{2+} (structural) per subunit (McCord & Fridovich, 1969; Tainer et al., 1982)	1 $Mn^{2+/3+}$ per subunit (Weisiger & Fridovich, 1973; Borgstahl et al., 1992)	1 $Cu^{2+/+}$, 1 Zn^{2+} per subunit (Marklund et al., 1982; Hjalmarsson et al., 1987)
Native molecular mass	~32 kDa (homodimer) (McCord & Fridovich, 1969; Tainer et al., 1982)	~88–96 kDa (homotetramer) (Weisiger & Fridovich, 1973; Borgstahl et al., 1992)	~135 kDa (homotetramer) (Marklund et al., 1982; Marklund, 1984a)
Subunit size	~16 kDa; 153 amino acids (Strange et al., 2003)	~22–24 kDa (mature); 222 amino acids after cleavage of N-terminal mitochondrial targeting sequence (Wispe et al., 1989; Borgstahl et al., 1992)	~30–33 kDa; 222 amino acids plus N-linked glycosylation (Hjalmarsson et al., 1987; Marklund, 1984b)
Quaternary structure	Homodimer (Tainer et al., 1982)	Homotetramer (Borgstahl et al., 1992)	Homotetramer (Marklund et al., 1982; Hjalmarsson et al., 1987)
Subcellular localization	Predominantly cytoplasm; also mitochondrial intermembrane space (Okado-Matsumoto & Fridovich, 2001; Sturtz et al., 2001)	Mitochondrial matrix (Weisiger & Fridovich, 1973; Slot et al., 1986)	Extracellular fluids (plasma, lymph, synovial fluid); bound to cell surfaces and extracellular matrix via heparan sulfate proteoglycans (Marklund et al., 1982; Sandstrom et al., 1992; Karlsson et al., 1988)
Secretion signal	None (cytosolic)	N-terminal mitochondrial targeting sequence, cleaved after import (Wispe et al., 1989)	N-terminal signal peptide for secretion (Hjalmarsson et al., 1987)
Post-translational modifications	Acetylation, glutathionylation, nitration, phosphorylation (Yamakura & Kawasaki, 2010)	Acetylation (Lys68, Lys122) modulates activity; tyrosine nitration inactivates enzyme (MacMillan-Crow et al., 1996; Williams, 2019; Yamakura & Kawasaki, 2010)	N-linked glycosylation; C-terminal heparin-binding domain (Marklund, 1984b; Sandstrom et al., 1992)
Isoelectric point (pI)	~4.9–5.2 (Marklund, 1980)	~6.5–7.0 (Marklund, 1980)	~4.5 (Marklund, 1984b)
Key structural features	Greek key β-barrel fold; active-site Cu coordinated by four histidines; electrostatic guidance mechanism (Tainer et al., 1982; Getzoff et al., 1983)	α-helical domain and mixed α/β domain; 4-helix bundle at dimer interface within the tetramer (Borgstahl et al., 1992)	Catalytic domain ~50% identical to SOD1; unique C-terminal heparin-binding region (Hjalmarsson et al., 1987; Sandstrom et al., 1992)

4 Sources, Extraction, and Purification

4.1 Natural Sources

SOD is ubiquitously distributed across all kingdoms of life, from bacteria to mammals, reflecting its

fundamental role in oxidative stress defense (Kim et al., 1991; Fridovich, 1995; Hatzinikolaou et al., 1998; Hadji et al., 2007; Miller, 2012; Ozdemir et al., 2021). Traditional sources for SOD extraction have included bovine erythrocytes (McCord & Fridovich, 1969), chicken liver (Weisiger & Fridovich, 1973), and various plant tissues (Hadji et al., 2007; Ozdemir et al., 2021), corn kernels (Pratiwi et al., 2025), and tea pollen. Microbial sources have gained prominence for industrial-scale production due to advantages in genetic manipulability, rapid growth, and high expression yields (Kim et al., 1991; Hatzinikolaou et al., 1997; Wang et al., 2016).

Recombinant DNA technology has enabled the production of human SOD isoforms in heterologous expression systems, including *Escherichia coli*, *Pichia pastoris*, and *Saccharomyces cerevisiae* (Hallewell et al., 1985; Hartman et al., 1986; Tibell et al., 1987). Recombinant human SOD1 (rhSOD) has been produced for clinical applications, offering advantages of human origin to minimize immunogenicity (Tsao et al., 1991; Xu et al., 2024).

4.2 Extraction Methodologies

The extraction of SOD from natural sources typically involves tissue homogenization, cell lysis, and initial fractionation steps. Traditional methods exploit the remarkable stability of SOD to organic solvents and heat (McCord & Fridovich, 1969; He et al., 2008). The classic Tsuchihashi extraction employs ethanol-chloroform mixtures to precipitate contaminating proteins while SOD remains in solution (McCord & Fridovich, 1969; Hatzinikolaou et al., 1997).

For animal tissues, erythrocytes are lysed, hemoglobin is removed by ethanol-chloroform treatment, and SOD is precipitated with acetone or ammonium sulfate (McCord & Fridovich, 1969; Kumagai et al., 1994). From bovine erythrocytes, an efficient pH-controlled ammonium sulfate-methanol extraction method yields approximately 14 mg of pure Cu,Zn-SOD with high specific activity (Kumagai et al., 1994). Plant-derived SOD extraction from garlic employs phosphate buffer extraction, heat treatment at 60-65°C to precipitate contaminating proteins, and a two-stage ultrafiltration process, achieving 139-fold purification with a yield of 91% and a specific activity of 2,867 U/mg (Ercan et al., 2010; He et al., 2008).

4.3 Purification Strategies

Purification of SOD to homogeneity typically requires chromatographic methods. Ion-exchange chromatography on DEAE-cellulose or DEAE-Sepharose columns has been widely employed, exploiting charge differences between SOD isoforms and contaminating proteins (McCord & Fridovich, 1969; Hatzinikolaou et al., 1997; He et al., 2008). Size-exclusion chromatography provides additional resolution based on molecular weight differences (Kumagai et al., 1994). Affinity chromatography using immobilized metal ions or heparin has been utilized for specific isoforms, particularly SOD3 with its heparin-binding domain (Marklund, 1980; Tibell et al., 1987).

For recombinant SOD, purification is facilitated by the incorporation of affinity tags, although tag-free purification methods are preferred for clinical applications to avoid potential immunogenicity (Hallewell et al., 1985; Hartman et al., 1986). Process optimization through response surface methodology has been applied to maximize yield and purity while minimizing purification steps (Hatzinikolaou et al., 1997).

5 Pharmacokinetics and Bioavailability

5.1 Absorption and Distribution

The pharmacokinetic properties of SOD have been extensively investigated in both animal models and human subjects. When administered orally, native SOD exhibits limited bioavailability due to degradation by gastric acid and proteolytic enzymes in the gastrointestinal tract (Regnault et al., 1996; Rosa et al., 2021). In rats, the maximum oral bioavailability was reported as 14% for free SOD, which could be improved to 22% when

encapsulated in liposomes, and to 57% when ceramides were added to liposomal formulations (Regnault et al., 1996). These findings underscore the critical barrier that gastrointestinal degradation poses to effective oral SOD delivery.

Following intravenous administration, SOD distributes rapidly from the vascular compartment, with a distribution half-life of approximately 5-10 minutes and an elimination half-life ranging from 20 to 35 minutes for the native enzyme (Tsao et al., 1991; Jadot et al., 1995). The short plasma half-life reflects rapid renal clearance, given that the molecular weight of SOD (32-135 kDa depending on isoform) permits glomerular filtration (Tsao et al., 1991).

5.2 Strategies to Improve Pharmacokinetics

Multiple strategies have been developed to enhance the pharmacokinetic profile of SOD:

Liposomal encapsulation: Entrapment of SOD within liposomes protects the enzyme from degradation, prolongs plasma half-life, and facilitates cellular uptake (Turrens et al., 1984; Jadot et al., 1995). Liposomal bovine Cu-SOD has been demonstrated to produce no acute or delayed toxic effects in humans, with improved pharmacokinetic characteristics including longer plasma half-life and slower release of the free enzyme (Jadot et al., 1995).

PEGylation: Covalent attachment of polyethylene glycol (PEG) chains to SOD increases the hydrodynamic radius, reducing renal clearance and extending plasma half-life (Beckman et al., 1988; Veronese et al., 1985). PEG-SOD conjugates have shown therapeutic efficacy in animal models of ischemia-reperfusion injury (Beckman et al., 1988; Li et al., 1998).

Lecithinization: Lecithinized recombinant human SOD (PC-SOD) has demonstrated a nonlinear pharmacokinetic profile with dose, attributed to a saturable clearing mechanism, and a relatively long half-life exceeding 24 hours (Suzuki et al., 2008). These properties support the investigation of PC-SOD as a protective agent in clinical conditions associated with free radical overload (Suzuki et al., 2008).

Nanoparticle-based delivery: Recent approaches employing biodegradable nanoparticles loaded with SOD have shown promise for sustained, targeted delivery. Intramyocardial administration of nanoparticle-encapsulated SOD improved left ventricular contractility at 3 hours post-reperfusion and preserved cardiac function at 4 weeks in a porcine model of myocardial ischemia-reperfusion injury (Altshuler et al., 2021).

5.3 Clinical Pharmacokinetic Studies

Phase I clinical trials have characterized the pharmacokinetics of recombinant human SOD in healthy volunteers. A randomized, double-blind, placebo-controlled study evaluated the safety, tolerability, and pharmacokinetics of recombinant human Cu,Zn-SOD (rhSOD) following subcutaneous administration of 40 mg every 12 hours in 16 healthy volunteers (Al Jalali et al., 2026). In another study, recombinant human superoxide dismutase was administered intravenously to 32 normal human volunteers at doses ranging from 1 mg/kg to 45 mg/kg in a single-blind, placebo-controlled crossover design, demonstrating good tolerability (Tsao et al., 1991). Subcutaneous rhSOD was found to be a promising therapeutic candidate for conditions characterized by excessive oxidative stress exposure (Al Jalali et al., 2026).

6 Pharmacological Actions and Mechanisms

As other regulators for biological network (Huang and Zhang, 2012; Li and Zhang, 2013; Zhang, 2016a-b, 2017, 2018, 2026a-b, 2027a-d, 2028a-c), SOD regulates various biochemical processes. Fig. 2 describes the metabolic and regulatory pathway of SOD.

6.1 Antioxidant Defense and Free Radical Scavenging

SOD constitutes the primary enzymatic antioxidant defense against superoxide radicals (Fridovich, 1995;

Halliwell & Gutteridge, 2015). By catalyzing the dismutation of superoxide to hydrogen peroxide and molecular oxygen, SOD prevents the formation of more reactive secondary radicals, including peroxynitrite ($ONOO^-$) from the diffusion-limited reaction between superoxide and nitric oxide, and hydroxyl radical (•OH) from the iron-catalyzed Haber-Weiss reaction (Beckman & Koppenol, 1996). The antioxidant function of SOD is integrated with downstream antioxidant enzymes: hydrogen peroxide generated by SOD is subsequently detoxified by catalase and glutathione peroxidase, preventing the accumulation of this potentially toxic intermediate (Michiels et al., 1994; Jomova et al., 2024). This coordinated enzymatic network, comprising SOD, catalase, and glutathione peroxidase, constitutes the first-line defense mechanism against oxidative stress (Ighodaro & Akinloye, 2018; Jomova et al., 2024).

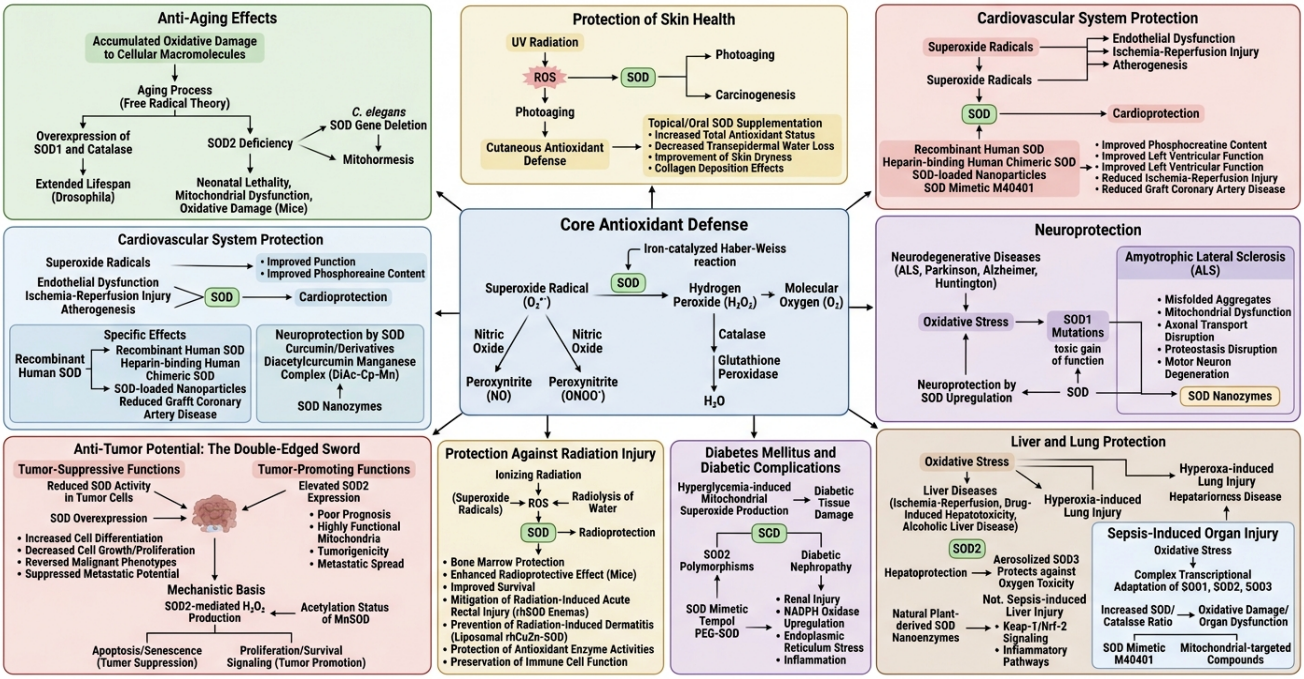

Fig. 2 The metabolic and regulatory pathway of superoxide dismutase.

6.2 Anti-Aging Effects

The free radical theory of aging, proposed by Denham Harman in 1956, posits that accumulated oxidative damage to cellular macromolecules drives the aging process (Harman, 1956; Harman, 1981). SOD plays a central role in this theory, and extensive research has investigated the relationship between SOD activity, oxidative stress, and aging. Studies in model organisms have provided strong evidence: overexpression of SOD1 and catalase in Drosophila melanogasterextended lifespan (Orr & Sohal, 1994), while SOD2-deficient mice exhibited neonatal lethality with severe mitochondrial dysfunction and oxidative damage (Li et al., 1995; Lebovitz et al., 1996). Conversely, in *Caenorhabditis elegans*, deletion of SOD genes paradoxically increased lifespan in some studies, suggesting complex relationships between ROS production, mitochondrial function, and aging (Van Raamsdonk & Hekimi, 2009; Van Raamsdonk & Hekimi, 2012). The relationship between SOD and aging is further complicated by the concept of mitohormesis, wherein moderate levels of ROS may activate protective stress responses (Ristow & Schmeisser, 2011).

6.3 Protection of Skin Health

The skin is continuously exposed to environmental pro-oxidant insults, particularly ultraviolet (UV) radiation,

which generates ROS and contributes to photoaging and carcinogenesis (Fisher et al., 1997; Rittié & Fisher, 2015). SOD plays a critical role in cutaneous antioxidant defense (Sander et al., 2002). Comprehensive studies of human skin in vivo have characterized age-related and photoaging-dependent changes in antioxidant enzyme activities, demonstrating complex patterns of SOD regulation during these processes (Rhie et al., 2001). Interestingly, while SOD and glutathione peroxidase activities were found to remain relatively stable during intrinsic aging and photoaging in human epidermis and dermis, other antioxidant parameters showed significant alterations (Rhie et al., 2001).

Topical and oral SOD supplementation has been investigated for anti-photoaging effects. A clinical study evaluating the effectiveness of oral SOD demonstrated significantly increased total antioxidant status, decreased transepidermal water loss, and improvement of skin dryness following 60 days of treatment in subjects with photoaged skin (Djawad and Anggraini, 2021). Corn kernel-derived SOD extract exhibited anti-photoaging activity through collagen deposition effects, suggesting potential utility in cosmetic and dermatological applications (Pratiwi et al., 2025). *Bacillus cereus* SOD was explored for its anti-photoaging potential in rabbit skin models, demonstrating protective effects against UV-induced damage (Indrayati et al., 2024).

6.4 Cardiovascular System Protection

The role of oxidative stress in cardiovascular pathophysiology is well established, with superoxide radicals implicated in endothelial dysfunction, ischemia-reperfusion injury, and atherogenesis (Griendling & FitzGerald, 2003; Münzel et al., 2017). SOD has been extensively studied for cardioprotective applications.

Ischemia-Reperfusion Injury: Reperfusion of ischemic myocardium generates a burst of superoxide radicals that contribute to tissue injury (Zweier et al., 1987; Bolli et al., 1989). Recombinant human SOD administered at the time of reperfusion significantly improved phosphocreatine content and left ventricular function in isolated heart models, demonstrating that a reversible oxygen radical-mediated component of reperfusion injury exists (Ambrosio et al., 1986). The endothelial dysfunction associated with cardiac ischemia-reperfusion is specifically mediated by superoxide anions rather than hydroxyl radicals, and can be prevented by SOD but not by catalase or hydroxyl radical scavengers (Mączewski et al., 2004; Maczewski et al., 2004).

Therapeutic SOD Formulations for Cardiac Protection: A novel heparin-binding human chimeric SOD was developed to target endothelial surfaces and demonstrated protection against ischemia-reperfusion injury in isolated rabbit hearts at doses nearly two orders of magnitude lower than native Mn-SOD or Cu,Zn-SOD (Sally et al., 2002). Superoxide dismutase-loaded nanoparticles attenuated myocardial ischemia-reperfusion injury and protected against chronic adverse ventricular remodeling in a large animal model, with improved left ventricular contractility maintained at 4 weeks post-reperfusion (Altshuler et al., 2021). The SOD mimetic M40401 reduced ischemia-reperfusion injury and graft coronary artery disease in rodent cardiac allografts by selectively removing superoxide anions (Murata et al., 2004).

6.5 Neuroprotection

Oxidative stress is implicated in the pathogenesis of numerous neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), Parkinson disease, Alzheimer disease, and Huntington disease (Barnham et al., 2004; Lin & Beal, 2006). SOD occupies a central position in neuroprotection research.

Amyotrophic Lateral Sclerosis and SOD1 Mutations: The discovery in 1993 that mutations in the SOD1gene cause a subset of familial ALS provided the first direct genetic link between SOD and neurodegenerative disease (Rosen et al., 1993). Over 180 mutations in SOD1 have been identified in ALS patients, with the majority following autosomal dominant inheritance (Andersen & Al-Chalabi, 2011; Saccon et al., 2013). Importantly, the pathogenic mechanism involves a toxic gain of function rather than loss of

dismutase activity, as SOD1 knockout mice do not develop motor neuron disease, while transgenic mice expressing mutant human SOD1 develop progressive motor neuron degeneration (Gurney et al., 1994; Bruijn et al., 1998). The mutant SOD1 protein forms misfolded aggregates that disrupt mitochondrial function, axonal transport, and proteostasis (Boillée et al., 2006; Pasinelli & Brown, 2006).

Neuroprotection by SOD Upregulation: Curcumin and its derivatives have demonstrated neuroprotective effects through upregulation of SOD expression, with particular relevance to neurodegenerative disease treatment (Khayatan et al., 2024; Patel et al., 2002; Zhang, 2027b). The diacetylcurcumin manganese complex (DiAc-Cp-Mn) exhibited SOD-mimetic activity with greater scavenging capacity against superoxide radicals, hydrogen peroxide, and hydroxyl radicals compared to the parent compound, and demonstrated neuroprotective effects against rotenone-induced neurotoxicity in SH-SY5Y Parkinson disease cell models (Khayatan et al., 2024). SOD nanozymes have emerged as promising tools for brain disease diagnosis and treatment, with research progressing on their mechanisms of action and therapeutic applications (Chen et al., 2024).

6.6 Anti-Tumor Potential: The Double-Edged Sword

The role of SOD in cancer biology is complex and context-dependent, exhibiting both tumor-suppressive and tumor-promoting functions (Oberley & Buettner, 1979; Hempel et al., 2011; Islam et al., 2026).

Tumor-Suppressive Functions: Early studies established that SOD activity is generally reduced in tumor cells compared to their normal counterparts, leading to the hypothesis that SOD functions as a tumor suppressor (Oberley & Buettner, 1979). Overexpression of SOD in vitro increased cell differentiation, decreased cell growth and proliferation, and reversed malignant phenotypes (Church et al., 1993; Zhang et al., 2002). SOD2 overexpression suppressed the metastatic potential of various cancer cell lines through mechanisms involving decreased matrix metalloproteinase expression and altered integrin-mediated adhesion (Li et al., 1995; Hempel et al., 2011).

Tumor-Promoting Functions: Paradoxically, elevated SOD2 expression has been associated with poor prognosis in certain cancer types, including ovarian clear cell carcinoma, breast cancer, and colorectal cancer (Hempel et al., 2011; Islam et al., 2026). In ovarian clear cell carcinoma, SOD2 was shown to maintain highly functional mitochondria to support the high metabolic activity of cancer cells, thereby promoting tumorigenicity and metastatic spread (Madhubhani et al., 2015). The dual role of Mn-SOD was highlighted by research showing that the enzyme can function as either a cancer suppressor or promoter depending on cellular context and tumor stage, with acetylation status of the enzyme representing a critical regulatory switch (Williams, 2019).

Mechanistic Basis of the Dual Role: The switch between tumor-suppressive and tumor-promoting functions of SOD2 involves complex regulation of redox signaling. SOD2-mediated hydrogen peroxide production can either promote apoptosis and senescence (tumor suppression) or activate proliferation and survival signaling pathways (tumor promotion), depending on the balance between hydrogen peroxide generation and the capacity of downstream antioxidant systems (Hempel et al., 2011; Islam et al., 2026). SOD2 plays a pivotal role in cancer progression by regulating oxidative stress, matrix metalloproteinase expression, multiple signaling pathways, cell adhesion, and cell death (Islam et al., 2026). The multifactorial role of SODs in human cancers has been comprehensively reviewed, emphasizing the need for context-dependent therapeutic strategies (Panda et al., 2024).

6.7 Protection Against Radiation Injury

Ionizing radiation generates ROS, including superoxide radicals, through radiolysis of water, contributing to radiation-induced cellular damage (Riley, 1994). SOD has been investigated as a radioprotective agent in multiple contexts.

Bone Marrow Protection: Bovine SOD administered intravenously both before and after X-irradiation enhanced the radioprotective effect in mice. The proliferative capacity of bone marrow stem cells irradiated in air was protected by exogenous SOD (Petkau, 1978; Petkau, 1987). In a study of γ-irradiated mice, intravenous administration of bovine erythrocyte SOD at 200 mg/kg one hour before irradiation improved survival by 50%, while post-irradiation administration was ineffective, suggesting a critical temporal window for protection (Xia et al., 1995).

Clinical Applications in Radiotherapy: Recombinant human Cu,Zn-SOD (rhCuZn-SOD) has been investigated in clinical settings to mitigate radiation-induced tissue injury. A multicenter, randomized, open-label, prospective trial evaluated the efficacy of rhSOD enemas for the prevention and treatment of radiation-induced acute rectal injury in patients with locally advanced cervical cancer undergoing concurrent chemoradiotherapy (Zhu et al., 2024). The results demonstrated that rhSOD enema was safe and significantly reduced the incidence, severity, and duration of radiation-induced acute rectal injury, protecting the rectal mucosa (Zhu et al., 2024). Liposomal recombinant human Cu,Zn-SOD (APN201) has been studied for the prevention of radiation-induced dermatitis in women with breast cancer, representing an ongoing area of clinical investigation (Apeiron Biologics).

Cellular Mechanisms: Both Cu,Zn-SOD and Mn-SOD play central roles in protecting cells against ionizing radiation through the removal of ROS and the protection of antioxidant enzyme activities (Lee et al., 2001). Recombinant human Cu,Zn-SOD administered to mice before and after γ-irradiation at 5-7 Gy protected antioxidant enzyme activities and preserved immune cell function (Chen et al., 1997). SOD protected model phospholipid membranes from radiation-induced damage, with the protective effect observed after both acute exposure and low-level radiation at natural background levels (Petkau & Chelack, 1976).

6.8 Diabetes Mellitus and Diabetic Complications

Oxidative stress plays a pivotal role in the pathogenesis of diabetes mellitus and its complications, with hyperglycemia-induced mitochondrial superoxide production identified as a unifying mechanism underlying diabetic tissue damage (Brownlee, 2001; Giacco & Brownlee, 2010).

Diabetic Nephropathy: SOD2 polymorphisms have been associated with the incidence and progression of diabetic nephropathy in subjects with type 1 diabetes, with faster decline in estimated glomerular filtration rate and alterations in plasma advanced oxidation protein products concentration and SOD activity, consistent with a protective role for SOD2 against oxidative stress and kidney disease (Mohammedi et al., 2014). The SOD mimetic tempol blunted diabetes-induced upregulation of NADPH oxidase and endoplasmic reticulum stress in a rat model of diabetic nephropathy, suggesting that antioxidant approaches targeting NADPH upregulation may attenuate diabetic nephropathy, at least in part by negatively regulating ER stress and inflammation (De Blasio et al., 2017). An antioxidant SOD mimetic prevented NADPH oxidase-induced oxidative stress and renal damage in the early stage of experimental diabetes and hypertension, with the conclusion that an imbalance in renal redox status is associated with markers of renal injury (Peixoto et al., 2008). PEG-SOD administration reduced oxidative and nitrosative stress-induced kidney injury in diabetic nephropathy animal models.

SOD1 Overexpression and Renal Protection: Overexpression of Cu,Zn-SOD in db/db mice (a model of type 2 diabetes) attenuated indexes of renal injury compared with nontransgenic db/db mice, demonstrating that increased SOD1 expression provides renoprotective effects in the setting of diabetes (Craven et al., 2001).

6.9 Liver and Lung Protection

Hepatoprotection: Oxidative stress is central to the pathogenesis of various liver diseases, including ischemia-reperfusion injury, drug-induced hepatotoxicity, and alcoholic liver disease (Jaeschke, 2003; Cederbaum et al., 2009). SOD2 is the key antioxidant enzyme responsible for protection of the lung against

hyperoxia-induced injury, and is induced by hyperoxia and cytokines such as TNF-α (Asikainen et al., 1998; Asikainen & White, 2004). Subcellular sites of superoxide production in the liver differentially affect the outcome of ischemia/reperfusion injury, with mitochondrial superoxide production being particularly detrimental (Zhou et al., 2001). Natural plant-derived SOD nanoenzymes have shown protective effects against sepsis-induced liver injury through activation of Keap-1/Nrf-2-mediated antioxidant signaling and inhibition of inflammatory pathways (dataset, 2025).

Pulmonary Protection: The lung is directly exposed to high oxygen concentrations and is particularly vulnerable to oxidative injury. Aerosolized human extracellular superoxide dismutase protected mice against oxygen toxicity and reduced mortality in a hyperoxic model, demonstrating the therapeutic potential of SOD3 in pulmonary applications (Yen et al., 2011). SOD activity in lung and liver may represent a compensatory response to selenium deficiency and influenza infection (Stýblo et al., 2007). Supplementation with human recombinant antioxidant enzymes, including SOD, may mitigate hyperoxic lung injury, although the optimal combination and concentration require further investigation (Zhu et al., 2006).

Sepsis-Induced Organ Injury: SOD has emerged as a protective factor in sepsis pathophysiology, mitigating oxidative stress through detoxification of superoxide anions (Bar-Or et al., 2015). Lung levels of SOD1 decreased 3 and 12 hours after sepsis induction, while SOD2 and SOD3 increased, along with total SOD activity, reflecting a complex transcriptional adaptation to septic oxidative stress (Constantino et al., 2014). The SOD/catalase ratio was increased in septic animals and correlated strongly with oxidative damage and organ dysfunction. The SOD mimetic M40401 modulated serum cytokine levels and preserved circulating catecholamines in an Escherichia colimodel of septic shock (Macarthur et al., 2003). Delivering antioxidants to the mitochondria using SOD mimetics and mitochondrial-targeted compounds represents a beneficial strategy in sepsis treatment (Galley, 2011).

7 Clinical Applications and Trials

7.1 Clinical Applications and Formulations

SOD-based therapeutics has been investigated in diverse clinical settings. Recombinant human SOD (rhSOD) has been developed for several indications, including prevention of radiation-induced tissue injury, treatment of inflammatory conditions, and organ protection in critically ill patients (Flohe, 1988; Zhu et al., 2024). PC-SOD (lecithinized SOD) has been evaluated for its prolonged pharmacokinetic profile in both Japanese and Caucasian volunteers, demonstrating a half-life exceeding 24 hours and supporting further clinical development (Suzuki et al., 2008).

7.2 Clinical Research Studies

Radiation-Induced Rectal Injury: A multicenter, randomized, open-label, prospective trial evaluated recombinant human SOD enemas for prevention and treatment of radiation-induced acute rectal injury in patients with locally advanced cervical cancer. The results demonstrated that rhSOD enema was safe and significantly reduced the incidence, severity, and duration of radiation-induced acute rectal injury, with protection of the rectal mucosa (Zhu et al., 2024).

Multiple Trauma and Organ Failure: In a prospective, randomized trial, recombinant human SOD (3,000 mg/day) or placebo was administered intravenously for 5 days to patients with multiple injuries (Injury Severity Score≥ 27). The results revealed attenuation of organ failure after trauma, most likely through decreased release of inflammatory mediators and reduction of leukocyte-mediated organ injury (Marzi et al., 1993).

Depression: A clinical study evaluated the effects of escitalopram alone and in combination with ascorbic acid, vitamin E, and levosulpride on SOD levels in depression patients. The combination therapy demonstrated

encouraging effects on SOD levels, highlighting the potential of personalized therapy approaches in modulating antioxidant enzyme activity.

Exercise and Health: Systematic reviews have demonstrated that physical exercise increases SOD levels, with ROS generated during exercise acting as the stimulus for this adaptive upregulation. SOD functions as both an endogenous antioxidant and a molecular signal transducer that promotes health benefits during physical exercise (Ayubi et al., 2024; Ahmed & Al-Rawi, 2024).

7.3 Quality Control and Quality Standards

The quality control of SOD-based products involves multiple analytical parameters, including enzyme activity assays, purity determination, molecular weight characterization, and stability testing. The NBT (nitroblue tetrazolium) reduction method represents one of the most widely used assays for SOD activity determination, based on the competitive inhibition of NBT reduction by superoxide radicals (Beauchamp & Fridovich, 1971). The pyrogallol autoxidation method provides an alternative approach (Marklund & Marklund, 1974). Validation of analytical methods for SOD activity determination should follow ICH guidelines, with careful attention to the specificity, precision, accuracy, and robustness of the assay, as the measured activity can be strictly related to the technique used, particularly in pharmaceutical quality control applications (Zhou and Prognon, 2006).

Gel electrophoresis-based methods, including native PAGE with activity staining, provide information on molecular weight, purity, and isoform identification. Commercial SOD controls based on human serum provide ready-to-use materials for accurate quality control and calibration of SOD assays, enabling laboratories to maintain high standards in oxidative stress testing and ensure compliance with ISO 15189, CAP, and CLIA standards (Biorex Diagnostics, 2021). The quality control and conformity analysis of PC-SOD has been established and verified using the NBT reduction method (Huang et al., 2007).

7.4 Safety Evaluation

The safety profile of SOD has been evaluated in numerous preclinical and clinical studies. SOD is generally regarded as nontoxic based on data from earlier studies, with investigations in animal models using doses ranging from 5 to 2,500 times the average human clinical dose of 0.04 mg/kg/day (Drugs.com, 2025). Newer formulations have been studied at doses up to 40,000 times the average human clinical dose of 0.1 mg/kg/day, though comprehensive safety data on these newer formulations remain limited (Drugs.com, 2025).

In human studies, bovine Cu-SOD (free or liposomal), although a foreign protein, was well tolerated and produced no acute or delayed toxic effects (Jadot et al., 1995). Phase I clinical trials of recombinant human SOD in healthy volunteers have demonstrated good tolerability following both intravenous and subcutaneous administration, with no serious adverse events reported (Tsao et al., 1991; Zhu et al., 2020). Oral SOD supplementation has been associated with limited and variable absorption, with dosing not standardized, and mild side effects including digestive upset, bloating, nausea, or headache occasionally reported (Ubie Doctor's Note, 2026). Topical formulations are generally considered lower risk but may cause irritation in sensitive skin (Ubie Doctor's Note, 2026). The safety of long-term SOD supplementation has not been adequately studied, and safety data for use during pregnancy and breastfeeding are lacking (EBSCO Health Library, 2024).

8 SOD Mimetics, Conjugates, and Nanozymes

8.1 Small-Molecule SOD Mimetics

The limitations of native SOD enzymes, including poor bioavailability, immunogenicity, and short plasma half-life, have motivated the development of small-molecule SOD mimetics—low-molecular-weight compounds that catalyze superoxide dismutation with high efficiency (Salvemini et al., 2002; Batinic-Haberle et al., 2010). Major classes of SOD mimetics include:

Metalloporphyrins: Manganese porphyrin-based SOD mimics, such as MnTE-2-PyP^{5+} and MnTnHex-2-PyP^{5+}, have been extensively characterized for their pharmacokinetic properties and therapeutic potential (Weitner et al., 2013; Batinic-Haberle et al., 2010). Comprehensive pharmacokinetic studies have demonstrated their oral bioavailability and tissue distribution (Weitner et al., 2013). BMX-001 (MnTnBuOE-2-PyP^{5+}) is currently in clinical development as a radioprotectant and chemotherapeutic adjuvant (Batinic-Haberle et al., 2014).

Manganese Cyclic Polyamines: M40401 (a manganese pentaazamacrocycle) and M40403 have demonstrated efficacy in animal models of ischemia-reperfusion injury, septic shock, and inflammatory conditions (Salvemini et al., 1999; Macarthur et al., 2003; Murata et al., 2004).

Salen-Manganese Complexes: EUK-8 and EUK-134 are salen-manganese complexes with dual SOD and catalase activities that have shown neuroprotective and cardioprotective effects in preclinical studies (Doctrow et al., 2002; Melov et al., 2001).

8.2 SOD Conjugates and Delivery Systems

PEGylated SOD, heparin-binding chimeric SOD, and lecithinized SOD represent conjugation strategies to improve pharmacokinetics and targeting (Beckman et al., 1988; Sally et al., 2002; Suzuki et al., 2008). Liposomal encapsulation has been successfully applied to both bovine and recombinant human SOD, improving cellular delivery and therapeutic efficacy (Jadot et al., 1995; Altshuler et al., 2021).

8.3 SOD Nanozymes

SOD nanozymes—nanomaterials with inherent SOD-like catalytic activity—represent an emerging frontier in antioxidant therapeutics (Dastmalchi et al., 2026; Chen et al., 2024). These nanozymes offer advantages over natural SOD enzymes, including high stability, tunable catalytic activity, ease of large-scale production, and multifunctionality. Carbon dots, metal oxide nanoparticles, and metal-organic frameworks have been engineered to exhibit SOD-like activity (Dastmalchi et al., 2026). In biomedical applications, SOD nanozymes have shown promise in treating brain diseases, sepsis-induced organ injury, and inflammatory conditions (Chen et al., 2024; dataset, 2025). However, challenges remain in optimizing catalytic specificity, biocompatibility, and in vivo stability, with artificial intelligence-driven design emerging as a promising approach to address these limitations (Chen et al., 2024).

9 Gene Regulation and Post-Translational Modifications

9.1 Transcriptional Regulation of SOD Genes

The regulation of sodgenes is complex and involves multiple transcription factors. The human SOD1 gene is regulated by Sp1, NF-κB, and AP-1 transcription factors (Miao & St. Clair, 2009; Milani et al., 2013). SOD2 gene expression is primarily regulated by NF-κB, AP-1, Sp1, and FoxO transcription factors, with epigenetic mechanisms including histone acetylation and DNA methylation also playing important roles (Miao & St. Clair, 2009; Hempel et al., 2011). The SOD3 gene is regulated by KLF2, Nrf2, and MEF2 transcription factors (Zelko et al., 2002; Kalmari and Colagar, 2024). Changes associated with sod2gene regulation lead to alterations in expression levels as well as protein function, with implications for disease susceptibility (Miao & St. Clair, 2009; Milani et al., 2013). In plants, SOD gene expression is regulated at transcriptional, post-transcriptional, and translational levels, with microRNAs playing significant post-transcriptional regulatory roles (Wang et al., 2014; Wang et al., 2016).

9.2 Post-Translational Modifications

SOD enzymes are subject to multiple post-translational modifications that modulate their activity, stability, and subcellular localization (Yamakura & Kawasaki, 2010). Key modifications include nitration of tyrosine residues, which inactivates Mn-SOD and has been observed in various pathological conditions including acute

and chronic allograft rejection and neurodegenerative diseases (MacMillan-Crow et al., 1996; Yamakura & Kawasaki, 2010). Phosphorylation, glutathionylation, and glycation have also been documented, with complex functional consequences (Yamakura & Kawasaki, 2010). The reaction of human Cu,Zn-SOD with peroxynitrite generates 6-nitrotryptophan, which has been proposed as a novel biomarker of reactive nitrogen species formation (Yamakura & Kawasaki, 2010). Acetylation of Mn-SOD at specific lysine residues has been shown to modulate its enzymatic activity and cellular localization, with implications for cancer biology (Williams, 2019).

10 Immune Regulation and Infectious Diseases

Beyond their canonical antioxidant functions, SODs function as immunomodulatory proteins, regulating the maturation, proliferation, and differentiation of immune cells (Liu et al., 2025). SODs maintain redox homeostasis through catalytic dismutation of superoxide anions in immune cells, and their expression is dynamically regulated during immune responses (Liu et al., 2025). In infectious diseases, SOD plays complex roles in host-pathogen interactions. Many bacterial pathogens express SOD isoforms that contribute to virulence by detoxifying superoxide produced by host phagocytes (Liu et al., 2025). *Candida albicans* expresses multiple SOD genes, with SOD5 identified as a hyphal-induced gene under complex transcriptional regulation, representing a potential virulence factor (Martchenko et al., 2004). In viral infections, host SOD activity is modulated as part of the oxidative stress response (Stýblo et al., 2007).

11 Gaps, Challenges, and Future Research Directions

11.1 Key Knowledge Gaps

Despite extensive research spanning over five decades, significant gaps remain in our understanding of SOD biology and its therapeutic applications. The precise mechanisms determining the switch between tumor-suppressive and tumor-promoting functions of SOD2 remain incompletely defined (Hempel et al., 2011; Islam et al., 2026). The role of SOD3 in health and disease is relatively under explored compared to SOD1 and SOD2, with its immense potential as a therapeutic target warranting further investigation (Kalmari and Colagar, 2024). The mechanisms by which SOD gene expression is regulated in response to environmental stresses, particularly at the post-transcriptional level, remain incompletely characterized (Miao & St. Clair, 2009; Milani et al., 2013). The relationship between SOD polymorphisms and disease susceptibility requires validation in large, diverse populations (Mohammedi et al., 2014).

11.2 Challenges in Clinical Translation

The clinical translation of SOD-based therapeutics faces several persistent challenges. Bioavailability remains the primary obstacle: oral SOD has limited and variable absorption, while parenterally administered SOD undergoes rapid renal clearance (Regnault et al., 1996; Rosa et al., 2021; McCord & Edeas, 2005). Immunogenicity concerns, particularly with non-human SOD preparations, require careful consideration, although human recombinant enzymes have largely mitigated this risk (Tsao et al., 1991; Al Jalali et al., 2026). The lack of standardized dosing and the variability in product quality across different manufacturers complicate clinical application and regulatory approval (Ubie Doctor's Note, 2026). Delivery to intracellular and intramitochondrial targets remains technically challenging, with novel delivery systems still in early stages of development (Altshuler et al., 2021).

11.3 Promising Research Directions

Development of Targeted Delivery Systems: Advanced nanoparticle-based delivery systems, cell-penetrating peptide conjugates, and mitochondria-targeted formulations hold significant promise for overcoming bioavailability and targeting limitations (Altshuler et al., 2021; Dastmalchi et al., 2026).

SOD Nanozyme Engineering: The rational design of SOD-mimicking nanozymes with enhanced catalytic specificity, biocompatibility, and in vivo stability represents a frontier with considerable therapeutic potential. Artificial intelligence-assisted design approaches may accelerate the discovery of optimized nanozyme structures (Dastmalchi et al., 2026; Chen et al., 2024).

Personalized Antioxidant Therapy: Understanding the role of SOD polymorphisms, epigenetic regulation, and tissue-specific expression patterns may enable personalized approaches to antioxidant therapy, with treatment strategies tailored to individual genetic and metabolic profiles (Miao & St. Clair, 2009; Mohammedi et al., 2014).

SOD in Immune Modulation and Infectious Diseases: The immunomodulatory functions of SOD and their relevance to inflammatory and infectious diseases represent an underexplored area with significant therapeutic potential (Liu et al., 2025).

Elucidating the SOD-Cancer Paradox: Systematic investigation of the molecular mechanisms governing the dual role of SOD in cancer, including the role of post-translational modifications such as acetylation, may identify novel therapeutic targets and biomarkers (Williams, 2019; Hempel et al., 2011; Islam et al., 2026).

Clinical Trials with Novel Formulations: Well-designed, adequately powered clinical trials employing novel SOD formulations with improved pharmacokinetic profiles are essential to establish the therapeutic efficacy of SOD-based interventions in specific disease contexts (Zhu et al., 2024; Altshuler et al., 2021).

12 Conclusions

Superoxide dismutase stands as one of the most extensively studied enzymes in biology, with its discovery in 1969 marking the birth of free radical biology and fundamentally transforming our understanding of oxidative stress in health and disease (McCord & Fridovich, 1969; Fridovich, 1995; Case, 2017). The SOD enzyme family, comprising structurally distinct isoforms with different metal cofactors, subcellular localizations, and regulatory mechanisms, provides essential protection against superoxide-mediated oxidative damage across all oxygen-metabolizing organisms (Miller, 2012; Wang et al., 2018).

The therapeutic potential of SOD has been demonstrated in diverse pathological conditions characterized by oxidative stress, including cardiovascular diseases, neurodegenerative disorders, cancer, diabetes and its complications, radiation injury, and inflammatory conditions (Zheng et al., 2023; Rosa et al., 2021). However, the translation of this potential into clinical practice has been limited by challenges related to bioavailability, delivery, and the context-dependent nature of SOD biology, particularly in cancer (McCord & Edeas, 2005; Hempel et al., 2011). Recent advances in SOD mimetics, nanozyme technologies, and targeted delivery systems have revitalized the field, offering new strategies to overcome historical limitations (Dastmalchi et al., 2026; Altshuleret al., 2021). As our understanding of the complex roles of SOD in redox signaling, immune regulation, and disease pathogenesis continues to deepen, the development of effective SOD-based therapies for a range of human diseases appears increasingly achievable.

References

al Jalali V, Bauer M, Jorda A, et al. 2026. Randomized, double-blind, phase I pharmacokinetic study of subcutaneous recombinant human superoxide dismutase (rhSOD) in healthy volunteers. Clinical Pharmacokinetics , 65: 71-80. https://link.springer.com/article/10.1007/s40262-025-01578-1

Altshuler PJ, Schiazza AR, Luo LJ, et al. 2021. Superoxide dismutase-loaded nanoparticles attenuate myocardial ischemia-reperfusion injury and protect against chronic adverse ventricular remodeling. Advanced Therapeutics, 4(6): 2100036.

https://scholars.uthscsa.edu/en/publications/superoxide-dismutase-loaded-nanoparticles-attenuate-myocardial-is/

Ambrosio G, Becker LC, Hutchins GM, Weisman HF, Weisfeldt ML. 1986. Reduction in experimental infarct size by recombinant human superoxide dismutase: Insights into the pathophysiology of reperfusion injury. Circulation, 74(6): 1424-1433. https://www.ahajournals.org/doi/10.1161/01.cir.74.6.1424?doi=10.1161/01.CIR.74.6.1424

Andersen PM, Al-Chalabi A. 2011. Clinical genetics of amyotrophic lateral sclerosis: what do we really know? Nature Reviews Neurology, 7(11): 603-615. https://pubmed.ncbi.nlm.nih.gov/21989245/

Argese E, Girotto R, Orsega EF. 1993. Comparative kinetic study between native and chemically modified Cu,Zn superoxide dismutases. Biochemical Journal, 292(2): 451-455. https://portlandpress.com/biochemj/article/292/2/451/30182/Comparative-kinetic-study-between-native-and

Asikainen TM, Raivio KO, Saksela M, Kinnula VL. 1998. Expression and developmental profile of antioxidant enzymes in human lung and liver. American Journal of Respiratory Cell and Molecular Biology, 19(6): 942-949. https://academic.oup.com/ajrcmb/article/19/6/942/8503068

Asikainen TM, White CW. 2004. Pulmonary antioxidant defenses in the preterm newborn with respiratory distress and bronchopulmonary dysplasia in evolution: implications for antioxidant therapy. Antioxid Redox Signal, 6(1): 155-167. https://pubmed.ncbi.nlm.nih.gov/14713347/

Ayubi N, Wibawa JC, Wibawa M, et al. 2024. Analyzing superoxide dismutase as a molecular signal transducer that is beneficial for health during physical exercise: a systematic review. Al-Kindy College Medical Journal, 20(2): 82-88. https://jkmc.uobaghdad.edu.iq/index.php/MEDICAL/article/view/1710

Barnham KJ, Masters CL, Bush AI. 2004. Neurodegenerative diseases and oxidative stress. Nature Reviews Drug Discovery, 3(3): 205-214. https://www.nature.com/articles/nrd1330

Barondeau DP, Kassmann CJ, Bruns CK, Tainer JA, Getzoff ED. 2004. Nickel superoxide dismutase structure and mechanism. Biochemistry, 43(25): 8038-8047. https://pubs.acs.org/doi/10.1021/bi0496081

Bar-Or D, Bar-Or R, Rael LT, Brody EN. 2015. Oxidative stress in severe acute illness. Redox Biology, 4: 340-345. https://www.sciencedirect.com/science/article/pii/S2212231715000075?via%3Dihub

Batinic-Haberle I, Rebouças JS, Spasojevic I. 2010. Superoxide dismutase mimics: chemistry, pharmacology, and therapeutic potential. Antioxidants & Redox Signaling, 13(6): 877-918. https://sage.cnpereading.com/doi/10.1089/ars.2009.2876

Batinic-Haberle I, Tovmasyan A, Roberts ER, Vujaskovic Z, Leong KW, Spasojevic I. 2014. SOD therapeutics: Latest insights into their structure-activity relationships and impact on the cellular redox-based signaling pathways. Antioxidants & Redox Signaling, 20(15): 2372-2415. https://sage.cnpereading.com/doi/10.1089/ars.2012.5147

Beauchamp C, Fridovich I. 1971. Superoxide dismutase: improved assays and an assay applicable to acrylamide gels. Analytical Biochemistry, 44(1): 276-287. https://doi.org/10.1016/0003-2697(71)90370-8

Beckman JS, Koppenol WH. 1996. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. American Journal of Physiology, 271(5): C1424-C1437. https://journals.physiology.org/doi/abs/10.1152/ajpcell.1996.271.5.C1424

Beckman JS, Minor RL, White CW, Repine JE, Rosen GM, Freeman BA. 1988. Superoxide dismutase and catalase conjugated to polyethylene glycol increases endothelial enzyme activity and oxidant resistance. Journal of Biological Chemistry, 263(14): 6884-6892. https://pubmed.ncbi.nlm.nih.gov/3129432/

Bedard K, Krause KH. 2007. The NOX family of ROS-generating NADPH oxidases: physiology and pathophysiology. Physiological Reviews, 87(1): 245-313.

https://journals.physiology.org/doi/full/10.1152/physrev.00044.2005

Boillée S, Vande Velde C, Cleveland DW. 2006. ALS: a disease of motor neurons and their nonneuronal neighbors. Neuron, 52(1): 39-59. https://www.sciencedirect.com/science/article/pii/S0896627306007252?via%3Dihub

Bolli R, Jeroudi MO, Patel BS, Aruoma OI, Halliwell B, Lai EK, McCay PB. 1989. Marked reduction of free radical generation and contractile dysfunction by antioxidant therapy begun at the time of reperfusion. Evidence that myocardial "stunning" is a manifestation of reperfusion injury. Circulation Research, 65(3): 607-622. https://www.ahajournals.org/doi/abs/10.1161/01.RES.65.3.607

Borgstahl GE, Parge HE, Hickey MJ, Beyer WF, Hallewell RA, Tainer JA. 1992. The structure of human mitochondrial manganese superoxide dismutase reveals a novel tetrameric interface of two 4-helix bundles. Cell, 71(1): 107-118. https://www.sciencedirect.com/science/article/pii/009286749290270M?via%3Dihub

Brownlee M. 2001. Biochemistry and molecular cell biology of diabetic complications. Nature, 414(6865): 813-820. https://www.nature.com/articles/414813a

Bruijn LI, Houseweart MK, Kato S, Anderson KL, Anderson SD, Ohama E, Reaume AG, Scott RW, Cleveland DW. 1998. Aggregation and motor neuron toxicity of an ALS-linked SOD1 mutant independent from wild-type SOD1. Science, 281(5384): 1851-1854. https://www.science.org/doi/10.1126/science.281.5384.1851

Carillon J, Rouanet JM, Cristol JP, Brion R. 2013. Superoxide dismutase administration, a potential therapy against oxidative stress related diseases: several routes of supplementation and proposal of an original mechanism of action. Pharmaceutical Research, 30(11): 2718-2728. https://link.springer.com/article/10.1007/s11095-013-1113-5

Carlioz A, Touati D. 1986. Isolation of superoxide dismutase mutants in *Escherichia coli*: is superoxide dismutase necessary for aerobic life? EMBO Journal, 5(3): 623-630. https://link.springer.com/article/10.1002/j.1460-2075.1986.tb04256.x

Carrico RJ, Deutsch HF. 1970. The presence of zinc in human cytocuprein and some properties of the apoprotein. Journal of Biological Chemistry, 245(4): 723-727. https://www.sciencedirect.com/science/article/pii/S002192581863323X

Case AJ. 2017. On the origin of superoxide dismutase: an evolutionary perspective of superoxide-mediated redox signaling. Antioxidants, 6(4): 82. https://www.mdpi.com/2076-3921/6/4/82

Cederbaum AI, Lu YK, Wu DF. 2009. Role of oxidative stress in alcohol-induced liver injury. Archives of Toxicology, 83(6): 519-548. https://link.springer.com/article/10.1007/s00204-009-0432-0

Chen XS, Luo XT, Zhou LJ, et al. 1997. Radioprotective effect of recombinant human CuZn-SOD on activities of antioxidases and immunocytes in irradiated mice. Chinese Journal of Radiological Medicine and Protection, 17(3):189-192. https://europepmc.org/article/cba/303428

Chen Y, Li B, Li K, Lin YQ. 2024. Superoxide dismutase nanozymes: current status and future perspectives on brain disease treatment and diagnosis. Chemical Communications, 31: 4140-4147. https://pubs.rsc.org/en/content/articlelanding/2024/cc/d3cc06288k

Church SL, Grant JW, Ridnour LA, Oberley LW, Swanson PE, Meltzer PS, Trent JM. 1993. Increased manganese superoxide dismutase expression suppresses the malignant phenotype of human melanoma cells. Proceedings of the National Academy of Sciences of the United States of America, 90(7): 3113-3117. https://www.pnas.org/doi/abs/10.1073/pnas.90.7.3113

Craven PA, Melhem MF, Phillips SL, DeRubertis FR. 2001. Overexpression of Zn^{2+}/Cu^{2+} superoxide dismutase protects against early diabetic glomerular injury in transgenic mice. Diabetes, 50(9): 2114-2125. https://diabetesjournals.org/diabetes/article-abstract/50/9/2114/11067/Overexpression-of-Cu2-Zn2-Supero

xide-Dismutase?redirectedFrom=fulltext

Constantino L, Gonçalves RC, Giombelli VR, et al. 2014. Regulation of lung oxidative damage by endogenous superoxide dismutase in sepsis. Intensive Care Medicine Experimental, 2(1): 17. https://link.springer.com/article/10.1186/2197-425X-2-17

Dastmalchi HZ, Dashtestani F, Ghourchian H. 2026. Superoxide dismutase nanozymes: A promising alternative to natural superoxide dismutase for biomedical and industrial applications. Colloids and Surfaces. B, Biointerfaces, 257: 115138. https://www.sciencedirect.com/science/article/pii/S0927776525006459?via%3Dihub

dataset. 2025. Natural plant-derived superoxide dismutase nanoenzyme for sepsis-induced liver injury therapy., geo, V1. https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE278841

De Blasio MJ, Ramalingam A, Cao AH, et al. 2017. The superoxide dismutase mimetic tempol blunts diabetes-induced upregulation of NADPH oxidase and endoplasmic reticulum stress in a rat model of diabetic nephropathy. European Journal of Pharmacology, 807: 12-20. https://www.sciencedirect.com/science/article/pii/S0014299917302844?via%3Dihub

Djawad K, Anggraini D. 2021. The effectiveness of oral superoxide dismutase (SOD) on total antioxidant status, transepidermal water loss (TEWL) and sebum concentration in photo aging skin. Medical Science of Ukraine, 17(1): 47-56. https://msu-journal.com/index.php/journal/article/view/264

Doctrow SR, Huffman K, Marcus CB, Tocco G, Malfroy E, Adinolfi CA, Kruk H, Baker K, Lazarowych N, Mascarenhas J, Malfroy B. 2002. Salen-manganese complexes as catalytic scavengers of hydrogen peroxide and cytoprotective agents: structure-activity relationship studies. Journal of Medicinal Chemistry, 45(20): 4549-4558. https://pubs.acs.org/doi/10.1021/jm020207y

Edwards RA, Baker HM, Whittaker MM, Whittaker JW, Jameson GB, Baker EN. 1998. Crystal structure of Escherichia coli manganese superoxide dismutase at 2.1 Å resolution. JBIC Journal of Biological Inorganic Chemistry, 3(2): 161-171. https://link.springer.com/article/10.1007/s007750050217

Fielden EM, Roberts PB, Bray RC, Lowe DJ, Mautner GN, Rotilio G, Calabrese L. 1974. The mechanism of action of superoxide dismutase from pulse radiolysis and electron paramagnetic resonance. Evidence that only half the active sites function in catalysis. Biochemical Journal, 139(1): 49-60. https://portlandpress.com/biochemj/article/139/1/49/5630/The-mechanism-of-action-of-superoxide-dismutase

Fisher CL, Cabelli DE, Tainer JA, Hallewell RA, Getzoff ED. 1994. The role of arginine 143 in the electrostatics and mechanism of Cu,Zn superoxide dismutase: computational and experimental evaluation by mutational analysis. Proteins, 19(1): 24-34. https://onlinelibrary.wiley.com/doi/10.1002/prot.340190105

Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. 1997. Pathophysiology of premature skin aging induced by ultraviolet light. New England Journal of Medicine, 337(20): 1419-1428. https://www.nejm.org/doi/full/10.1056/NEJM199711133372003

Flohe L. 1988. Superoxide dismutase for therapeutic use: Clinical experience, dead ends and hopes. Molecular and Cellular Biochemistry, 84(2): 123-131. https://link.springer.com/article/10.1007/BF00421046

Forman HJ. 1973. On the stability of bovine superoxide dismutase: The effects of metals. Journal of Biological Chemistry, 248(8): 2645-2649. https://scispace.com/papers/on-the-stability-of-bovine-superoxide-dismutase-the-effects-3l7ugxlpc5?citations_page=24

Fridovich I. 1995. Superoxide radical and superoxide dismutases. Annual Review of Biochemistry, 64: 97-112. https://www.annualreviews.org/content/journals/10.1146/annurev.bi.64.070195.000525

Galley HF. 2011. Oxidative stress and mitochondrial dysfunction in sepsis. British Journal of Anaesthesia,

107(1): 57-64. https://www.sciencedirect.com/science/article/pii/S0007091217331525?via%3Dihub

Getzoff ED, Cabelli DE, Fisher CL, Parge HE, et al. 1992. Faster superoxide dismutase mutants designed by enhancing electrostatic guidance. Nature, 358(6384): 347-351. https://www.nature.com/articles/358347a0

Getzoff ED, Tainer JA, Weiner PK, Kollman PA, Richardson JS, Richardson DC. 1983. Electrostatic recognition between superoxide and copper, zinc superoxide dismutase. Nature, 306(5940): 287-290. https://www.nature.com/articles/306287a0

Giacco F, Brownlee M. 2010. Oxidative stress and diabetic complications. Circulation Research, 107(9): 1058-1070. https://www.ahajournals.org/doi/10.1161/circresaha.110.223545

Griendling KK, FitzGerald GA. 2003. Oxidative stress and cardiovascular injury: Part I: basic mechanisms and in vivo monitoring of ROS. Circulation, 108(16): 1912-1916. https://www.ahajournals.org/doi/10.1161/01.CIR.0000093660.86242.BB

Gurney ME, Pu HF, Chiu AY, Dal Canto MC, et al. 1994. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science, 264(5166): 1772-1775. https://www.science.org/doi/10.1126/science.8209258

Hadji I, Marzouki MN, Ferraro D, et al. 2007. Purification and characterization of a Cu,Zn-SOD from garlic (Allium sativum L.). Antioxidant effect on tumoral cell lines. pplied Biochemistry and Biotechnology, 143: 129–141. https://link.springer.com/article/10.1007/s12010-007-0042-3

Hallewell RA, Masiarz FR, Najarian RC, Purna JP, Quiroga MR, Randolph A, et al. 1985. Human Cu/Zn superoxide dismutase cDNA: Isolation of clones synthesising high levels of active or inactive enzyme from an expression library. Nucleic Acids Research, 13(6): 2017-2034. https://academic.oup.com/nar/article/13/6/2017/2381677

Halliwell B, Gutteridge JM. 2015. Free Radicals in Biology and Medicine. Fifth Edition. Oxford University Press, Oxford, UK. https://global.oup.com/academic/product/free-radicals-in-biology-and-medicine-9780198717485

Harman D. 1956. Aging: a theory based on free radical and radiation chemistry. Journal of Gerontology, 11(3): 298-300. https://academic.oup.com/geronj/article/11/3/298/616585

Harman D. 1981. The aging process. Proceedings of the National Academy of Sciences of the United States of America, 78(11): 7124-7128. https://www.pnas.org/doi/abs/10.1073/pnas.78.11.7124

Hartman JR, Geller T, Yavin Z, et al. 1986. High-level expression of enzymatically active human Cu/Zn superoxide dismutase in *Escherichia coli*. Proceedings of the National Academy of Sciences of the United States of America, 83(19): 7142-7146. https://www.pnas.org/doi/abs/10.1073/pnas.83.19.7142

Hatzinikolaou DG, Tsoukia C, Kekos D, Macris BJ. 1998. An efficient and optimized purification procedure for the superoxide dismutase from *Aspergillus niger*. Partial characterization of the purified enzyme. Bioseparation, 7(1): 39-46. https://link.springer.com/article/10.1023/A:1007986510153

He L, Li QB, Sun DH, Ling XP. 2008. Isolation, purification and characterization of superoxide dismutase from garlic. Biochemical Engineering Journal, 38(1): 33-38. https://www.sciencedirect.com/science/article/pii/S1369703X07002239?via%3Dihub

Hjalmarsson K, Marklund SL, Engström A, Edlund T. 1987. Isolation and sequence of complementary DNA encoding human extracellular superoxide dismutase. Proceedings of the National Academy of Sciences of the United States of America, 84(18): 6340-6344. https://www.pnas.org/doi/abs/10.1073/pnas.84.18.6340

Huang JQ, Zhang WJ. 2012. Analysis on degree distribution of tumor signaling networks. Network Biology, 2(3): 95-109. http://www.iaees.org/publications/journals/nb/articles/2012-2(3)/analysis-on-degree-distribution-of-tumor-signaling-networks.pdf

Ighodaro OM, Akinloye OA. 2018. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. Alexandria Journal of Medicine, 54(4): 287-293. https://www.tandfonline.com/doi/full/10.1016/j.ajme.2017.09.001

Indrayati A, Nurfitriyawatie, Rukmana RM. 2024. Exploring the anti-photoaging potential of *Bacillus cereus* superoxide dismutase in New Zealand rabbit skin. HAYATI Journal of Biosciences 31(2): 357-366. https://journal.ipb.ac.id/hayati/article/view/46215

Islam MR, Alam R, Islam F, Nagar P, Rahman MA. 2026. Mitochondrial antioxidant enzyme (SOD2) at the crossroads of redox signaling and cancer progression. Free Radical Research, 61(2): 1-18. https://www.tandfonline.com/doi/full/10.1080/10715762.2026.2643692

Jadot G, Vaille A, Maldonado J, Vanelle P. 1995.1994. Clinical pharmacokinetics and delivery of bovine superoxide dismutase. Clinical Pharmacokinetics, 28(1): 17-25. https://link.springer.com/article/10.2165/00003088-199528010-00003

Jaeschke H. 2003. Molecular mechanisms of hepatic ischemia-reperfusion injury and preconditioning. American Journal of Physiology-Gastrointestinal and Liver Physiology, 284(1): G15-G26. https://journals.physiology.org/doi/full/10.1152/ajpgi.00342.2002

Jomova K, Alomar SY, Alwasel SH, et al. 2024. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. Archives of Toxicology, 98(5): 1323-1367. https://link.springer.com/article/10.1007/s00204-024-03696-4

Kalmari A, Colagar AH. 2024. Exploration of SOD3 from gene to therapeutic prospects: a brief review. Molecular Biology Reports, 51(1): 980. https://link.springer.com/article/10.1007/s11033-024-09919-2

Karlsson K, Lindahl U, Marklund SL. 1988. Binding of human extracellular superoxide dismutase C to sulphated glycosaminoglycans. Biochemical Journal, 256(1): 29-33. https://portlandpress.com/biochemj/article/256/1/29/36607/Binding-of-human-extracellular-superoxide

Hempel N, Carrico PM, Melendez JA. 2011. Manganese superoxide dismutase (Sod2) and redox-control of signaling events that drive metastasis. Anti-Cancer Agents in Medicinal Chemistry, 11(2): 191–201. https://www.benthamscience.com/article/117708

Khayatan D, Razavi SM, Arab ZN, et al. 2024. Superoxide dismutase: a key target for the neuroprotective effects of curcumin. Molecular and Cellular Biochemistry, 479(3): 693-705.

Kim SW, Lee SO, Lee TH. 1991. Purification and characterization of superoxide dismutase from Aerobacter aerogenes. Agric Biol Chem, 55(1):101-108. https://pubmed.ncbi.nlm.nih.gov/1368658/

Klug-Roth D, Fridovich I, Rabani J. 1973. Pulse radiolytic investigations of superoxide-catalyzed disproportionation: Mechanism of bovine erythrocyte superoxide dismutase. Journal of the American Chemical Society, 95(8): 2786-2790. https://pubs.acs.org/doi/abs/10.1021/ja00790a007

Kumagai Y, Shinyashiki M, Sun GF, et al. 1994. An efficient method for purification of cuprozinc superoxide dismutase from bovine erythrocytes. Experientia, 7: 673-676. https://ouci.dntb.gov.ua/en/works/426n2De4/

Lebovitz RM, Zhang H, Vogel H, et al. 1996. Neurodegeneration, myocardial injury, and perinatal death in mitochondrial superoxide dismutase-deficient mice. Proceedings of the National Academy of Sciences of the United States of America, 93(18): 9782-9787. https://www.pnas.org/doi/abs/10.1073/pnas.93.18.9782

Lee JH, Choi IY, Kil IS, Kim SY, Yang ES, Park JW. 2001. Protective role of superoxide dismutases against ionizing radiation in yeast. Biochimica et Biophysica Acta, 1526(2): 191-198. https://www.sciencedirect.com/science/article/pii/S030441650100126X?via%3Dihub

Li JJ, Oberley LW, St. Clair DK, Ridnour LA, Oberley TD. 1995. Phenotypic changes induced in human

breast cancer cells by overexpression of manganese-containing superoxide dismutase. Oncogene, 10(10): 1989-2000. https://pubmed.ncbi.nlm.nih.gov/7761102/

Li JR, Zhang WJ. 2013. Identification of crucial metabolites/reactions in tumor signaling networks. Network Biology, 3(4): 121-132. http://www.iaees.org/publications/journals/nb/articles/2013-3(4)/crucial-metabolites-reactions-in-tumor-signaling.pdf

Li QH, Bolli R, Qiu YM, Tang XL, Murphree SS, French BA. 1998. Gene therapy with extracellular superoxide dismutase attenuates myocardial stunning in conscious rabbits. Circulation, 98(14): 1438-1448. https://doi.org/10.1161/01.CIR.98.14.1438

Li YB, Huang TT, Carlson EJ, Melov S, Ursell PC, Olson JL, Noble LJ, Yoshimura MP, Berger C, Chan PH, Wallace DC, Epstein CJ. 1995. Dilated cardiomyopathy and neonatal lethality in mutant mice lacking manganese superoxide dismutase. Nature Genetics, 11(4): 376-381. https://www.nature.com/articles/ng1295-376

Liu T, Shang JJ, Chen QJ. 2025. Superoxide dismutases in immune regulation and infectious diseases. Antioxidants, 14(7): 809. https://www.mdpi.com/2076-3921/14/7/809

Lin MT, Beal MF. 2006. Mitochondrial dysfunction and oxidative stress in neurodegenerative diseases. Nature, 443(7113): 787-795. https://www.nature.com/articles/nature05292

Mączewski M, Duda M, W. Pawlak W, et al. 2004. 2001. Endothelial protection from reperfusion injury by ischemic preconditioning and diazoxide involves a SOD-like anti-$O_2^{\bullet-}$ mechanism. Journal of Physiology and Pharmacology, 55(3): 537-550. https://pubmed.ncbi.nlm.nih.gov/15381825/

Macarthur H, Couri DM, Wilken GH, et al. 2003. Modulation of serum cytokine levels by a novel superoxide dismutase mimetic, M40401, in an Escherichia coli model of septic shock: Correlation with preserved circulating catecholamines. Critical Care Medicine, 31(1): 237-245. https://journals.lww.com/ccmjournal/fulltext/2003/01000/modulation_of_serum_cytokine_levels_by_a_novel.37.aspx

MacMillan-Crow LA, Crow JP, Kerby JD, Beckman JS, Thompson JA. 1996. Nitration and inactivation of manganese superoxide dismutase in chronic rejection of human renal allografts. Proceedings of the National Academy of Sciences of the United States of America, 93(21): 11853-11858. https://www.pnas.org/doi/abs/10.1073/pnas.93.21.11853

Maczewski M, Duda M, Pawlak W, Beresewicz A. 2004. Endothelial protection from reperfusion injury by ischemic preconditioning and diazoxide involves a SOD-like anti-$O_2^{\bullet-}$ mechanism. Journal of Physiology and Pharmacology, 55(3): 537-550. https://pubmed.ncbi.nlm.nih.gov/14726606/

Madhubhani LP, Hemachandra P, Shin DH et al. 2015. Mitochondrial superoxide dismutase has a protumorigenic role in ovarian clear cell carcinoma. Cancer Research, 75: 4973-4984. https://pdfs.semanticscholar.org/842b/3f15da7e42ef175ce346dae2f5cf309590a4.pdf

Mann T, Keilin D. 1938. Haemocuprein and hepatocuprein, copper-protein compounds of blood and liver in mammals. Proceedings of the Royal Society of London B: Biological Sciences, 126(844): 303-315. https://royalsocietypublishing.org/rspb/article/126/844/303/29295/Haemocuprein-and-hepatocuprein-copper-protein

Marklund SL. 1980. Distribution of CuZn superoxide dismutase and Mn superoxide dismutase in human tissues and extracellular fluids. Acta Physiologica Scandinavica, 492: 19-23. https://pubmed.ncbi.nlm.nih.gov/6939296/

Marklund SL. 1984a. Extracellular superoxide dismutase and other superoxide dismutase isoenzymes in tissues from nine mammalian species. Biochemical Journal, 222(3): 649-655.

https://portlandpress.com/biochemj/article/222/3/649/18854/Extracellular-superoxide-dismutase-and-other

Marklund SL. 1984b. Properties of extracellular superoxide dismutase from human lung. Biochemical Journal, 220(1): 269-272. https://portlandpress.com/biochemj/article/220/1/269/15598/Properties-of-extracellular-superoxide-dismutase

Marklund SL, Holme E, Hellner L. 1982. Superoxide dismutase in extracellular fluids. Clinica Chimica Acta, 126(1): 41-51. https://www.sciencedirect.com/science/article/abs/pii/0009898182903606

Marklund SL, Marklund G. 1974. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. European Journal of Biochemistry, 47(3): 469-474. https://febs.onlinelibrary.wiley.com/doi/10.1111/j.1432-1033.1974.tb03714.x

Martchenko M, Alarco AM, Harcus D, Whiteway M. 2004. Superoxide dismutases in Candida albicans: Transcriptional regulation and functional characterization of the hyphal-induced SOD5 gene. Molecular Biology of the Cell, 15(2): 456-467. https://www.ncbi.nlm.nih.gov/pubmed/14617818

Marzi I, Bühren V, Schüttler A, Trentz O. 1993. Value of superoxide dismutase for prevention of multiple organ failure after multiple trauma. The Journal of Trauma: Injury, Infection, and Critical Care, 35(1): 110-120. https://journals.lww.com/jtrauma/abstract/1993/07000/value_of_superoxide_dismutase_for_prevention_of.18.aspx

McCord JM, Edeas MA. 2005. SOD, oxidative stress and human pathologies: a brief history and a future vision. Biomedicine & Pharmacotherapy, 59(4): 139-142. https://www.sciencedirect.com/science/article/pii/S0753332205000387?via%3Dihub

McCord JM, Fridovich I. 1969. Superoxide dismutase: An enzymic function for erythrocuprein (hemocuprein). Journal of Biological Chemistry, 244(22): 6049-6055. https://www.sciencedirect.com/science/article/pii/S0021925818635045

Melov S, Doctrow SR, Schneider JA, Haberzon J, Patel M, Coskun PE, Huffman K, Wallace DC, Malfroy B. 2001. Lifespan extension and rescue of spongiform encephalopathy in superoxide dismutase 2 nullizygous mice treated with superoxide dismutase-catalase mimetics. Journal of Neuroscience, 21(21): 8348-8353. https://www.jneurosci.org/content/21/21/8348

Miao L, St. Clair DK. 2009. Regulation of superoxide dismutase genes: Implications in disease. Free Radical Biology and Medicine, 47(4): 344-356. https://www.sciencedirect.com/science/article/pii/S0891584909002986?via%3Dihub

Michiels C, Raes M, Toussaint O, Remacle J. 1994. Importance of Se-glutathione peroxidase, catalase, and Cu/Zn-SOD for cell survival against oxidative stress. Free Radical Biology and Medicine, 17(3): 235-248. https://www.sciencedirect.com/science/article/abs/pii/0891584994900795?via%3Dihub

Milani P, Ambrosi G, Gammoh O, Blandini F, Cereda C. 2013. SOD1 and DJ-1 converge at Nrf2 pathway: A clue for antioxidant therapeutic potential in neurodegeneration. Oxidative Medicine and Cellular Longevity, 2013: 836760. https://onlinelibrary.wiley.com/doi/10.1155/2013/836760

Miller AF. 2012. Superoxide dismutases: Ancient enzymes and new insights. FEBS Letters, 586(5): 585-595. https://febs.onlinelibrary.wiley.com/doi/10.1016/j.febslet.2011.10.048

Mohammedi K, Bellili-Muñoz N, Driss F, Roussel R, Seta N, Fumeron F, Hadjadj S, Marre M, Velho G. 2014. Manganese superoxide dismutase (SOD2) polymorphisms, plasma advanced oxidation protein products (AOPP) concentration and risk of kidney complications in subjects with type 1 diabetes. PLoS ONE, 13(4): e0195720. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0096916

Murata S, Miniati DN, Kown MH, et al. 2004. Superoxide dismutase mimetic M40401 reduces

ischemia-reperfusion injury and graft coronary artery disease in rodent cardiac allografts. Transplantation, 78(8): 1166-1171. https://journals.lww.com/transplantjournal/fulltext/2004/10270/superoxide_dismutase_mimetic_m40401_reduces.15.aspx

Münzel T, Camici GG, Maack C, Bonetti NR, Fuster V, Kovacic JC. 2017. Impact of oxidative stress on the heart and vasculature: Part 2 of a 3-Part Series. Journal of the American College of Cardiology, 70(2): 212-229. https://pmc.ncbi.nlm.nih.gov/articles/PMC5663297/

Oberley LW, Buettner GR. 1979. Role of superoxide dismutase in cancer: a review. Cancer Research, 39(4): 1141-1149. https://pubmed.ncbi.nlm.nih.gov/217531/

Okado-Matsumoto A, Fridovich I. 2001. Subcellular distribution of superoxide dismutases (SOD) in rat liver: Cu,Zn-SOD in mitochondria. Journal of Biological Chemistry, 276(42): 38388-38393. https://www.sciencedirect.com/science/article/pii/S0021925820740858?via%3Dihub

Orr WC, Sohal RS. 1994. Extension of life-span by overexpression of superoxide dismutase and catalase in Drosophila melanogaster. Science, 263(5150): 1128-1130. https://www.science.org/doi/10.1126/science.8108730

Ozdemir C, Gulesci N, Bilgin R. 2021. Purification and characterization of superoxide dismutase enzyme from *Punica granatum* L. Asian Journal of Research in Biochemistry, 9(3): 30-35. https://journalajrb.com/index.php/AJRB/article/view/159?__cf_chl_tk=w7RPtKX_DAXiXQS9Kk9XK4sipwF8K1K7BEJfevg5Rc4-1777943049-1.0.1.1-2Uy7_g_z61sdDA2.b0zBD9KNioVg3In2y1zl61QNHm4

Panda B, Tripathy A, Srimanta Patra S, et al. 2024. Imperative connotation of SODs in cancer: Emerging targets and multifactorial role of action. IUBMB Life, 76(9):592-613. https://iubmb.onlinelibrary.wiley.com/doi/10.1002/iub.2821

Parker MW, Blake CCC. 1988. Iron- and manganese-containing superoxide dismutases can be distinguished by analysis of their primary structures. FEBS Letters, 229(2): 377-382. https://febs.onlinelibrary.wiley.com/doi/10.1016/0014-5793%2888%2981160-8

Pasinelli P, Brown RH. 2006. Molecular biology of amyotrophic lateral sclerosis: insights from genetics. Nature Reviews Neuroscience, 7(9): 710-723. https://www.nature.com/articles/nrn1971

Patel Y, Moraes YC, Latchman D, et al. 2002. Neuroprotective effects of copper/zinc-dependent superoxide dismutase against a wide variety of death-inducing stimuli and proapoptotic effect of familial amyotrophic lateral sclerosis mutations. Molecular Brain Research, 109(1-2): 189-197. https://www.sciencedirect.com/science/article/pii/S0169328X02005600?via%3Dihub

PDB-101. 2026. https://pdb101.rcsb.org/motm/94. Accessed on April 28, 2026

Peixoto EBM, Pessoa BS, Biswas SK, Lopes de Faria JB. 2008. Antioxidant SOD mimetic prevents NADPH oxidase-induced oxidative stress and renal damage in the early stage of experimental diabetes and hypertension. American Journal of Nephrology, 29(4): 309-318. https://karger.com/ajn/article/29/4/309/25603/Antioxidant-SOD-Mimetic-Prevents-NADPH-Oxidase

Petkau A. 1978. Radiation protection by superoxide dismutase. Photochemistry and Photobiology, 28(4-5): 765-774. https://onlinelibrary.wiley.com/doi/10.1111/j.1751-1097.1978.tb07015.x

Petkau A. 1987. Role of superoxide dismutase in modification of radiation injury. British Journal of Cancer, 55(Suppl 8): 87-95.

Petkau A, Chelack WS. 1976. Radioprotective effect of superoxide dismutase on model phospholipid membranes. Biochimica et Biophysica Acta, 433(3): 445-456. https://www.sciencedirect.com/science/article/abs/pii/0005273676902728?via%3Dihub

Pratiwi ME, Barus AA, Tobi CH. 2025. Collagen deposition effect of superoxide dismutase corn kernel extract

(*Zea mays* L.) as skin photoaging treatment. Journal of Food and Pharmaceutical Sciences 13(2): 136-148. https://www.researchgate.net/publication/395974140_Collagen_Deposition_Effect_of_Superoxide_Dismutase_Corn_Kernel_Extract_Zea_mays_L_as_Skin_Photoaging_Treatment

Regnault C, Soursac M, Roch-Arveiller M, Postaire E, Hazebroucq G. 1996. Pharmacokinetics of superoxide dismutase in rats after oral administration. Biopharmaceutics & Drug Disposition, 17(2): 165-174. https://onlinelibrary.wiley.com/doi/abs/10.1002/%28SICI%291099-081X%28199603%2917%3A2%3C165%3A%3AAID-BDD945%3E3.0.CO%3B2-N

Rhie G, Shin MH, Seo JY, Choi WW, Cho KH, Kim KH, Park KC, Eun HC, Chung JH. 2001. Aging- and photoaging-dependent changes of enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. Journal of Investigative Dermatology, 117(5): 1212-1217. https://www.sciencedirect.com/science/article/pii/S0022202X15414435?via%3Dihub

Riley PA. 1994. Free radicals in biology: oxidative stress and the effects of ionizing radiation. International Journal of Radiation Biology, 65(1): 27-33. https://www.tandfonline.com/doi/abs/10.1080/09553009414550041

Ristow M, Schmeisser S. 2011. Extending life span by increasing oxidative stress. Free Radical Biology and Medicine, 51(2): 327-336. https://www.sciencedirect.com/science/article/pii/S0891584911003121?via%3Dihub

Rittié L, Fisher GJ. 2015. Natural and sun-induced aging of human skin. Cold Spring Harbor Perspectives in Medicine, 5(1): a015370. https://perspectivesinmedicine.cshlp.org/content/5/1/a015370

Rosa AC, Corsi DJ, Cavi N, et al. 2021. Superoxide dismutase administration: A review of proposed human uses. Molecules, 26(7): 1844. https://www.mdpi.com/1420-3049/26/7/1844

Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, et al. 1993. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. Nature, 362(6415): 59-62. https://www.nature.com/articles/362059a0

Rotilio G, Bray RC, Fielden EM. 1972. A pulse radiolysis study of superoxide dismutase. Biochimica et Biophysica Acta, 268(2): 605-609. https://www.sciencedirect.com/science/article/abs/pii/0005274472903592

Saccon RA, Bunton-Stasyshyn RK, Fisher EMC, Fratta P. 2013. Is SOD1 loss of function involved in amyotrophic lateral sclerosis? Brain, 136(8): 2342-2358. https://academic.oup.com/brain/article/136/8/2342/424144

Sally K Nelson SK, Gao BF, Bose S, et a;. 2002. A novel heparin-binding, human chimeric, superoxide dismutase improves myocardial preservation and protects from ischemia-reperfusion injury. The Journal of Heart and Lung Transplantation, 21(12): 1296-1303. https://www.sciencedirect.com/science/article/pii/S1053249802004618?via%3Dihub

Salvemini D, Riley DP, Lennon PJ, Wang ZQ, Currie MG, Macarthur H, Misko TP. 1999. Protective effects of a superoxide dismutase mimetic and peroxynitrite decomposition catalysts in endotoxin-induced intestinal damage. British Journal of Pharmacology, 127(3): 685-692. https://bpspubs.onlinelibrary.wiley.com/doi/10.1038/sj.bjp.0702604

Salvemini D, Riley DP, Cuzzocrea S. 2002. SOD mimetics are coming of age. Nature Reviews Drug Discovery, 1(5): 367-374. https://www.nature.com/articles/nrd796

Sander CS, Chang H, Salzmann S, Müller CSL, Ekanayake-Mudiyanselage S, Elsner P, Thiele JJ. 2002. Photoaging is associated with protein oxidation in human skin in vivo. Journal of Investigative Dermatology, 118(4): 618-625. https://www.sciencedirect.com/science/article/pii/S0022202X15416173?via%3Dihub

Sandstrom J, Carlsson L, Marklund SL, Edlund T. 1992. The heparin-binding domain of extracellular superoxide dismutase C and formation of variants with reduced heparin affinity. Journal of Biological Chemistry, 267(25): 18205-18209. https://www.sciencedirect.com/science/article/pii/S002192581937173X

Sies H. 1997. Oxidative stress: Oxidants and antioxidants. Experimental Physiology, 82(2): 291-295. https://physoc.onlinelibrary.wiley.com/doi/10.1113/expphysiol.1997.sp004024

Sines JJ, Allison SA, McCammon JA. 1990. Point charge distributions and electrostatic steering in enzyme/substrate encounter: Brownian dynamics of modified copper/zinc superoxide dismutases. Biochemistry, 29(40): 9403-9412. https://pubs.acs.org/doi/10.1021/bi00492a014

Slot JW, Geuze HJ, Freeman BA, Crapo JD. 1986. Intracellular localization of the copper-zinc and manganese superoxide dismutases in rat liver parenchymal cells. Laboratory Investigation, 55(3): 363-371. https://pubmed.ncbi.nlm.nih.gov/3528671/

Smith MW, Doolittle RF. 1992. A comparison of evolutionary rates of the two major kinds of superoxide dismutase. Journal of Molecular Evolution, 34(2): 175-184. https://link.springer.com/article/10.1007/BF00182394

Stalling WC, Pattridge KA, Strong RK, Ludwig ML. 1984. Manganese and iron superoxide dismutases are structural homologs. Journal of Biological Chemistry, 259(17): 10695-10699. https://doi.org/10.1016/S0021-9258(18)90567-3

Strange RW, Antonyuk S, Hough MA, Doucette PA, Rodriguez JA, Hart PJ, Hayward LJ, Valentine JS, Hasnain SS. 2003. The structure of holo and metal-deficient wild-type human Cu, Zn superoxide dismutase and its relevance to familial amyotrophic lateral sclerosis. Journal of Molecular Biology, 328(4): 877-891. https://www.sciencedirect.com/science/article/pii/S0022283603003553?via%3Dihub

Sturtz LA, Diekert K, Jensen LT, Lill R, Culotta VC. 2001. A fraction of yeast Cu,Zn-superoxide dismutase and its metallochaperone, CCS, localize to the intermembrane space of mitochondria: A physiological role for SOD1 in guarding against mitochondrial oxidative damage. Journal of Biological Chemistry, 276(41): 38084-38089. https://www.sciencedirect.com/science/article/pii/S0021925819649835?via%3Dihub

Stýblo M, Walton FS, Harmon AW, et al. 2007. Activation of superoxide dismutase in selenium-deficient mice infected with influenza virus. Journal of Trace Elements in Medicine and Biology, 21(1): 52-62. https://www.sciencedirect.com/science/article/pii/S0946672X0600160X?via%3Dihub

Suzuki J, Broeyer F, Cohen A, et al. 2008. Pharmacokinetics of PC-SOD, a lecithinized recombinant superoxide dismutase, after single and multiple dose administration to healthy Japanese and Caucasian volunteers. The Journal of Clinical Pharmacology, 48(2): 184-192. https://accp1.onlinelibrary.wiley.com/doi/10.1177/0091270007309705

Tainer JA, Getzoff ED, Beem KM, Richardson JS, Richardson DC. 1982. Determination and analysis of the 2 Å structure of copper, zinc superoxide dismutase. Journal of Molecular Biology, 160(2): 181-217. https://www.sciencedirect.com/science/article/abs/pii/0022283682901747

Tibell L, Hjalmarsson K, Edlund T, Skogman G, Engström Å, Marklund SL. 1987. Expression of human extracellular superoxide dismutase in Chinese hamster ovary cells and characterization of the product. Proceedings of the National Academy of Sciences of the United States of America, 84(19): 6634-6638. https://www.pnas.org/doi/abs/10.1073/pnas.84.19.6634

Tsao C, Greene P, Odlind B, Brater DC. 1991. Pharmacokinetics of recombinant human superoxide dismutase in healthy volunteers. Clinical Pharmacology & Therapeutics, 50: 713-720. https://ascpt.onlinelibrary.wiley.com/doi/10.1038/clpt.1991.211

Turrens JF. 2003. Mitochondrial formation of reactive oxygen species. Journal of Physiology, 552: 335-344. https://physoc.onlinelibrary.wiley.com/doi/full/10.1111/j.1469-7793.2003.00335.x

Turrens JF, Crapo JD, Freeman BA. 1984. Protection against oxygen toxicity by intravenous injection of liposome-entrapped catalase and superoxide dismutase. Journal of Clinical Investigation, 73(1): 87-95. https://www.jci.org/articles/view/111210

Ursby T, Adinolfi BS, Al-Karadaghi S, De Vendittis E, Bocchini V. 1999. Iron superoxide dismutase from the archaeon Sulfolobus solfataricus: analysis of structure and thermostability. Journal of Molecular Biology, 286(1): 189-205. https://www.sciencedirect.com/science/article/pii/S0022283698924718

Van Raamsdonk JM, Hekimi S. 2009. Deletion of the mitochondrial superoxide dismutase sod-2 extends lifespan in Caenorhabditis elegans. PLoS Genetics, 5(2): e1000361. https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1000361

Van Raamsdonk JM, Hekimi S. 2012. Superoxide dismutase is dispensable for normal animal lifespan. Proceedings of the National Academy of Sciences of the United States of America, 109(15): 5785-5790. https://www.pnas.org/doi/full/10.1073/pnas.1116158109

Veronese FM, Largajolli R, Boccù E, Benassi CA, Schiavon O. 1985. Surface modification of proteins: activation of monomethoxy-polyethylene glycols by phenylchloroformates and modification of ribonuclease and superoxide dismutase. Applied Biochemistry and Biotechnology, 11(2): 141-152. https://link.springer.com/article/10.1007/BF02798546

Wagner UG, Frolow F, Sussman JL, et al. 1993. Comparison of the crystal structures of genetically engineered human manganese superoxide dismutase and manganese superoxide dismutase from Thermus thermophilus: differences in dimer-dimer interaction. Protein Science, 2(5): 814-825. https://onlinelibrary.wiley.com/doi/10.1002/pro.5560020511

Wang W, Xia MX, Chen J, et al. 2016. Gene expression characteristics and regulation mechanisms of superoxide dismutase and its physiological roles in plants under stress. Biochemistry, 81: 465-480. https://link.springer.com/article/10.1134/S0006297916050047

Wang X, Liu XF, Zhou YJ, et al. 2014. Molecular mechanism of expression and regulation of SOD gene in plant. Chinese Journal of Oil Crop Sciences, 36(2): 275. http://www.jouroilcrops.cn/EN/10.7505/j.issn.1007-9084.2014.02.021

Wang Y, Branicky R, Noë A, Hekimi S. 2018. Superoxide dismutases: dual roles in controlling ROS damage and regulating ROS signaling. Journal of Cell Biology, 217(6): 1915-1928. https://rupress.org/jcb/article/217/6/1915/39308/Superoxide-dismutases-Dual-roles-in-controlling

Weisiger RA, Fridovich I. 1973. Mitochondrial superoxide dismutase: site of synthesis and intramitochondrial localization. Journal of Biological Chemistry, 248(13): 4793-4796. https://pubmed.ncbi.nlm.nih.gov/4578091/

Weitner T, Kos I, Sheng HX, Tovmasyan A, et al. 2013. Comprehensive pharmacokinetic studies and oral bioavailability of two Mn porphyrin-based SOD mimics, MnTE-2-PyP^{5+} and MnTnHex-2-PyP^{5+}. Free Radical Biology and Medicine, 58: 73-80. https://www.sciencedirect.com/science/article/pii/S0891584913000075?via%3Dihub

Williams A. 2019. Uncovering enzyme's dual role in cancer suppression and growth. Northwestern Medicine News Center. https://news.feinberg.northwestern.edu/2019/06/03/uncovering-enzymes-dual-role-in-cancer-suppression-and-growth/

Wispe JR, Clark JC, Burhans MS, Kropp KE, Korfhagen TR, Whitsett JA. 1989. Synthesis and processing of the precursor for human mangano-superoxide dismutase. Biochimica et Biophysica Acta, 994(1): 30-36. https://www.sciencedirect.com/science/article/abs/pii/0167483889900587?via%3Dihub

Wuerges J, Lee JW, Yim YI, Yim HS, Kang SO, Carugo KD. 2004. Crystal structure of nickel-containing

superoxide dismutase reveals another type of active site. Proceedings of the National Academy of Sciences of the United States of America, 101(23): 8569-8574. https://www.pnas.org/doi/full/10.1073/pnas.0308514101

Xia SL, Li MJ, Chen Y. 1995. Radioprotective effect of bovine erythrocyte superoxide dismutase on mice. Chinese Journal of Radiological Medicine and Protection, 15(3): 189-192.

Yamakura F, Kawasaki H. 2010. Post-translational modifications of superoxide dismutase. Biochimica et Biophysica Acta, 1804(2): 318-325. https://www.sciencedirect.com/science/article/pii/S1570963909002994?via%3Dihub

Yen CC, Lai YW,Chen HL, et al. 2011. Aerosolized human extracellular superoxide dismutase prevents hyperoxia-induced lung injury. PLOS One, 6(10): e26870. https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0026870

Yost FJ, Fridovich I. 1973. An iron-containing superoxide dismutase from *Escherichia coli*. Journal of Biological Chemistry, 248(14): 4905-4908. https://doi.org/10.1016/S0021-9258(19)43652-1

Youn HD, Kim EJ, Roe JH, Hah YC, Kang SO. 1996. A novel nickel-containing superoxide dismutase from Streptomyces spp. Biochemical Journal, 318(3): 889-896. https://portlandpress.com/biochemj/article/318/3/889/32962/A-novel-nickel-containing-superoxide-dismutase

Zelko IN, Mariani TJ, Folz RJ. 2002. Superoxide dismutase multigene family: a comparison of the CuZn-SOD (SOD1), Mn-SOD (SOD2), and EC-SOD (SOD3) gene structures, evolution, and expression. Free Radical Biology and Medicine, 33(3): 337-349. https://www.sciencedirect.com/science/article/pii/S089158490200905X?via%3Dihub

Zhang HJ, Zhao WL, Venkataraman S, Robbins MEC, Buettner GR, Kregel KC, Oberley LW. 2002. Activation of matrix metalloproteinase-2 by overexpression of manganese superoxide dismutase in human breast cancer MCF-7 cells involves reactive oxygen species. Journal of Biological Chemistry, 277(23): 20919-20926. https://www.sciencedirect.com/science/article/pii/S0021925820849473

Zhang WJ. 2016a. Detecting connectedness of network: A Matlab program and application in tumor pathways and a phylogenic network. Selforganizology, 3(4): 117-120. http://www.iaees.org/publications/journals/selforganizology/articles/2016-3(4)/detecting-connectedness-of-network.pdf

Zhang WJ. 2016b. Selforganizology: The Science of Self-Organization. World Scientific, Singapore. https://doi.org/10.1142/9685

http://www.iaees.org/publications/journals/np/articles/2017-2(3)/classification-and-network-analysis-of-medicinal-functions.pdf

Zhang WJ. 2017. Finding the shortest tree in the network: A Matlab program and application in tumor pathway. Network Pharmacology, 2(1): 13-16. http://www.iaees.org/publications/journals/np/articles/2017-2(1)/finding-the-shortest-tree-in-the-network.pdf

Zhang WJ. 2018. Fundamentals of Network Biology. World Scientific Europe, London, UK. https://doi.org/10.1142/q0149

Zhang WJ. 2026a. Astaxanthin: Sources, biosynthesis, bioactivities, clinical applications, and future perspectives. Network Biology, 16(4): 515-524. http://www.iaees.org/publications/journals/nb/articles/2026-16(4)/3-Zhang-Abstract.asp

Zhang WJ. 2026b. Telomerase: Biochemistry, biological functions, molecular mechanisms, therapeutic frontiers, and perspectives. Network Biology, 16(4): 525-551.

http://www.iaees.org/publications/journals/nb/articles/2026-16(4)/4-Zhang-Abstract.asp

Zhang WJ. 2027a. Berberine in China: History, pharmacological research, clinical trials, industrialization application and market consumption. Network Pharmacology, 12(3-4): 9-14. http://www.iaees.org/publications/journals/np/articles/2027-12(3-4)/1-Zhang-Abstract.asp

Zhang WJ. 2027b. Curcumin: From molecules to markets. Ornamental and Medicinal Plants, 10(1-4): 1-5. http://www.iaees.org/publications/journals/omp/articles/2027-10(1-4)/1-Zhang-Abstract.asp

Zhang WJ. 2027c. Nicotinamide Adenine Dinucleotide (NAD+): Molecular mechanisms, clinical translation, and industrial application. Selforganizology, 14(3-4): 25-33. http://www.iaees.org/publications/journals/selforganizology/articles/2027-14(3-4)/1-Zhang-Abstract.asp

Zhang WJ. 2027d. Baicalein: Molecular mechanisms, pharmacological properties, clinical applications, and challenges. Network Biology, 17(1): 1-19. http://www.iaees.org/publications/journals/nb/articles/2027-17(1)/1-Zhang-Abstract.asp

Zhang WJ. 2028a. Matrine: Molecular mechanisms, pharmacological properties, pharmacokinetics, clinical applications, and challenges. Selforganizology, 15(1-2): 1-20. http://www.iaees.org/publications/journals/selforganizology/articles/2028-15(1-2)/1-Zhang-Abstract.asp

Zhang WJ. 2028b. Nattokinase: Biological activities, pharmacological mechanisms, therapeutic applications, challenges and perspetives. Network Pharmacology, 13(1-2): 1-26. http://www.iaees.org/publications/journals/np/articles/2028-13(1-2)/1-Zhang-Abstract.asp

Zhang WJ. 2028c. Salvianolic acids: Molecular mechanisms, pharmacological properties, pharmacokinetics, clinical applications, and future perspectives. Ornamental and Medicinal Plants, 11(1-4): 1-19. http://www.iaees.org/publications/journals/omp/articles/2028-11(1-4)/1-Zhang-Abstract.asp

Zheng ML, Liu YT, Zhang GF, Yang ZK, et al. 2023. The applications and mechanisms of superoxide dismutase in medicine, food, and cosmetics. Antioxidants, 12(9): 1675. https://www.mdpi.com/2076-3921/12/9/1675

Zhou JY, Prognon P. 2006. 2005. Raw material enzymatic activity determination: a specific case for validation and comparison of analytical methods—the example of superoxide dismutase (SOD). Journal of Pharmaceutical and Biomedical Analysis, 40(5): 1143-1148. https://www.sciencedirect.com/science/article/pii/S0731708505006448?via%3Dihub

Zhou WH, Zhang YL, Hosch MS, et al. 2001. Subcellular site of superoxide dismutase expression differentially controls AP-1 activity and injury in mouse liver following ischemia/reperfusion. Hepatology, 33(4): 902-914. https://www.sciencedirect.com/science/article/abs/pii/S027091390190120X

Zhu JH, Zhang XM, McClung JP, Lei XG. 2006. Impact of Cu, Zn-superoxide dismutase and Se-dependent glutathione peroxidase-1 knockouts on acetaminophen-induced cell death and related signaling in murine liver. Free Radical Biology and Medicine, 231(11): 1726-1732. https://pubmed.ncbi.nlm.nih.gov/17138759/

Zhu JW, Li XF, Huang MN, et al. 2024. Application of recombinant human superoxide dismutase in radical concurrent chemoradiotherapy for cervical cancer to prevent and treat radiation-induced acute rectal injury: a multicenter, randomized, open-label, prospective trial. International Journal of Radiation Oncology, Biology, Physics, 120(3): 720-729. https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S0360301624006114?returnurl=https:%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0360301624006114%3Fshowall%3Dtrue&referrer=

Zweier JL, Flaherty JT, Weisfeldt ML. 1987. Direct measurement of free radical generation following reperfusion of ischemic myocardium. Proceedings of the National Academy of Sciences of the United States of America, 84(5): 1404-1407. https://www.pnas.org/doi/abs/10.1073/pnas.84.5.1404