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# An insight on superoxide dismutase (SOD) from plants for mammalian health enhancement

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ABSTRACT

Superoxide dismutase (SOD) is an antioxidant enzyme functional for physiological defense strategies in animals and plants against free radicals and reactive oxygen species (ROS) generated from biotic and abiotic stress. Supplementation of SOD from plants in mammalian diet is a new approach in terms of health improvement against pathological conditions. There is a research gap about the feasibility of including plant-derived SOD in animal diet as health enhancer due to poor bioavailability upon oral administration. Commercially available wheat gliadin encapsulated melon SOD has been proven to enhance mammalian health, but gluten/gliadin intolerance in certain animals and human may limit its marketability. Therefore, this review aims to highlight the sources of SOD from underutilized plants and potential encapsulation of SOD using soluble dietary fibers to be incorporated in animal diet as health enhancing supplements. This review provides a sustainable solution for the development of therapeutic approaches in agricultural industry.

## 1. Introduction

Free radicals and reactive oxygen species (ROS) are common terms related to pathophysiology of cancer, diabetes, hepatotoxicity, nephrotoxicity, osteoarthritis, and many other severe ailments (Holohan, Schaeybroeck, Longley, & Johnston, 2013). ROS such as singlet oxygen and free radicals are normally generated in the extracellular and intracellular environments during common metabolic processes and electron transfer reactions (Kumari, Badana, Murali, Shailender, & Malla, 2018; Liou & Storz, 2010). However, when the concentration of ROS has exceeded normal equilibrium, they will begin to steal electrons from the most vulnerable part of cell that happens to be the lipid membrane (Sies, 2017). A sudden increase in the concentration of ROS is a condition called oxidative stress. An example is when light reacts with photosensitizer in a particular cell in presence of oxygen, it initiates the formation of numerous ROS especially singlet oxygen. This stress triggers a chain reaction, which ultimately destroys the cell membrane structure along with other proteins and DNA, leading to cell death through apoptosis (Irshad & Chaudhuri, 2002; Mu & Liu, 2017). Therefore, ROS are similar to double-edged swords that can either regulate cell proliferation or lead to apoptosis (Michael & Navdeep, 2014). It is important to maintain a balance in the concentrations of intracellular and extracellular ROS. The amount of ROS produced and eliminated is controlled by several factors within the cellular environment. These factors are known as antioxidants and antioxidant enzymes. A normal molecule or compound becomes unstable once it loses an electron, which in turn finds for free electrons to become stable again (Gnanaraj, Shah, Tan, & Iqbal, 2017). Unlike normal molecules, antioxidants have the tendency to donate electrons without losing balance in their structure by forming a bond with each other (Hossain, Gnanaraj, Shah, & Iqbal, 2011). Natural antioxidants that are present in mammals include bilirubin, thiols like reduced glutathione (GSH), some classes of vitamins and minerals from dietary polyphenols, etc. (Gothai et al., 2018). Antioxidants in the cellular environment prevent ROS from stealing electrons from cellular structures. Hence, antioxidants are needed in an adequate concentration within the cells to maintain the balance of ROS concentration. Although antioxidants are helping in scavenging the overwhelming free radicals, the concentration of intracellular antioxidants will depreciate if the electron donating process continues as a forward reaction. Now comes the role of antioxidant

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enzymes as the regulator of antioxidants.

Antioxidant enzymes are cluster of proteins that are present in the cellular environment to facilitate and regulate antioxidants in scavenging the free radicals. The basic function of antioxidant enzymes is to ease the electron donating mechanism of antioxidants and to recycle the oxidized antioxidants back to its reduced form as in a reverse reaction (Lei et al., 2016). There are few antioxidant enzymes within the biological system and the common ones with important roles in scavenging free radicals are superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) (Krishnamurthy & Wadhwani, 2012). Collectively these three enzymes work together to defend cells against oxidative stress. CAT functions to convert hydrogen peroxide ($H_2O_2$) into water ($H_2O$) and oxygen ($O_2$) within the sub-organelle fragments of cells such as peroxisomes (Batinic-Haberle, Tovmasyan, & Spasojevic, 2015). GPx has a tendency to scavenge ROS, especially lipid peroxides and $H_2O_2$ by reducing them in a coupled reaction with oxidization of GSH (Çelik et al., 2011). CAT and GPx are commonly found in the cytoplasm and mitochondrial matrix of cells. SOD in the mitochondria of cells functions to eliminate superoxide anions by transforming them into $H_2O_2$ and $O_2$ (Holley, Dhar, & Clair, 2010). Superoxide ion ($O_2^{\cdot -}$), hydrogen peroxide ($H_2O_2$) and hydroxyl radicals ($^{\cdot}OH$) are the most common ROS for all organisms to cope with. SOD dismutates $O_2^{\cdot -}$ into $H_2O_2$ with the release of molecular oxygen·$H_2O_2$ is the only ROS that can diffuse through aquaporins in the membranes and is quite stable compared with other ROS. Low concentration of $H_2O_2$ signals biological processes to defend against different biotic and abiotic stress while high concentration of $H_2O_2$ induces programmed cell death. Both $O_2^{\cdot -}$ and $H_2O_2$ may be transformed into other more harmful reactive species through Haber-Weiss reaction that lead to cellular damage. Thus CAT and peroxidase have to act synergistically with SOD in removing to $O_2^{\cdot -}$ and $H_2O_2$ to prevent the adverse effect of ROS. SOD mostly encounters the initial stages of ROS in singlet oxygen form and free radicals that are expelled sequentially with the help of GPx and CAT. Fig. 1 shows the simple mechanism of superoxide anion scavenging by SOD, GPx, and CAT.

Farm animals are normally vulnerable to various diseases due to environmental stress, pollution, stress, and many other factors (Kumar, Kumar, Roy, Kushwaha, & Vaswani, 2014). To maintain the health of livestock and to prevent unwanted spreading of diseases, farm owners practice administration of antibiotics and other synthetic xenobiotic in the animal diet (Srivastava, Chauhan, & Pawar, 2016). This practice is not favored by many consumers and veterinarians since it could affect the quality of product produced by livestock, moreover it might induce unwanted health defects to humans who consume the livestock products (Kasapidou, Sossidou, & Mitlianga, 2015). Therefore, research to incorporate natural products or xenobiotic of natural origin with health and immune enhancing effects into livestock feed, has been intensified (Bakshi, 2016; Das, Huque, Amanullah, & Makkar, 2019). This is because natural products are normally safe for consumption, with minimal or no side effects when consumed in moderate recommended concentrations. In this review, the importance and presence of SOD in under-utilized plants will be discussed to emphasize the pharmacological potential of plant SOD as an animal feed supplement.

## 2. Physiological properties and nature of SOD

SOD has been characterized to convert oxygen free radicals, produced by xanthine oxidase, into oxygen and hydrogen peroxide. SOD is regarded as the main intracellular antioxidant defense against free radicals (Miller, 2013). The first studied SOD was originated from bovine erythrocytes (Miller, 2011). Subunits of SOD comprise of two-domain structure, where one domain consists of α-helices and the other domain contains α-helices and β-sheets (Perry, Shin, Getzoff, & Tainer, 2010). Until date, researchers have found a few forms of SOD, which are metal-containing oligomeric proteins with cofactors like iron, manganese, or copper and zinc (Harris, Auffret, Northrop, & Walker, 2005). These cofactors are required by SOD to perform a maximized catalytic activity in metabolizing toxic intermediates. The metal binding site locates between the two domains of SOD and the side chains comprise aspartate, histamine and histidine (Miller, Yikilmaz, & Vathyam, 2010; Perry et al., 2010). These cofactors tend to donate electron to ROS and regenerate throughout the catalytic mechanism as shown in Fig. 2. Three major isoforms of SOD found in all mammalian cells are copper-zinc SOD (Cu/Zn-SOD) homodimer isoform that is present in nucleus, cytoplasm, plasma, and inter-membrane space of mitochondria; manganese SOD (Mn-SOD) homotetramer isoform which is predominantly found in the matrix and inner membrane of mitochondria; and Cu/Zn SOD (EC-SOD) tetrameric glycoprotein isoform which is localized in the extracellular environment (Holley, Bakthavatchalu, Velez-Roman, & Clair, 2011; Miller, 2011). SOD isoforms present in bacteria are iron

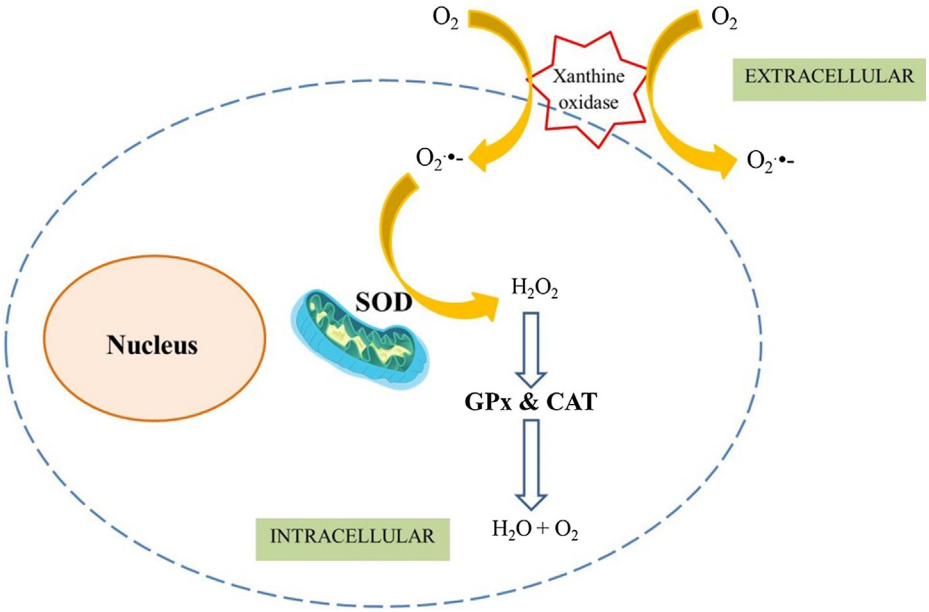


**Fig. 1.** Simple representation of molecular $O_2$ conversion into superoxide anions and cascade effects of intracellular antioxidant enzymes to scavenge the superoxide anion. Adapted from Krishnamurthy and Wadhwani (2012).

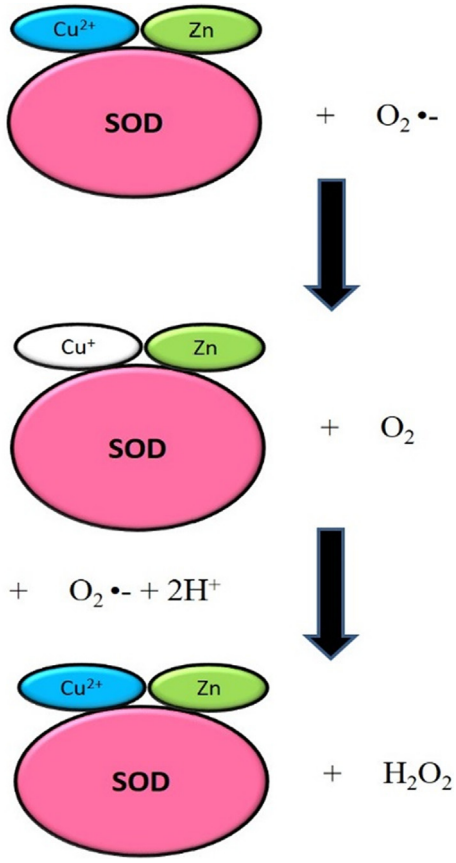


**Fig. 2.** The general catalytic mechanism for dismutation of $O_2$ by Cu/Zn-SOD. Adapted from Perry et al. (2010).

SOD (Fe-SOD) or Mn-SOD (Nishiyama, Fukamizo, Yoneda, & Araki, 2017). Three isoforms of SOD are found in plants, which are chloroplastic and cytosolic Cu/Zn-SOD isoform; chloroplastic Fe-SOD isoform; and Mn-SOD isoform found in the mitochondria (Jamdhade, Sunkar, & Hivrale, 2017; Pilon, Ravet, & Tapken, 2011). SOD scavenges oxygen free radicals through an oxidation/reduction cycle by the transition metal ion present at its active site at an extremely high rate of reaction (Bafana, Dutt, Kumar, Kumar, & Ahuja, 2011). All isoforms of SOD binds only single charged anions like fluoride and azide. Yet, there are discrete variations among affinities of the three isoforms, for instance, Cu/Zn-SOD is competitively inhibited by anions like $F^-$, $CN^-$, and $N_3^-$. Mn-SOD isoform contains one manganese atom per subunit, where the two step dismutation of superoxide anions cycles Mn (III) to Mn (II) and back to Mn (III) (Harris et al., 2005). Since Mn-SOD is mitochondria-based, oxygen radicals are largely supplied from the respiratory chain reactions. Mn-SOD isoform is characterized to be mildly influenced by oxidants but mostly regulated by cytokines (Holley et al., 2011). Mn-SOD isoform is considered to be essential for life as observed through several experiments conducted on knockout mice models and bacteria (Bafana et al., 2011; Sarsour, Kalen, & Goswami, 2014). On the other hand, Cu/Zn-SOD isoform, which has a major role in the first line antioxidant defense, was found to be non-essential for life in the same knockout mice experiment (Bafana et al., 2011). However, other researchers emphasized the importance of Cu/Zn-SOD by stating that deficiency of Cu/Zn-SOD isoform causes overwhelming oxidative stress which leads to carcinogenesis (Elchuri et al., 2004; Olofsson, Marklund, & Behndig, 2009). Extracellular EC-SOD isoform has high susceptibility for several glycosaminoglycans including heparin and heparan sulphate, thus preventing cellular injuries and inflammation caused by ROS. EC-SOD isoforms are largely found in extracellular fluids and tissue interstitial spaces (Kim et al., 2005). Similar to Mn-SOD isoform, this SOD isoform is also mainly regulated by cytokines rather than oxidants or its response to substrates. The Fe-SOD isoform found in plants and bacteria is classified as a chelator due to the presence of multiple atom donor groups for attaching a metal ion (Jamdhade et al., 2017). In specific, Fe-SOD is a tetradentate protein with three histidines and one aspartic acid donor groups which stabilizes the iron ion bound to the active site of the enzyme (Pilon et al., 2011). The dismutation of superoxide anions at the active site of Fe-SOD isoform cycles Fe (III) to Fe (II) and back to Fe (III). The Fe-SOD isoform from plants may contribute as a potential free radical scavenging mediator due to its ability to withhold multiple atom donors. Yet, exogenous Fe-SOD in excess could overturn the balance of life essential endogenous Mn-SOD which becomes a life threating event (Miller, 2013)

## 3. Presence of SOD in plants

Superoxide dismutase plays a major role in defense against oxygen radical-mediated toxicity in aerobic organisms. In plants, environmental adversity such as drought, high or low temperature, flood, presence of heavy metal and macronutrient deficit often leads to the increased generation of reduced oxygen species and, consequently, SOD is suggested to play an important role in plant stress tolerance (Bela, Bangash, Riyazuddin, & Csiszár, 2017). The superoxide radical, $O_2^-$ is unstable, hence it often dismutes spontaneously and is susceptible to be degraded by transition metal ions that may be present in the reaction medium. Methods so far used to measure SOD activity in plant materials are the xanthine/xanthine oxidase (X–XOD), the NitroBlue Tetrozolium/Riboflavin (NBT/RF) and the pyrogallol autooxidation method (Janknegt, Rijstenbil, van de Poll, Gechev, & Buma, 2007; Li, 2012). A unit of enzyme activity is generally defined as the amount of enzyme that inhibits the reaction of $O_2^-$ with an indicator by 50%. These are indirect methods involve the inhibition by SOD on a product resulting from the reaction between an indicator and $O_2^-$. The $O_2^-$ is produced enzymatically or non-enzymatically during the autoxidation of a compound. It acts as the chain-propagating species and the end product is usually measurable spectroscopically (Bannister & Rotillio, 1987). Research on plant superoxide dismutase mainly focused on how the antioxidant enzyme alone (Lima et al., 2018; Tewari, Kumar, Tewari, Srivastava, & Sharma, 2004; Yordanova, Christov, & Popova, 2004) or in combination with other plant indigenous parameters (Dias, Ponte, & Santos, 2019; Ju, Yue, Zhao, Zhao, & Fang, 2018; Li et al., 2018; Lin et al., 2013; Meloni, Oliva, Martinez, & Cambraia, 2003; Rady, Semida, Abd El-Mageed, Hemida, & Rady, 2018; Rajan & Pushpa, 2015; Yi et al., 2016) were affected by environmental stress or by genotype (Gupta, Webb, Holaday, & Allen, 1993; Huseynov, Aliyev, & Aliyev, 2014; Sales et al., 2013; Singh, Sharma, & Singh, 2010)

Higher plants have several SOD isoforms, among the isoforms, Cu/Zn-SOD isoforms are widely distributed whereas the occurrence of Fe-SODs is probably limited to the chloroplasts (Pilon, Ravet, & Tapken, 2011). Ascorbate peroxidase (APX) activity and the Fe-SOD and Cu/Zn-SOD isoforms work efficiently in scavenging ROS, specifically in drought tolerant genotype of sugarcane (Sales et al., 2013). Durum wheat plants contain three types of isoforms of superoxide dismutase: Mn-, Fe- and Cu/Zn-containing SOD(Huseynov et al., 2014); SOD activity was stimulated in the drought tolerant genotype Barakatli-95, during the wax ripeness and milk ripeness phases. For maize plant, deficiency of each of the macronutrients (N, P, K, Ca, Mg or S) enhanced SOD activity and also showed new SOD isoforms, i.e. the plants subjected to the deficiencies of P and Mg exhibited a maximum of nine (three new) SOD isoforms out of a maximum of 10 isoforms of SOD in maize (Tewari et al., 2004). The enhancement in the activity of chloroplastidial Fe-SOD in coordination with peroxidase (to scavenge $H_2O_2$) was important for plant protection when photochemistry and $CO_2$ assimilation are severely reduced. Elevated SOD activity, without an accompanying increase in the ability to scavenge $H_2O_2$ (with increase in peroxidase) can result in enhanced cytotoxicity by the even more

**Table 1**
List of plants reported with presence of SOD.

| Plant leaves | Type of quantitative SOD assay | SOD activity | Findings | References |
|---|---|---|---|---|
| Barley plants (*Hordeum vulgare cv. Alfa*) | NBT-RF | Chloroplastic SOD: 5–15 EU/mg protein<br>Cytosolic SOD: 35–40 EU/mg protein | Fe-SOD activity lowered by about 55%, after 120 h of flooding treatment. | Yordanova et al. (2004) |
| Bitter melon (*Momordicacharantia* L.), sponge gourd (*Luffa cylindrical*), winter squash (*Cucurbitamoschata* L.) | SOD assay kit (based on X-XOD) | 84.3–99.4 μmol/g FW (Bitter melon)<br>86.8–203.1 μmol/g FW (Winter squash) | SOD activity in leaves of winter squash plants increased significantly while those of bitter melon plants remained low throughout the entire chilling duration while. | Lin et al. (2013) |
| Black plum (*Syzygium cumini*) and Bitter gourd (*Momordica charantia*) | NBT-RF | 90–160 U/g | Maximum activity of SOD was shown by the methanolic leaf extract of the *Momordica charantia* and leaf extract of *Syzygium cumini* (not stated environmental stress imposed). | Rajan and Pushpa (2015) |
| Cabbage (*Brassica oleracea* var. *capitata* L.) | NBT-RF | 4.86–7.63 U/min/g FW | SOD of purple leaf genotypes (Kinner Red, Red Rock Mammoth and Red Cabbage) showed higher activity than those of the green leaf genotypes.<br>SOD of the savoy type genotypes, i.e. bumpy leaf surface (PusaMukta, C-4, C-2, C-6, C-8 and C-3) expressed lower activity. | Singh et al. (2010) |
| Cashew plant (*Anacardium occidentale* L.) leaves | NBT-RF | 2–3 U/mg protein/ min | SOD showed a strong increase in water deficit-plants which were exposed to low and high light intensity (200–2000 μmol $m^{-2}$ $s^{-2}$). | Lima et al. (2018) |
| Cotton plant (*Gossypium herbaceum* L.) | NBT-RF | 25–30 U/mg protein | SOD showed an increase in activity, together with other antioxidative enzymes such as, ascorbate peroxidase (APX) and peroxidase (POD) in water deficit plants. | Yi et al. (2016) |
| Cotton plant, Pora and Guazuncho cultivar (hybrids between *G. hirsutum* × *G. Arboretum* × *G. raimondii*) | NBT-RF | 1.2–2.7 U/mg protein | SOD significantly increase in Pora (salt-tolerant cultivar) but not in Guazuncho after an exposure to salinity stress of 21 days. | Meloni et al. (2003) |
| Durum wheat : stress tolerant (Barakatli-95) and sensitive (Garagylchyg-2) varieties | SOD assay kit (based on X-XOD) | 0.5–10 U/mg protein | SOD activity exhibited the highest level in the beginning of drought, it decreased at the end of the flowering in both tolerant (Barakatli-95) and sensitive (Garagylchyg-2) varieties. | Huseynov et al. (2014) |
| Grapevine (*Vitis vinifera* L.) leaves | NBT-RF | 304.47–553.53 U/mg protein | SOD activity increased after drought stress and reached the highest level at day 10. | Ju et al. (2018) |
| Maize plant (*Zea mays* L. cv. GSF-2) leaves | NBT-RF | 7.92–32.2 U/mg protein | SOD activity was significantly enhanced due to deficient supplies of all macronutrients (N, P, K, Ca, Mg or S). | Tewari et al. (2004) |
| Onion plants (*Allium cepa* L. variety Giza 20) | NBT-RF | 0.13–0.27 μmol/mg protein | SOD activity increased significantly under saline soil conditions and exogenous 50 mM glycine betaine, (GB) treatment. | Rady et al. (2018) |
| Pea (*Pisum sativum*) plants | NBT-RF | 100–300 μmol/min/mg FW | SOD activity was lower in leaves exhibited lower Pb accumulation, oxidative damages and changes in phytohormone pools. | Dias et al. (2019) |
| Sugarcane plant (*Saccharum* spp.) plants cv. IACSP94-2094, a drought resistant genotype and IACSP97-7065, a drought-sensitive genotype) | NBT-RF | cv. IACSP94-2094: 25–44 U/min/g FW<br>IACSP97-7065: 5–15 U/min/g FW | The chloroplastidial Fe-SOD increased significantly in both genotypes, cv. IACSP94-2094 and IACSP97-7065 under combined stressors (drought and low temperature) compared to drought alone. | Sales et al. (2013) |
| Tartary buckwheat (*Fagopyrum tataricum*) leaves | NBT-RF | 12.7 U/mg protein | SOD extracted from buckwheat leaves is a Cu/Zn-SOD with a molecular weight of 31000, a homodimer. | Wang et al. (1993) |
| Tea plant (*Camellia sinensis* (L.) O. Kuntze) | SOD assay kit (based on X-XOD) | 170–220 U/g, FW | SOD activity was stimulated in tea leaves under cold stress, thus improving the plant's cold resistance through the exogenous application of melatonin. | Li (2012) |
| Transgenic tobacco plants *(Nicotiana tabacum)* | NBT-RF | 25.7–127 U/mg protein | The increase in SOD activity in plant underwent photosynthesis at 3 °C led to the enhancement of the active oxygen-scavenging system and increased oxidative stress protection in SOD + plants | Gupta et al. (1993) |

FW: Fresh weight; NBT-RF: NitroBlue Tetrozolium/Riboflavin; X-XOD: xanthine/xanthine oxidase; GR: glutadione reductase; APX: ascorbate peroxidase; POD: peroxidase; CAT: catalase SOD+: plant that express a chimeric gene that encodes chloroplast-localized Cu/Zn-SOD

destructive hydroxyl radical generated from $H_2O_2$ in a metal-catalyzed Haber–Weiss reaction (Yordanova et al., 2004). Thus, peroxidase activity increased with an increase in SOD activity to cope with oxidative stress as observed in cotton plant(Meloni et al., 2003; Yi et al., 2016), onion plant(Rady et al., 2018), tea leaves(Li et al., 2018), and tobacco leaves (Gupta et al., 1993)

Meanwhile research on purification and characterization of the enzyme has led to a patented preparation of a heat stable plant-based SOD (WO04A217134A2). Commercial available melon SOD is stabilized with gliadin. There are other plant SOD that may be developed into feed supplement or nutraceuticals, dependent on its stability and abundance. Table 1 lists SOD activities originated from the leaves of different plant. Though some plant leaves such as sugarcane (5–44 U/min/g fresh weight) and durum wheat (0.5–10 U/mg protein) exhibited relatively low SOD activity, further purification steps such as ammonium sulfate precipitation and anion exchange chromatography could definitely increase the activity more than 100 fold, like in the case of buckwheat leaves (Wang, Lin, Zhang, & Zhou, 1993). Another possible way to increase the SOD in plant leaves would be applying environmental stress such as salinity, water deficit and low temperature on selected stress tolerant genotype such as the examples of cotton plant and sugarcane plant (Meloni et al., 2003; Río, Corpas, López-Huertas, & Palma, 2018; Sales et al., 2013; Szollosi, 2014). Further research is warranted to investigate whether the leaves of industrial food crop could be converted to a source of superoxide dismutase for higher value applications.

## 4. Pharmacological benefits in supplementation of SOD in mammals

Past researchers have targeted the use of SOD against various ailments. The initial approach on SOD involving humans was performed in the early 1980s on fibrosis and in the 1990s bovine SOD was supplemented to evaluate its effects on AIDS (Carillon, Rouanet, Cristol, & Brion, 2013). The clinical approach on bovine SOD supplementation was indeed promising against a number of pathological conditions. A major epidemic hurdle, the Creutzfeldt-Jakob disease around 1985 caused the retrieval of bovine SOD from the market (Jones et al., 2005). The fatal degenerative brain disorder spread from cows and caused the clinically promising bovine SOD to be retracted from clinical research. Learning their therapeutic potential, alternative sources of exogenous SOD, extracted from plants or grown in bacteria were tested against animal and human ailments (Cristiana, Elena, & Nina, 2014; Oleary, Bellizzi, Domann, & Mezhir, 2013). For a better understanding of the mechanism and effects of SOD in mammalian models, over-expression of SOD and mimetic SOD models were also studied (Borgstahl & Oberley-Deegan, 2018; Cho et al., 2008). SOD has been linked with cellular structure protection and DNA damage prevention at vulnerable conditions. Cell culture and animal model studies have provided evidence that external SOD supplement could prevent cellular apoptosis against chemically-induced cell lysis (Che, Wang, Li, Wang, & Zheng, 2016; Fukai & Ushio-Fukai, 2011; Hitchler, Oberley, & Domann, 2008; Hour et al., 2010; Murley, Kataoka, & Grdina, 2012). Performing horses that were orally administered with melon SOD showed high resistance in blood hemolysis (Carillon et al., 2013). Another study on cats under hemorrhagic shock treated with bovine Cu/Zn-SOD showed significant hepatocellular protection via prevention of lipid membrane damage (Naso, Dias, Porawski, & Marroni, 2011). Various routes of SOD administration such as oral, intravenous, intradermal, intraperitoneal, etc. have been studied against multiple pathological conditions in human and animal models and mostly positive results were obtained. Supplementation of exogenous SOD has been reported to boost the antioxidant defense of host (Manolov et al., 2017). Plant-derived SOD was administered as dietary intake to animal and human models under oxidative stress, resulting in an enhanced antioxidant circulation and reduced oxidative stress (Buettner, 2011). The study of human Mn-SOD on irradiated mice model demonstrated a resistance to radiation and its side effect in the mice model. Intravenous injection of human Mn-SOD in irradiated mice model increased the survival rate of mice compared to irradiated control mice (Shinde, Fairman, Epperly, Dixon, & Greenberger, 2014). Various routes of administration of different SOD isoforms showed protective effects on the pathophysiology of multiple organs in pre and post-irradiated rodent models. Development of fibrosis is the side effect due to radiation, and oral administration of SOD resulted in prevention of post-radiation fibrosis formation and reduction of pro-fibrotic markers (Robbins & Zhao, 2011). Sub-cutaneous and intramuscular injection of SODs in irradiated animal models has resulted in prevention of collagen deposition and curative effect on post-radiation fibrotic areas (Rabbani, Jackson, Zhang, Xu, & Vujaskovic, 2010). Similarly, topical application of tomato-derived Cu/Zn-SOD was proven effective in a clinical study on fibrotic areas in humans undergoing radiotherapy.Teoh-Fitzgerald & Domann, 2012

Administration of SOD has attenuated inflammatory effects in animal models especially in paw swelling of rodents and other inflammatory diseases. Inflammation of joints, similar to rheumatic and polyarthritic diseases was alleviated by SOD in human and animal models signifying its role in anti-inflammatory reactions (Hart et al., 2015; Romao, 2015; Skarpanska-Stejnborn et al., 2011). Moreover, administration of different isoforms of SOD was able to overcome ischemia in intestine and paw of animal models. Oral administration of recombinant Mn-SOD and subcutaneous injection of Cu/Zn-SOD were able to prevent inflammation in the colon of colitis-induced animals (Pan, Qin, Liu, Li, & Zhang, 2016; Segui et al., 2004). Several in-vitro and in-vivo models of inflammation-induced tumors have suggested that exogenous SOD supplementation were able to prevent the tumor formations. These studies have suggested that SOD has anti-cancer abilities through prevention of oxidative stress (Connor et al., 2007; Dhar, Tangpong, Chaiswing, Oberley, & Clair, 2011; Doñate et al., 2008; Elchuri, Naeemuddin, Sharpe, Robinson, & Huang, 2007). Administration of SOD in liposome has demonstrated cancer preventive effects in animal models. Treatment with Cu/Zn-SOD had promising therapeutic effects on multiple myeloma (Elchuri et al., 2007; Hodge et al., 2005). Early clinical trials using SOD were proven safe on cancer treatment especially as a dietary supplement that enhances the antioxidant effect in-vivo (Ganapathy et al., 2011; Sibenaller et al., 2014; Wilkes, Alexander, & Cullen, 2017). Oxidative stress related conditions such as liver damage, atherosclerosis, brain ischemia-reperfusion, neurodegenerative disorders, and diabetes in animal models were all reported to have been treated by exogenous SOD administration. Oral supplementation of melon SOD has attenuated obesity-induced steatohepatitis and aortic lipid deposition in animal models (Carillon et al., 2013; Wang, Jia, Zheng, Liu, & Zong, 2019). Intravenous injection of Cu/Zn-SOD has reversed the allergic asthma in rabbit model and prevented pulmonary emphysema in mice model (Assa'ad et al., 1998). SOD administration had decreased the manifestation of respiratory disease in several studies (Fu et al., 2011; Hernandez-Saavedra, Swain, Tuder, Petersen, & Nozik-Grayck, 2017; Tanaka, Azuma, Miyazaki, Sato, & Mizushima, 2012). Male fertility is assumed could be improved upon administration of SOD as described in an in-vitro study using stallion semen samples, which showed the integrity and mobility of the semen cells, were improved after addition of SOD (Negri et al., 2017). Supplementation of SOD has also given promising results on infectious diseases by improving the immune response. Oral administration of melon SOD was able to restore the levels of CD4 + /CD8 + ratio in FIV-infected cats (Romao, 2015; Webb, Lehman, & Mccord, 2008). An in-vitro study has shown that bovine Cu/Zn-SOD significantly inhibited HIV replication and protective effects on DNA of the human host cell (Lartigue et al., 2015). A list of effective exogenous SOD supplementation against various diseases is given in Table 2. Understanding the pharmacological and therapeutic abilities of exogenous SOD supplementation, a new approach on the administration of SOD is needed be optimized for mammalian consumption.

**Table 2**
Proven therapeutic effects of exogenous SOD administration in several studies.

| Evaluated conditions | Route of SOD administration | SOD Formulation | References |
|---|---|---|---|
| Inflammatory diseases | Oral administration | Liposome encapsulation | Regnault et al. (1995) |
| | Intraarticular injection | Pure drug (orgotein) | Lin et al. (1994) |
| | Subcutaneous injection | Pure drug (ontosein) | Segui et al. (2004) |
| | Oral administration | Bacterial source | Watterlot et al. (2010) |
| | Intravenous injection | Polyethylene glycol encapsulation | Stone et al. (1992) |
| | Intraperitoneal injection | Purified from erythrocytes, liposome encapsulation | Jadot and Michelson (1986) and Vaille et al. (1990) |
| | Oral supplementation | GliSODin® | Cloarec et al. (2007) |
| Cancer prevention | cDNA transfection | Plasmid recombination (mimetic) | Zhang et al. (2002) |
| | Adenoviral transduction | Adenoviral vector (mimetic) | Weydert et al. (2006) |
| | Dietary supplement | Plant mixture (Protandim) | Robbins et al. (2010) |
| | Transgenic recombination | Vector (mimetic) | Kim et al. (2011) |
| | Oral supplementation | Liposome encapsulation | Tarhini et al. (2011) |
| | Oral administration | Oxykine-Gliadin biopolymer | Okada et al. (2006) |
| | Intravenous injection | Lecithinized | Suzuki et al. (2008) |
| Type 2 diabetes | Oral administration | Oxykine-Gliadin biopolymer | Naito et al. (2004) |
| | Oral administration | GliSODin® | Trea et al. (2013) |
| Respiratory diseases | Aerosol inhalation | Mimetic | Simonson et al. (1997) and Welty-Wolf et al. (1997) |
| | Intravenous injection | Polyethylene glycol encapsulation | Assa'ad et al. (1998) |
| | Intravenous injection | Lecithinized | Tanaka et al. (2011) |
| | Aerosol inhalation | Lecithinized | Tanaka et al. (2012) |
| Cardiovascular diseases | Oral administration | Melon-Gliadin biopolymer | Kick et al. (2007) |
| | Oral supplementation | Melon juice (Extramel®) | Décordé et al. (2010) |
| | Injection (catheter) | Liposome encapsulation | Laursen et al. (1997) |
| | Intravenous injection | Yeast lysate (purified) | Nakazono et al. (1991) |

## 5. Recommendation on potential approach for oral administration of SOD

Many past researchers have described the routes of administration for SOD in pharmacological studies. Animal models involving pathological diseases were mostly treated with intravenous, subcutaneous, intramuscular, and intraperitoneal (i.p.) injections of SOD (Cloarec et al., 2007; Décordé et al., 2010; Jadot & Michelson, 1986; Kick et al., 2007; Kim et al., 2011; Laursen et al., 1997; Lin, Pape, & Friedrich, 1994; Naito et al., 2004; Nakazono et al., 1991; Okada et al., 2006; Regnault et al., 1995; Robbins et al., 2010; Simonson et al., 1997; Stone, Bjorling, Southard, Galbreath, & Lindsay, 1992; Suzuki, Matsumoto, Okamoto, & Hibi, 2008; Tanaka et al., 2011; Tarhini et al., 2011; Trea, Ouali, Baba-Ahmed, & Kadi, 2013; Vaille, Jadot, & Elizagaray, 1990; Vouldoukis et al., 2004; Watterlot et al., 2010; Welsh et al., 2012; Welty-Wolf et al., 1997; Weydert et al., 2006; Zhang, Zhao, Zhang, Domann, & Oberley, 2002). Several researchers have supplied SOD directly at the site of infection, for instance plant Cu/Zn-SOD was applied as ointment against skin fibrosis in breast irradiated women to evaluate the anti-fibrotic properties of SOD (Houghton, Steels, Fassett, & Coombes, 2011; Teoh-Fitzgerald & Domann, 2012). Researchers have also administered aerosolized SOD for the evaluation of respiratory diseases in animal models. The remaining studies were all performed as oral administration of SOD, either by including it in the diet or force-feeding. However, the various routes of SOD administration have limited access into the affected body parts of the model host (Abdelrauf, Rahman, Abdel-Maksoud, Farag, & Hashad, 2017; Kang, Sullivan, & Pollock, 2018; Zhang, Qin, & Guo, 2014). This is because exogenous SOD is a high molecular weight protein that could not be easily transported into cells at normal metabolic functions. The concentration of exogenous SOD reaching the blood circulation and plasma depends on the route of administration (Borgstahl & Oberley-Deegan, 2018; Carillon et al., 2013). Studies have shown that the enzymes that were administered through injection will be accumulated in the kidneys to be excreted after circulating the body (Fukai & Ushio-Fukai, 2011). The amount of SODs administered is not guaranteed to reach the target organ in the desired concentration. Looking at the research studies that have proven the therapeutic effectiveness of SOD in various routes of administration, the circulation of SOD to target organs is believed to be valid although there is no evidence to proof the cellular uptake of exogenous SOD. Oral administration of a drug is assumed to be effective for most therapeutic events since the intestinal absorption of the active constituents will circulate all over the body, especially to the relevant organs that are in need. However, the oral administration of SOD has been proven non-effective in animal and human models due to the diminished bioavailability of free SODs (Bannister & Rotillio, 1987). The enzymes are digested and denatured by the stomach gastric upon administration, which hinders the SODs from migrating into the intestinal barriers. In order to increase the bioavailability of orally administered SOD, several researchers have incorporated encapsulation techniques to protect the physical structure of SOD until it reaches the target organ (Cloarec et al., 2007; Romao, 2015). Examples of early encapsulation method of SOD include cationic liposomes as carriers of Cu/Zn-SOD, which was proven to possess improved antioxidant effects with increased half-life upon reaching the site of inflammation compared to free SODs, in an experimental colitis model (Jadot & Michelson, 1986). Another prominent encapsulation technique is the wheat-gliadin biopolymer encapsulated SOD, a widely studied technique that is proven to be effective against several chronic ailments. Oral administration of wheat-gliadin encapsulated melon SOD has remarkably reduced oxidative stress and prevented severe ailments including Type 2 diabetes, ischemia–reperfusion injury, tumor formation, atherosclerosis, Alzheimer's, viral infections, and inflammation in animal and human models (Carillon, Rouanet, Cristol, & Brion, 2013; Kick et al., 2007; Romao, 2015). Effectiveness of oral gliadin biopolymer-SOD administration against several health conditions was credible to the bioadhesive properties of gliadin, which enhances the delivery of SOD at target sites across intestinal barriers, and its ability to entrap and protect the physical structure of SOD during digestion in the stomach (Cloarec et al., 2007; Houghton et al., 2011; Naito et al., 2004; Vouldoukis et al., 2004). The promising effect of gliadin-SOD in multiple diseases led to the formulation of clinically proven commercialized health supplement, GliSODin (Menvielle-Bourg, 2005). Certain humans and animals with gluten/gliadin intolerance tend to develop allergic reactions or chronic intestinal inflammation known as Celiac disease, are unable to consume the gliadin-based commercial product (Ferretti, Bacchetti, Masciangelo,

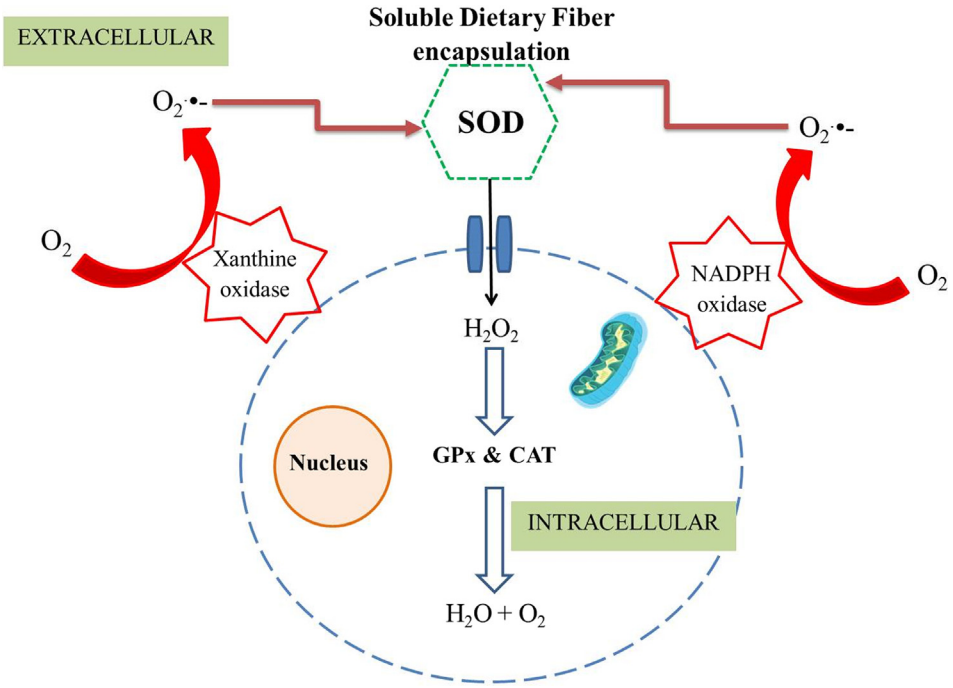


**Fig. 3.** Proposed mechanism of action of dietary fiber encapsulated SOD in the extracellular environment. Xanthine oxidase and NADPH oxidase enzymes will consistently produce superoxide anions in the extracellular and intracellular environments. Superoxide anions at the extracellular environment are assumed to be attracted by the antioxidant properties of dietary fiber. The superoxide anions will be converted into $H_2O_2$ by the encapsulated SOD and transported across cellular membrane to be transformed into $H_2O$ and $O_2$. Adapted from Krishnamurthy and Wadhwani (2012).

& Saturni, 2012). Therefore, other encapsulation methods of SOD are being studied to develop a healthy nutritional supplement without side effects. Hence, the most reliable sources of plants such as gum-Arabic, shellac, vegetable oils, and so on are experimented to encapsulate SOD to preserve its therapeutic effect (Carillon et al., 2013). There is a clinically proven commercial livestock feed supplement of melon SOD encapsulated with shellac gum under brand name SOD B® (Lemaire, Le Quere, Simoneau, & Lacan, 2016)

A potential new approach in encapsulating SOD is using naturally occurring dietary fibers from plants. Dietary fibers are indigestible parts of plants that could easily entrap phenolic and other phytochemical compounds (Das, Huque, Amanullah, Dharmapuri, & Makkar, 2018; Mahima et al., 2013). In a review on the efficiency of dietary fiber added phenolic compounds, the author has suggested that passing the dietary fiber added phenolic compound through digestive tract could proof the ability dietary fibers in protecting the physiochemical structure of antioxidants (Sauceda et al., 2014; Saura-Calixto, 2011). From our previous study, underutilized agromass such as capsicum seed, cabbage outer leaves contained high levels of antioxidant fiber and considerable prebiotic activity (Liang, Yeow, Teo, Gnanaraj, & Chang, 2019). Prebiotics are oligosaccharides or polysaccharides that provide energy to colonies of beneficial bacteria, the probiotics in the gut so that they can thrive (Gaggia, Mattarelli, & Biavati, 2010). Prebiotics are mostly derived from dietary fibers that are not digestible or only partially digestible in the intestinal tract. Types of prebiotics used in the livestock industry include indigestible sugars like fructooligosaccharides (FOS), galactooligosaccharides, mannan oligosaccharides, beta glucans, inulin and lactulose (Singh, Kerketta, Yogi, Kumar, & Ojha, 2017). A recent study has shown that ultrasound-modified soluble dietary fibers from garlic has improved oil holding, water holding, cholesterol binding, and swelling capacity together with high antioxidant activity against DPPH free radicals (Huang, Zhang, Cheng, & Lu, 2019). Soluble dietary fibers are water soluble fibers that forms a gel like solution upon digestion in the gastrointestinal tract. The gel like formation supports the entrapment of phenolic compounds and proteins like SOD, while preventing structural damage of the enzyme, it is permeable for ROS to be scavenged. Therefore, we postulate that SOD encapsulated in soluble fiber-rich extract of plant could enhance the health of livestock. SOD is a high weight molecular compound and is considered difficult to permeate the intestinal barrier into intracellular environment of small intestine. A recent review on the intestinal permeability of polyphenols has suggested that dietary intake of polyphenols might modulate the intestinal permeability, hence preventing pathological and inflammatory conditions (Bernardi et al., 2019). Although the underlying mechanism is not fully elucidated, the results from animal and human trials of microencapsulated SOD consumption were proven effective against various diseases thus the intestinal permeability could have been modulated.

Future studies on oral administration of plant SOD incubated with soluble dietary fibers from underutilized plants to animal models should be performed to evaluate their bioavailability and therapeutic efficacy compared to commercial GliSODin. The mechanism of entrapment and release of SOD by the soluble dietary fibers should be studied through in-vitro and in-vivo models to optimize the oral administration method. The pharmacokinetics of the SOD-dietary fiber in the digestive system must be understood in order to evaluate the enzymatic reaction against ailments. Considering the antioxidant activity of soluble dietary fibers, it can be postulated that oral administration of SOD-dietary fiber would have higher affinity to attract and bind superoxide anions without the need to release SOD into extracellular environment. The proposed mechanism of action is shown in Fig. 3. If this approach could be proven successful, a promising health booster can be developed for livestock in near future. Moreover, further clinical research on the oral administration of SOD in dietary fiber will enable the development of a new health supplement without side effects for human consumption. Underutilized plants, vegetables, and fruits could serve as the natural source of SOD and soluble dietary fibers. Re-utilizing vegetable and fruit wastes from the food processing industries for therapeutic purposes would reduce the amount of environmental waste and pollution besides preventing over-exploitation of fresh plants and other plant products. Therefore, a sustainable solution could be achieved in the development of therapeutic approaches in the agricultural sector.

## Contribution of authors

All authors made equal contribution in the preparation of this article.

## Note

The authors declare no competing financial interest.

## Ethical statement

No animals or human subjects were studied in this review.

## Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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