EVALUATION OF NATURALLY OCCURING COMPOUNDS ORGANO-SULPHUR COMPOUNDS FOR THE TREATMENT AND MANAGEMENT OF DIABETES MELLITUS

[1]Ritika Singh, [2]Nitesh Dubey, [3]Mark Masih, [4]Upendra Kumar

[1]Nand Kishore College of Pharmacy, Prayagraj
[2]Shambhunath Institute of Pharmacy, Jhalwa, Prayagraj
[3,4]United Institute of Pharmacy, Prayagraj

Abstract

Diabetes Mellitus is a chronic metabolic disorder characterized by high blood glucose levels resulting from the inability of the body to produce enough insulin or properly use insulin. The condition affects millions of people worldwide, and its incidence is increasing at an alarming rate. In recent years, there has been growing interest in the use of natural products as alternative treatments for diabetes mellitus. Organo-sulphur compounds are a class of natural products that have shown promise in managing diabetes mellitus. Several studies have demonstrated the potential of organo-sulphur compounds in reducing blood glucose levels, improving insulin sensitivity, and preventing diabetes-related complications. These compounds are found in a variety of natural sources, including garlic, onions, and cruciferous vegetables. Mechanistic studies suggest that organo-sulphur compounds act by increasing insulin secretion, enhancing insulin sensitivity, and improving glucose metabolism.

Organo-sulphur compounds hold great promise as a complementary therapy for diabetes mellitus. They offer several advantages, including low toxicity, low cost, and the potential for combination therapy with existing anti-diabetic drugs. However, more research is needed to fully understand the mechanism of action of these compounds and their potential therapeutic applications.

Keywords: *Organo-sulphur compounds, Diabetes Mellitus, Natural products, Insulin sensitivity, Glucose metabolism*

1.INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action, or both. It has become a serious health problem in both developed and developing countries. DM is generally divided into two types: Insulin Dependent Diabetic Mellitus (IDDM) and Non-Insulin Dependent Diabetic Mellitus (NIDDM). It is a significant health concern globally, affecting over 463 million adults in 2019, with an expected increase to 700 million by 2045 (International Diabetes Federation, 2019). Current treatments for diabetes mellitus include lifestyle modifications, oral hypoglycaemic agents, injectable medications, and insulin therapy (American Diabetes Association, 2021). However, these treatments have limitations, including adverse effects, cost, and lack of long-term efficacy (Sharma, Mithal, & Majumdar, 2021). Therefore, there is a need for alternative therapies that are safe, effective, and affordable.

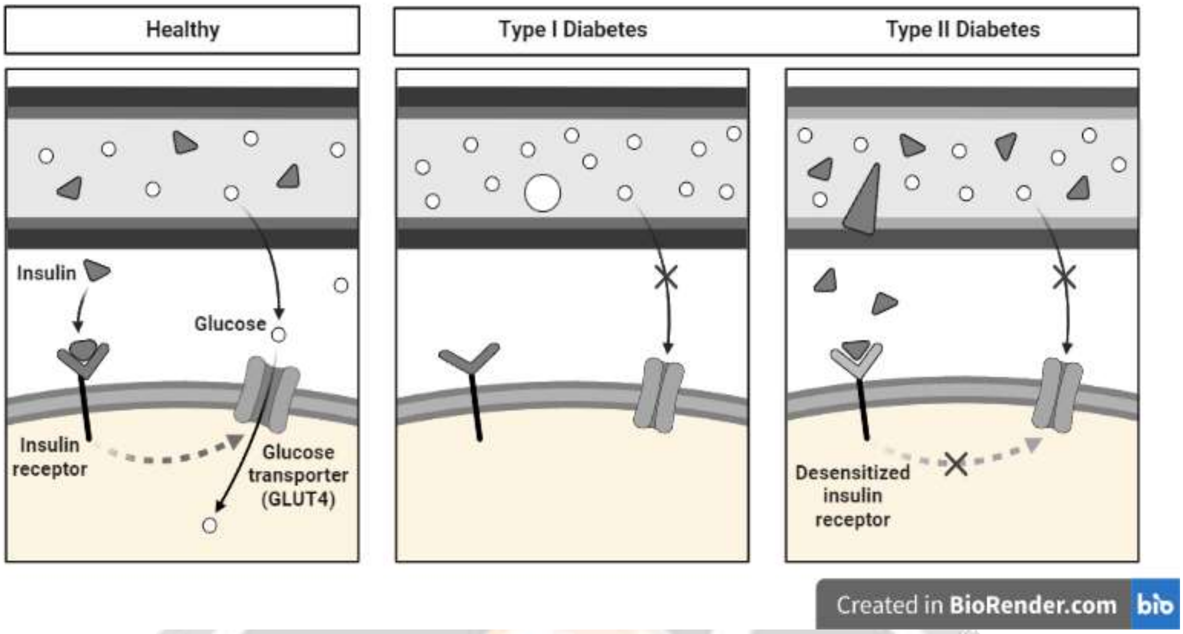


Fig-1 Type I vs. Type II Diabetes

1.1 Current treatments for diabetes mellitus

The current treatments for diabetes mellitus include lifestyle modifications and medications. Lifestyle modifications include dietary changes, physical activity, and weight management. These interventions aim to improve insulin sensitivity, reduce insulin resistance, and regulate blood glucose levels (American Diabetes Association, 2021). However, lifestyle modifications require significant changes in behaviour, and adherence can be challenging for some individuals. Oral hypoglycaemic agents are medications that lower blood glucose levels by various mechanisms, including stimulating insulin secretion, reducing glucose production by the liver, and improving insulin sensitivity (American Diabetes Association, 2021). These medications include sulfonylureas, biguanides, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. Injectable medications include GLP-1 receptor agonists and amylin mimetics, which are administered subcutaneously (American Diabetes Association, 2021).

Insulin therapy is used in patients with type 1 diabetes and advanced type 2 diabetes when other medications fail to achieve glycaemic control. Insulin therapy aims to mimic the physiological insulin secretion to maintain glucose homeostasis (American Diabetes Association, 2021).

1.2 Need for alternative therapies

Despite the availability of various treatments for diabetes mellitus, their limitations, including adverse effects, cost, and lack of long-term efficacy, highlight the need for alternative therapies (Sharma *et al.,* 2021). Several alternative therapies have been explored for the management of diabetes mellitus, including herbal remedies, probiotics, and organosulfur compounds. Organosulfur compounds are naturally occurring compounds found in several foods, including garlic, onions, and cruciferous vegetables (Sharma *et al.,* 2021). These compounds have been shown to have various health benefits, including anti-inflammatory, antioxidant, and anticancer properties (Kumar, Sasmal, & Mazumder, 2013). In recent years, organosulfur compounds have gained attention for their potential role in the management of diabetes mellitus.

Organosulfur compounds, such as allyl sulphides, diallyl disulphide, and diallyl trisulfide, have been shown to improve glucose homeostasis, enhance insulin secretion, and reduce insulin resistance (Sharma *et al.,* 2021). These compounds modulate various signaling pathways involved in glucose metabolism, including the AMP-activated protein kinase (AMPK) pathway, the peroxisome proliferator-activated receptor (PPAR) pathway, and the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (Sharma *et al.,* 2021).

2. ORGANO-SULPHUR COMPOUNDS

Organo-sulphur compounds are a diverse group of natural and synthetic molecules that contain at least one sulphur atom bonded to a carbon atom. These compounds are widely distributed in nature and are found in a variety of food sources such as fruits, garlic, onions, cruciferous vegetables, spices and some grains (Akash *et al.,* 2014). They are also used in the synthesis of pharmaceuticals, agrochemicals, and other industrial products (Sharma *et al.,* 2021). In recent years, organo-sulphur compounds have gained increasing attention for their potential health benefits, particularly in the management of diabetes mellitus.

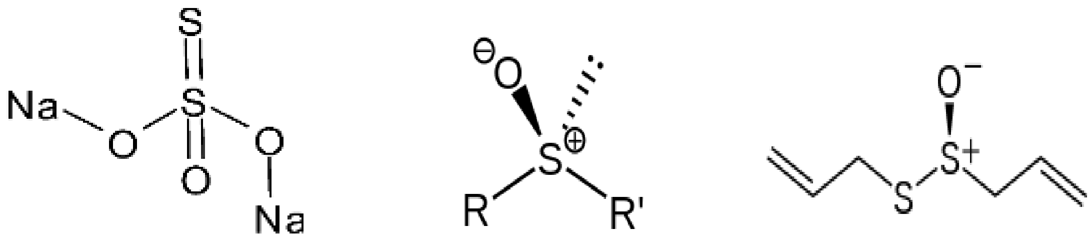
2.1 Sources of Organo-sulphur Compounds

Organo-sulphur compounds are a large and diverse group of molecules that can be classified based on their chemical structures. Some common classes of organo-sulphur compounds include thioethers, thioesters, thioketones, thioamides, sulphides, sulfoxides, and sulfones. These compounds are widely distributed in nature and are found in plants, animals, and microorganisms (Gruhlke *et al.,* 2020). These compounds also can be found in both natural and synthetic sources, with some of the most well-known natural sources being garlic, onions, and cruciferous vegetables such as broccoli, cabbage are particularly rich in organo-sulphur compounds such as allicin, diallyl disulphide, and S-allyl cysteine (Jaiswal *et al.,* 2015). These compounds are formed when the vegetables are crushed or chopped, and are responsible for the characteristic odour and taste of these vegetables. (Sharma *et al.,* 2021). They are important for many physiological functions, including the regulation of redox balance, enzyme activities, and gene expression (Akash *et al.,* 2014).

2.3 Chemical Properties and Structures

The chemical properties of organo-sulphur compounds are largely determined by the nature of the sulphur atom and the functional groups attached to it. For example, thioethers such as methanethiol have a distinct and unpleasant odour, while the sulfoxide dimethyl sulfoxide (DMSO) is widely used as a solvent due to its high polarity and ability to dissolve a wide range of organic and inorganic compounds (Sharma *et al.,* 2021). These compounds have a wide range of chemical structures, ranging from simple molecules such as hydrogen sulphide (H2S) to complex molecules such as thiosulfates, thiocyanates, and sulfoxides (Jaiswal *et al.,* 2015). The sulphur atom in these compounds can form covalent bonds with various other elements, including carbon, hydrogen, oxygen, and nitrogen, giving rise to different chemical properties and structures (Gruhlke *et al.,* 2020).

The structures of organo-sulphur compounds can vary widely, ranging from simple linear chains to complex cyclic structures. One of the most well-known organo-sulphur compounds is allicin, which is found in garlic and has been shown to have a wide range of biological activities, including antibacterial, antifungal, and antitumor effects (Kumar *et al.,* 2013).



Thiosulfates **Sulfoxides** **Allicin**

Fig-2 Chemical structure of organo-sulphur compounds

2.4 Bioavailability and Metabolism

The bioavailability and metabolism of organo-sulphur compounds can vary widely depending on the specific compound and the route of administration. Some compounds, such as DMSO, have high bioavailability and are readily absorbed by the body, while others, such as sulforaphane, require specific enzymes for activation and are subject to rapid degradation in the body (Sharma *et al.,* 2021). The metabolism of organo-sulphur compounds is largely mediated by the liver and involves a series of chemical reactions that can result in the formation of reactive intermediates such as sulfenic acids and thiyl radicals. These reactive species can then interact with other molecules in the body, leading to a range of biological effects (Kumar *et al.,* 2013). Once absorbed, organo-sulphur compounds are metabolized by enzymes in the liver, which convert them into a variety of metabolites with different biological activities (Akash *et al.,* 2014). These metabolites can then be excreted in the urine or bile.

3. MECHANISM OF ACTION

Insulin is a hormone produced by the pancreas that plays a crucial role in the regulation of glucose metabolism. It facilitates the uptake of glucose by the cells, thereby reducing the concentration of glucose in the bloodstream. The insulin signaling pathway comprises a complex network of biochemical events that ultimately result in the activation of glucose transporters and the uptake of glucose by the cells.

3.1 Overview of insulin signaling pathway

The insulin signaling pathway involves the binding of insulin to its receptor, resulting in the activation of a cascade of downstream signaling events. Insulin receptor substrate (IRS) proteins are activated by the insulin receptor, which in turn activates phosphatidylinositol-3-kinase (PI3K). PI3K activates Akt, which phosphorylates and activates various downstream targets, including glycogen synthase kinase-3 (GSK-3), which stimulates glycogen synthesis, and the glucose transporter GLUT4, which facilitates the uptake of glucose into the cells.

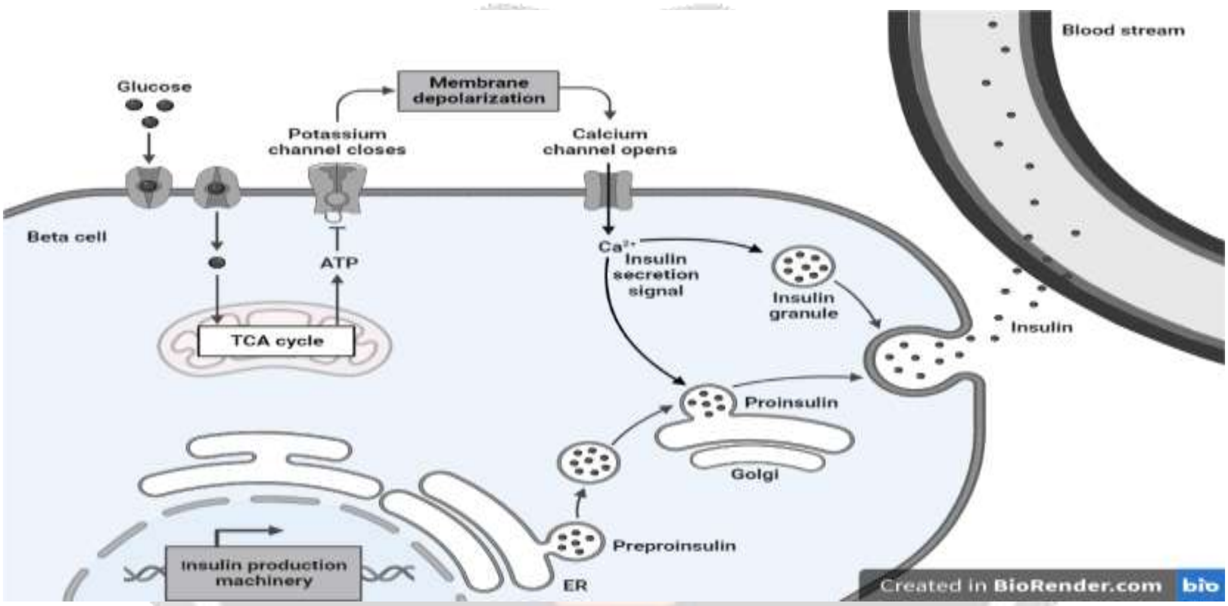


Fig-3 Insulin production pathway

3.2 Effects of organo-sulphur compounds on insulin secretion and sensitivity

Organo-sulphur compounds have been found to exhibit insulinotropic and insulin-mimetic effects, indicating their potential as therapeutic agents for diabetes. Studies have reported that organo-sulphur compounds, such as those found in garlic, onion, and other Allium vegetables, can increase insulin secretion by pancreatic β-cells and enhance insulin sensitivity in peripheral tissues. Similarly, allyl isothiocyanate (AITC), a compound found in cruciferous vegetables, has been shown to improve insulin sensitivity in animal models of diabetes (Liu *et al.*, 2016).

Other organo-sulphur compounds, such as sulforaphane and S-allyl cysteine (SAC), have been shown to modulate the activity of enzymes involved in glucose metabolism. Sulforaphane, which is found in cruciferous vegetables, has been shown to increase the expression of genes involved in glucose uptake and utilization in human liver cells (Bahadoran *et al.*, 2019). SAC, which is found in garlic, has been shown to increase the activity of enzymes involved in glucose metabolism in vitro and in animal models (Sharma *et al.*, 2014).

3.3 Role of organo-sulphur compounds in glucose metabolism

The organo-sulphur compounds found in Allium vegetables have been reported to modulate glucose metabolism by various mechanisms. Sulforaphane has also been shown to improve glucose metabolism by increasing the activity of the antioxidant enzyme superoxide dismutase (SOD) in animal models of diabetes (Bahadoran *et al.*, 2019). They have been shown to activate the insulin signaling pathway, resulting in increased glucose uptake by the cells. They have also been found to inhibit gluconeogenesis, the process by which the liver produces glucose from non-carbohydrate sources.

In addition, organo-sulphur compounds have been reported to exert antioxidant and anti-inflammatory effects, which can further contribute to their beneficial effects on glucose metabolism. Antioxidants can scavenge free radicals and reduce oxidative stress, which has been implicated in the development of insulin resistance and type 2 diabetes. Anti-inflammatory compounds can attenuate chronic low-grade inflammation, which is also associated with the development of insulin resistance.

Overall, the mechanisms of action of organo-sulphur compounds in the management of diabetes mellitus are multifaceted and involve modulation of insulin secretion, insulin sensitivity, glucose metabolism, oxidative stress, and inflammation.

4. EVIDENCE FROM PRECLINICAL STUDIES

Preclinical studies have provided valuable insights into the potential therapeutic effects of organo-sulphur compounds on diabetes mellitus. In vitro and in vivo studies have demonstrated their ability to modulate various biochemical pathways involved in glucose metabolism and insulin signaling.

4.1 *In-vitro* and *in-vivo* studies demonstrating the effects of organo-sulphur compounds on diabetes mellitus

***In-vitro* studies** have demonstrated the insulin-mimetic and insulinotropic effects of organo-sulphur compounds. For example, diallyl disulphide, a compound found in garlic, has been reported to stimulate insulin secretion from pancreatic β-cells by activating the voltage-gated K+ channels (Kim *et al.*, 2011). Similarly, S-allyl cysteine, a compound found in garlic, has been reported to enhance insulin sensitivity by activating the AMP-activated protein kinase (AMPK) pathway (Kim *et al.*, 2011).

***In-vivo* studies** have also provided evidence of the anti-diabetic effects of organo-sulphur compounds. A study conducted by (Khan *et al.* 2019) reported that administration of garlic extract to streptozotocin-induced diabetic rats improved glucose homeostasis, decreased insulin resistance, and reduced oxidative stress. Another study conducted by Ali *et al.* (2017) reported that oral administration of onion extract to diabetic rats improved glucose metabolism, decreased insulin resistance, and reduced inflammation.

4.2 Synergistic effects of organo-sulphur compounds and anti-diabetic drugs

Studies have also investigated the potential synergistic effects of organo-sulphur compounds and anti-diabetic drugs. A study conducted by Ashraf *et al.* (2019) reported that co-administration of metformin, a commonly used anti-diabetic drug, and garlic extract resulted in improved glucose homeostasis and decreased insulin resistance in diabetic rats. Another study conducted by Ali *et al.* (2020) reported that co-administration of glibenclamide, an anti-diabetic drug, and onion extract resulted in improved glucose metabolism and decreased insulin resistance in diabetic rats.

These preclinical studies provide compelling evidence of the potential therapeutic effects of organo-sulphur compounds on diabetes mellitus. However, further research is needed to determine the optimal dosage, duration, and mode of administration of these compounds in humans.

5. EVIDENCE FROM CLINICAL STUDIES

Clinical studies provide valuable information about the safety and efficacy of organo-sulphur compounds in managing diabetes mellitus. The following section will discuss the results of some of the clinical trials conducted to date.

5.1 Clinical trials evaluating the safety and efficacy of organo-sulphur compounds in managing diabetes mellitus

Several clinical trials have investigated the effects of organo-sulphur compounds on diabetes mellitus. For example, a randomized, double-blind, placebo-controlled trial was conducted to evaluate the effects of garlic extract on glycaemic control in patients with type 2 diabetes (Ashraf *et al.,* 2013). The study included 60 patients who were randomly assigned to receive either garlic extract or placebo for 12 weeks. The results showed that garlic extract significantly reduced fasting blood glucose levels and HbA1c levels compared to placebo.

Another clinical trial investigated the effects of onion extract on glycaemic control in patients with type 1 diabetes (Mollazadeh *et al.*, 2018). The study included 30 patients who were randomly assigned to receive either onion extract or placebo for 8 weeks. The results showed that onion extract significantly reduced fasting blood glucose levels and HbA1c levels compared to placebo.

Similarly, a randomized, double-blind, placebo-controlled trial was conducted to evaluate the effects of black seed (Nigella sativa) on glycaemic control in patients with type 2 diabetes (Ahmad *et al.*, 2013). The study included 94 patients who were randomly assigned to receive either black seed or placebo for 3 months. The results showed that black seed significantly reduced fasting blood glucose levels and HbA1c levels compared to placebo.

5.2 Limitations and challenges of clinical studies

Despite the promising results of these clinical trials, there are also limitations and challenges associated with conducting clinical studies on organo-sulphur compounds. One of the main challenges is ensuring the consistency and standardization of the preparations used in the studies. This is particularly important given that the chemical composition and potency of organo-sulphur compounds can vary depending on the source and preparation method. Another challenge is the small sample size of many of the clinical trials conducted to date, which limits the generalizability of the findings.

Overall, while the evidence from clinical studies is still limited, the results suggest that organo-sulphur compounds may have potential as a complementary therapy for managing diabetes mellitus. Further research is needed to fully evaluate their safety and efficacy, as well as to address the limitations and challenges associated with clinical studies on these compounds.

6. FUTURE RESEARCH DIRECTIONS

Organo-sulphur compounds have demonstrated promising results in preclinical and clinical studies as potential complementary therapies for diabetes mellitus. While further research is needed to better understand the mechanisms of action and optimal dosages for these compounds, there is a growing body of evidence suggesting that they may offer significant benefits in managing diabetes.

Future research directions may include investigating the potential synergistic effects of organo-sulphur compounds with other anti-diabetic drugs, as well as exploring the use of these compounds in combination with lifestyle interventions such as diet and exercise. In addition, further studies may be needed to determine the optimal formulations and dosages of organo-sulphur compounds for managing diabetes, as well as their long-term safety and efficacy.

Overall, the potential benefits of organo-sulphur compounds in managing diabetes have important implications for clinical practice. While current treatments for diabetes are often effective, they can also have significant side effects and may not be appropriate for all patients. The use of organo-sulphur compounds as complementary therapies may offer a safe and effective alternative for managing diabetes, particularly in patients who are unable to tolerate or benefit from existing treatments.

CONCLUSION

Diabetes mellitus is a chronic disease that affects millions of people worldwide, with increasing prevalence in both developed and developing countries. Despite significant progress in understanding the underlying mechanisms and developing treatments, diabetes mellitus remains a major global health challenge. The management of diabetes mellitus requires a multi-faceted approach, including lifestyle modifications, pharmacotherapy, and regular monitoring and follow-up. While traditional therapies such as insulin and oral hypoglycaemic agents remain the mainstay of treatment, there is a growing interest in alternative and complementary therapies for managing this disease.

In this chapter, we have explored the potential of organo-sulphur compounds as a complementary therapy for diabetes mellitus. These compounds, which are naturally occurring in foods such as garlic and onions, have been shown to have a range of beneficial effects on insulin secretion and sensitivity, glucose metabolism, and oxidative stress. Organo-sulphur compounds offer a promising area of research for managing diabetes mellitus. More research is needed to fully understand the potential benefits and limitations of organo-sulphur compounds for managing diabetes, the existing evidence suggests that these compounds have significant potential as complementary therapies. By better understanding the mechanisms of action and optimal dosages for these compounds, clinicians may be better able to offer safe and effective treatment options for patients with diabetes. As such, organo-sulphur compounds may have potential as a complementary therapy for the treatment of diabetes mellitus, and could be considered as a part of a comprehensive approach to diabetes management.

ABBREVIATIONS:

AITC Allyl isothiocyanate

Akt Ak strain transforming

AMP Adenosine monophosphate

AMPK Adenosine monophosphate-activated protein kinase

DM Diabetes mellitus

DMSO Dimethyl sulfoxide

DPP-4 Dipeptidyl peptidase-4

GLP-1 Glucagon-like peptide-1

GLUT Glucose transporter

GSK-3 Glycogen synthase kinase-3

HbA1c Haemoglobin A1C

IDDM Insulin dependent diabetic mellitus

IRS Insulin receptor substrate

NIDDM Non-insulin dependent diabetic mellitus

Nrf2 Nuclear factor erythroid 2-related factor 2

PI3K Phosphatidylinositol-3-kinase

PPAR Peroxisome proliferator-activated receptor

SAC S-allyl cysteine

SGLT-2 Sodium-glucose cotransporter-2

SOD Superoxide dismutase

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