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Review

Superoxide Dismutase Inhibitors as Cancer Chemopreventive Agents: A New Survey

Mohammad Mahboubi-Rabbani[1*], Atefeh Jozian[1], Gita Faraji[1], Sana Khatami[1], Kiana Ravanshad[1], and Maryam Bayanati[2]

[1*] Department of Pharmaceutical Chemistry, School of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

[2] Department of Food Technology Research, National Nutrition, and Food Technology Research Institute/Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

Reactive oxygen species (ROS) are important factors to carcinogenesis, serving as both initiators and promoters of tumor growth. Superoxide dismutases (SODs), a kind of antioxidant enzyme, regulate ROS levels by converting superoxide anions into hydrogen peroxide. While SODs have generally served protective roles, current research has revealed a paradoxical involvement in cancer cell survival and resistance to treatment. This review presents a complete overview of current understanding about SOD inhibitors and their potential as cancer chemopreventive medicines, with a focus on processes, molecular targets, and treatment methods. Eighteen references are mentioned to lay a solid basis for future study in this promising field of cancer.

Keywords: Reactive Oxygen Species (ROS), Superoxide Dismutases, Protective Roles, Cancer Cell Survival, Cancer Chemopreventive

Introduction

Cancer remains a huge worldwide health burden, and chemoprevention - acting in the early stages of carcinogenesis - is a potential technique for lowering incidence and death [1]. Oxidative stress, induced by an imbalance of ROS and antioxidants, is strongly connected to DNA damage and

*Corresponding author email address: jrsoroush@gmail.com

cancer growth [2]. Superoxide dismutases (SODs) (Fig. 1), notably SOD1 (cytosolic), SOD2 (mitochondrial), and SOD3 (extracellular), play critical roles in ROS detoxification and redox regulation [3]. Cancer cells, on the other hand, frequently exploit these antioxidant defenses, allowing them to survive in the face of oxidative stress. This contradiction has generated interest in using particular inhibitors to target SODs as a chemopreventive strategy.

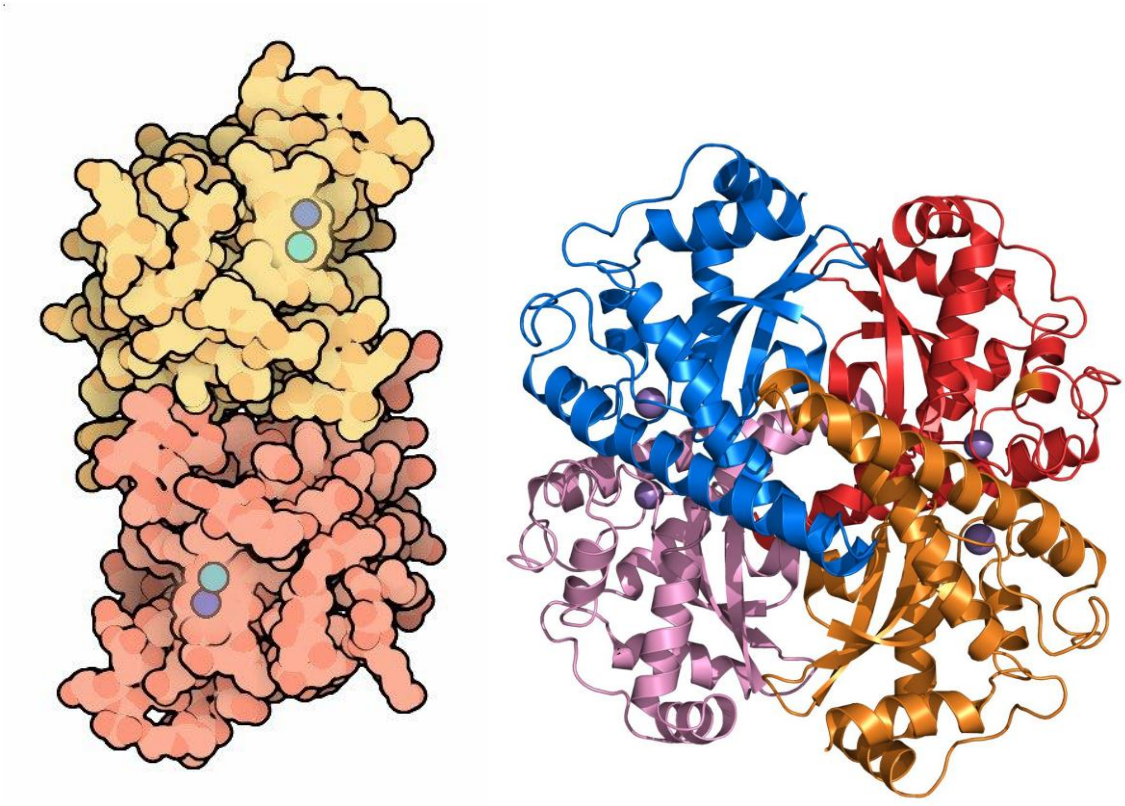

Figure 1. The three-dimensional structure of SOD as a metalloenzyme.

Recent findings in redox biology highlight the intricacy of ROS in cancer biology. While high ROS levels can cause cellular damage and death, moderate levels are required for cell signaling and proliferation [4]. Cancer cells take advantage of this dual nature, responding to high ROS environments by upregulating antioxidant systems such as SODs. This adaptation generates a vulnerability that can be therapeutically exploited by selectively suppressing SODs, so shifting the redox balance toward oxidative stress-induced cell death. The notion of targeting redox homeostasis brings up new possibilities for cancer chemoprevention, particularly in genetically predisposed or high-risk groups.

Superoxide Dismutases and Their Role in Cancer

SODs comprise metalloproteins that convert superoxide (O_2^-) into oxygen and hydrogen peroxide (H_2O_2) [5]. Each isoform has distinct roles. SOD1 (Cu/Zn-SOD) is mostly cytosolic and overexpressed in a variety of malignancies, including breast, colon, and pancreatic tumors [6]. SOD2 (Mn-SOD), found in the mitochondrial matrix, has a dual role in cancer, acting as a tumor suppressor in initial stages as well as a promoter in established tumors. Lastly, SOD3 (EC-SOD) is an extracellular enzyme that has received little attention in cancer research but has the potential to alter the tumor microenvironment and affect angiogenesis [7]. SOD expression has been shown to be elevated in a variety of cancers, which is associated with tumor aggressiveness and a bad prognosis. Inhibiting SOD activity may impair redox balance and specifically destroy tumor cells [8].

Mechanism of Action of SOD Inhibitors

SOD inhibitors elevate intracellular superoxide levels, resulting in oxidative DNA damage, lipid peroxidation, and mitochondrial malfunction [9]. This induces apoptosis via ROS-mediated signaling (p53, ASK1, and JNK pathways) [10]. Other implications include inhibition of proliferation owing to cell cycle arrest and poor DNA repair, as well as sensitivity to chemotherapeutics and radiation, both of which rely on oxidative stress for effectiveness [11].

SOD inhibitors have the potential to disrupt several physiological processes in addition to directly causing oxidative stress [12]. Elevated quantities of superoxide can inhibit protein phosphatases, disrupt calcium homeostasis, and impede mitochondrial respiration. These results cause an energy crisis and the activation of intrinsic apoptosis mechanisms. In cancers with p53 mutations, SOD inhibition can activate alternative apoptotic pathways such as endoplasmic reticulum stress and ferroptosis. Furthermore, elevated ROS can cause immunogenic cell death, which boosts anticancer immune responses. This demonstrates the possibility for combining SOD inhibitors and immunotherapies [13].

Major SOD Inhibitors with Chemopreventive Potential

ATN-224 (Choline Tetrathiomolybdate) (Fig. 2) is a potent SOD inhibitor. A copper chelator that indirectly inhibits SOD1 by reducing the copper cofactor. It has demonstrated antiangiogenic and

antiproliferative properties in preclinical and early clinical studies [14]. The other small-molecule inhibitor, LCS-1 (Fig. 2), exclusively targets SOD1, inducing ROS buildup and death in cancer cells. Effective in glioma, colorectal, and prostate cancer models [15].

Disulfiram (DSF) (Fig. 2) is the third drug that was originally used to treat alcoholism. DSF inhibits SOD1 and ALDH1, resulting in ROS-mediated apoptosis. Anticancer properties have been observed in breast and pancreatic malignancies [16]. 2-methoxyestradiol (2-ME) (Fig. 2) is another notable SOD1 inhibitor; this endogenous estrogen metabolite breaks microtubules and inhibits SOD2, resulting in mitochondrial ROS buildup [17].

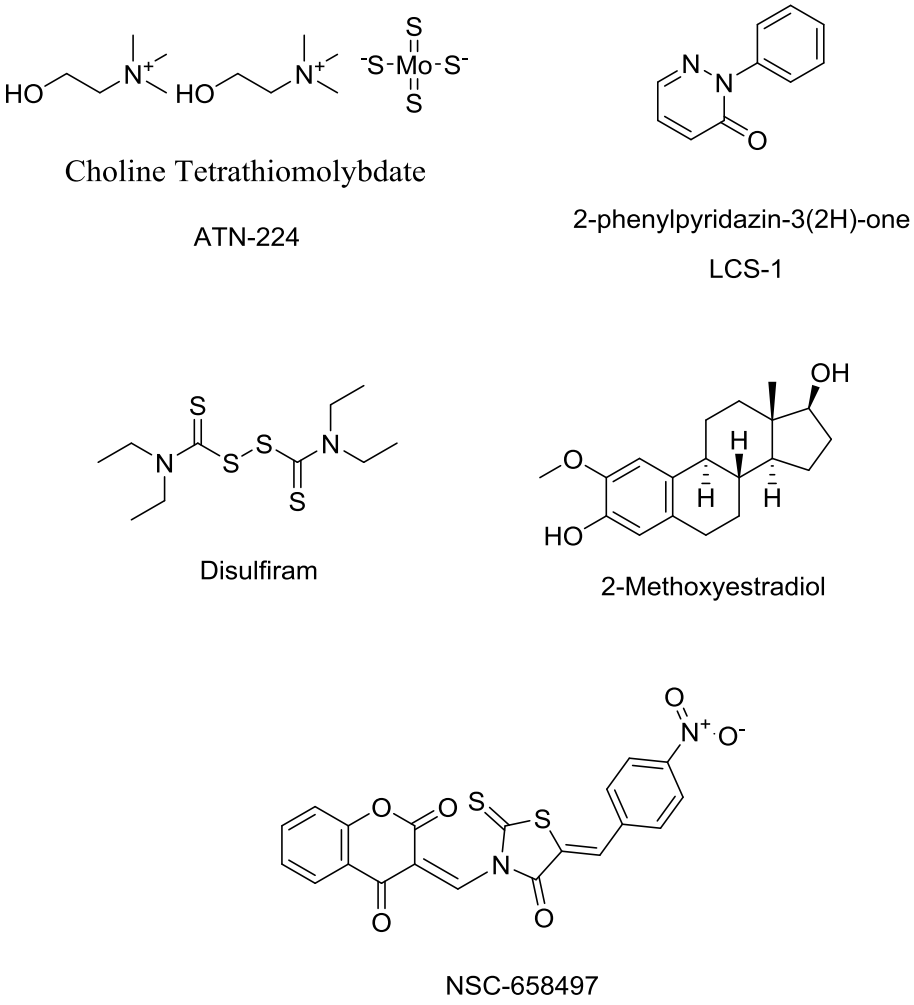

Figure 2. The chemical structures of the most prominent SOD inhibitors

Preclinical and Clinical Evidence

Multiple investigations have shown that SOD inhibitors reduce tumor start and development in vivo. For instance, in one research, ATN-224 (Fig. 2) decreased tumor burden along with angiogenesis in prostate and lung cancer xenograft models [18]. LCS-1 (Fig. 2) is another chemical that inhibits glioma development by raising superoxide levels and affecting mitochondrial function. Disulfiram in combination with copper improved survival in preclinical breast and liver cancer mice.

Furthermore to the above mentioned medicines, several investigational SOD inhibitors have shown effectiveness in leukemia, melanoma, and renal cancer models. The results obtained demonstrate the approach's broad applicability across a variety of tumor types. Furthermore, SOD inhibitors have showed potential in treating resistance to standard therapy [11]. In platinum-resistant ovarian cancer models, inhibiting SOD1 resensitized cells to cisplatin, indicating a role in chemoresistance. Despite these gains, clinical translation is still limited, highlighting the need for additional robust clinical studies.

Challenges and Limitations

Although SOD inhibitors offer potential, various issues must be addressed. The very first one is about specificity. Broad inhibition can kill normal cells, thus isoform-specific inhibitors are required. Toxicity is another big concern. Systemic ROS buildup may cause unintended consequences. Cancer cells may also upregulate alternative antioxidant systems (such as catalase and glutathione peroxidase). Biomarker identification is also required. Predictive indications for the response to SOD inhibition are few.

The difference in how normal and malignant tissues respond to redox disturbance is becoming a growing concern. Tissues with high basal antioxidant capacity, such as the liver and kidney, may be more susceptible to off-target effects. Thus, tailored delivery strategies (such as nanoparticles or prodrug formulations) are being investigated to enhance treatment indices. Furthermore, cancer heterogeneity indicates that not all tumors will rely similarly on SODs. Genomic and proteomic analysis may assist in determining which cancers are most likely to react to this method.

Future Directions

Investigation should prioritize the development of SOD isoform-selective inhibitors, combination treatments with ROS-inducing chemotherapeutics, and biomarker discoveries for patient stratification. Furthermore, clinical trials evaluating efficacy and safety in chemoprevention, particularly in high-risk groups, should be considered one of the next steps. Developments in nanotechnology and drug delivery are predicted to significantly improve the effectiveness and safety of SOD inhibitors. Nanoparticle-based carriers, for example, can allow inhibitors to be released specifically to tumors, reducing overall toxicity. Additionally, combining SOD inhibition with metabolic reprogramming techniques or DNA repair inhibitors may enhance anticancer effects. The creation of prognostic biomarkers, such as SOD expression levels or ROS signatures, will be critical for patient classification in therapeutic trials. Finally, a multidisciplinary strategy involving molecular biology, pharmacology, and bioengineering will be required to realize the full potential of SOD inhibitors in cancer chemoprevention.

Conclusion

Superoxide dismutase inhibitors have tremendous promise as cancer chemopreventive medicines because they exploit cancer cells' reliance on antioxidant defense systems. Preclinical data suggests their effectiveness in inhibiting carcinogenesis and improving therapy efficacy. Future research should focus on specificity, toxicity, and clinical application to realize their full therapeutic potential.

References

[1] Soerjomataram, I. & Bray, F. *Nature reviews Clinical oncology* **18**, 663 (2021).
[2] Klaunig, J. E., Kamendulis, L. M. & Hocevar, B. A. *Toxicologic pathology* **38**, 96 (2010).
[3] McCord, J. M. & Fridovich, I. *Free Radical Biology and Medicine* **5**, 363 (1988).
[4] Trachootham, D., Alexandre, J. & Huang, P. *Nature reviews Drug discovery* **8**, 579 (2009).
[5] Zelko, I. N., Mariani, T. J. & Folz, R. J. *Free radical biology and medicine* **33**, 337 (2002).
[6] Oberley, L. W. & Oberley, T. D. *Molecular and cellular biochemistry* **84**, 147 (1988).
[7] Venkataraman, S. *et al. Oncogene* **24**, 77 (2005).
[8] Fukai, T. & Ushio-Fukai, M. *Antioxidants & redox signaling* **15**, 1583 (2011).
[9] Wang, R. *et al. Aging (Albany NY)* **8**, 1184 (2016).

[10] Palit, S., Kar, S., Sharma, G. & Das, P. K. *Journal of cellular physiology* **230**, 1729 (2015).
[11] Liou, G.-Y. & Storz, P. *Free radical research* **44**, 479 (2010).
[12] Pelicano, H., Carney, D. & Huang, P. *Drug resistance updates* **7**, 97 (2004).
[13] Nogueira, V. & Hay, N. *Clinical Cancer Research* **19**, 4309 (2013).
[14] Brewer, G. J. *Experimental Biology and Medicine* **226**, 665 (2001).
[15] Somwar, R. *et al. Proceedings of the National Academy of Sciences* **108**, 16375 (2011).
[16] Liu, P. *et al. British journal of cancer* **109**, 1876 (2013).
[17] Mabjeesh, N. J. *et al. Cancer cell* **3**, 363 (2003).
[18] Li, J. *et al. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research* **25**, 2032 (2019).