Catalase Function In Age-Related Degenerative Diseases

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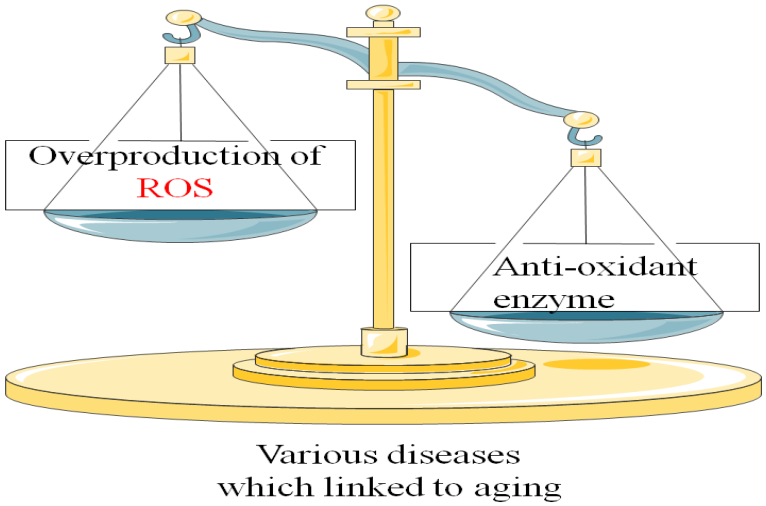
Abstract : Cellular macromolecules such as nucleic acids, proteins, and lipids can chemically react with reactive oxygen species (ROS) created in the cell during normal metabolic processes. Later oxidative changes could alter their chemical compositions and harm their biological functions. Fortunately, cells have developed several antioxidant defense mechanisms (such as metabolites, vitamins, and enzymes). One of the essential antioxidant enzymes, catalase, decomposes cellular hydrogen peroxide to create water and oxygen, reducing oxidative stress to a significant extent. Catalase deficiency influences the pathophysiology of several age related degenerative disorders. Later include diabetes mellitus, hypertension, anemia, vitiligo, Parkinson's disease, and bipolar disorder. As a result, numerous laboratories are attempting to investigate its potential as a medicine for treating such disorders. This review discusses the direct and indirect roles of catalase deficiency or modification in developing certain severe diseases, including Vitiligo, Parkinson's disease, Alzheimer's disease, and Diabetes mellitus.

Keywords — Degenrative disease, Anti-oxidant enzyme, Aging, Catalase, Oxidative damage

Graphical abstract



I. INTRODUCTION

Reactive species are highly active; some are direct oxidants, creating some inside the cell during cellular metabolism. They may also contain oxygen or oxygen-like electronegative components. Certain reactive oxygen species (ROS) are non-radical, like hydrogen peroxide, while others are free radicals, like hydroxyl and superoxide radicals. Any independent species with one or more unpaired electrons in its atomic or molecular orbital is considered free radical. All biological macromolecules, including nucleic acids, proteins, and lipids, are susceptible to oxidation by free radicals [5].

During cellular metabolism, these free radicals are produced in the cell due to processes involving the cytochrome P450 enzyme, the mitochondrial electron transport chain, the -oxidation of fatty acids, and the respiratory burst during the immunological defense. An imbalance causes oxidative stress in the production and these reactive molecules via antioxidant systems. The theory of free radicals can explain the underlying mechanisms of aging. Later has linked numerous degenerative metabolic and neurological conditions to oxidative stress. Degenerative disorders, such as Alzheimer's disease, Parkinson's disease, diabetes, and cardiovascular disease, where the structure and functionality of a tissue deteriorate with time, have been linked to oxidative stress and the normal aging process.

A few proteins, low molecular weight compounds, and a specific enzyme compensate for the antioxidant system. The antioxidant enzymes can reduce the reactive oxygen species catalytically. For instance, catalase (CAT) or glutathione peroxidase (GPx) degrades superoxide dismutase into hydrogen peroxide. As a result, oxidative stress, aging, and degenerative diseases are all linked.

II. About Catalase (CAT)

One of the most significant antioxidant enzymes is catalase. Almost all aerobic organisms have it. In a two-step reaction, catalase reduces two molecules of hydrogen peroxide into one oxygen molecule and two molecules of water. A covalent oxyferryl species

(FeIVO) with a porphyrin-cation radical is formed as the first product of the reaction process when one hydrogen peroxide molecule is reduced as in Eq.1 [1]. Compound I is declined in the second step by redox reactions resulting in the free enzyme, oxygen, and water as in Eq. 2 [3].

$$H_2O_2 + Fe(III)\text{-}E \rightarrow H_2O + O{=}Fe(IV)\text{-}E(.+) \quad H_2O_2^{+} \qquad (1)$$

$$O{=}Fe(IV)\text{-}E(.+) \rightarrow H_2O + Fe(III)\text{-}E + O^{\cdot} \qquad (2)$$

(H_2O_2- hydrogen peroxide, Fe- Iron, E- enzyme, H_2O- water, $O^{\cdot}$- free radical)

Both eukaryotic and prokaryotic organisms have catalase. There are three primary forms of catalase, which differ in their structure and sequences. The most common enzyme is the monofunctional heme-containing one. Catalase-peroxidase with dual functions is a member of the second class, which is less prevalent. Later also contains a heme group. It shares structural and sequence similarities with plant peroxidases, indicating close kinship. The third class is represented by the catalase group, which lacks the heme group and contains manganese (Mn). Humans have a monofunctional heme-containing catalase with a ferrous protoporphyrin IX prosthetic group that reacts with peroxide. It r is found in the peroxisomes and has a molecular weight of roughly 220-240 kDa. It contains four domains: the N-terminal threading arm, the C-terminal helices, the wrapping loop, and the barrel [8].

This review aims to link the function of catalase to the development of oxidative stress-related disorders.

III. The linkage between catalase and other antioxidant enzymes.

Various enzymes can neutralize hydrogen peroxide, catalase, glutathione peroxidase, and other peroxidases [5]. A crucial enzyme called catalase uses hydrogen peroxide, a non-radical ROS, as a substrate. This enzyme is in a change of neutralizing hydrogen peroxide, which is also necessary for cellular signaling activities. The enzyme's role in numerous diseases and infections, directly and indirectly, provides evidence of its significance.

IV. Catalase-Related Diseases

Numerous diseases, including *Diabetes mellitus*, Vitiligo, Cardiovascular diseases, Hypertension, Anemia, certain dermatological conditions, and Alzheimer's disease, were linked to catalase dysfunction [15] (Fig. 1).

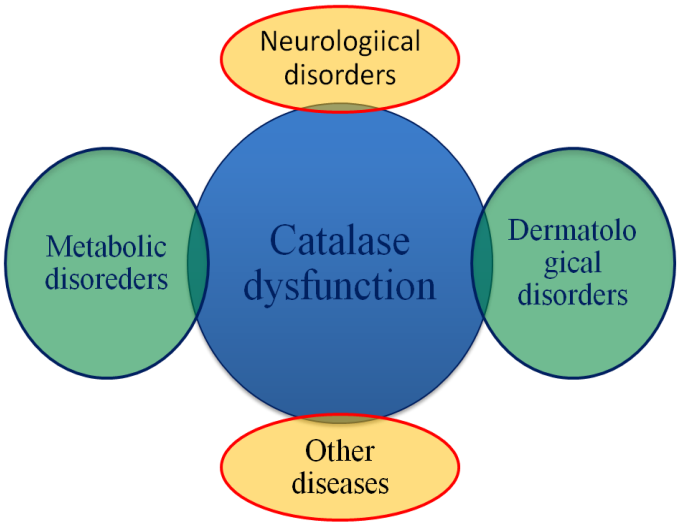


Figure: 1 Catalase dysfunction causes numerous disorders

Table: 1 List of multiple diseases along with their causes.

Sr. No.	Types of diseases	Diseases	Functionality loss	References
1.	Diabetes mellitus	1.Type-1	β-chain	[10]
		2.Type-2	Insulin receptor	[2]
2.	Neurological disorder	1.Alzheimer's Disease	Accumulation of β-amyloid	[9]
		2. Parkinson's Disease	α-synuclein	[13]
3.	Dermatological disease	Vitiligo	Tyrosinase enzyme	[12]

- **Diabetes Mellitus**

The blood glucose levels (Fig. 2) were elevated due to improper insulin secretion, a symptom of various metabolic diseases. Other secondary conditions might cause nerve damage, blindness, heart disease, stroke, and renal disease. Adults with diabetes were expected to be elevated, with developing nations like India accounting for the majority of the rise.

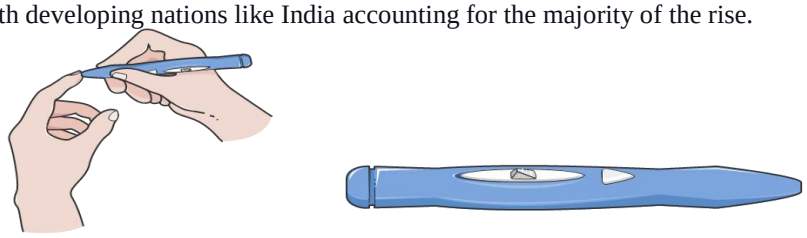


Figure: 2 Measurement of glucose level

Type-1 diabetes mellitus could develop in adults and children, accounting for 10% of all instances of insulin-dependent diabetes [10]. In this instance, autoimmune reactions disrupt pancreatic cells, preventing them from synthesizing insulin. Particular antibodies primarily bind to conformational epitopes on the β-chain of insulin. The genomic characteristic has been demonstrated a link between specific HLA complex alleles and type 1 diabetes.

About 90% of all instances of diabetes were type 2 diabetes mellitus. It arises mainly because the body produces insufficient insulin than it needs to, but it could also happen because the cells have been resistant to insulin. Langerhans' cells' islets were damaged, preventing them from producing insulin. Oxidative stress plays a vital role in the development of type 2 diabetes. Hydrogen peroxide has been shown to act as an oxidant, disrupt cells, and alter the signaling process that causes insulin synthesis [2].

A typical form of diabetes in pregnant women has Gestational diabetes mellitus (GDM). Type 2 diabetes mellitus and GDM sound similar. Various disorders, including hypertension, and chronic renal disease, were more likely to occur in the children of pregnant diabetic women [18]. Birth abnormalities may be caused due to arises in reactive oxygen species (ROS) and a decrease in antioxidant protection [18], [4]. One of the research revealed that pregnant GDM women's blood catalase activity was lower than that of healthy control pregnant and non-diabetic women [14]. However, in pregnant women with GDM, the blood catalase activity was seen to elevate in the third trimester compared to the second [14].

Neurological Disorders

- **Alzheimer's Disease**

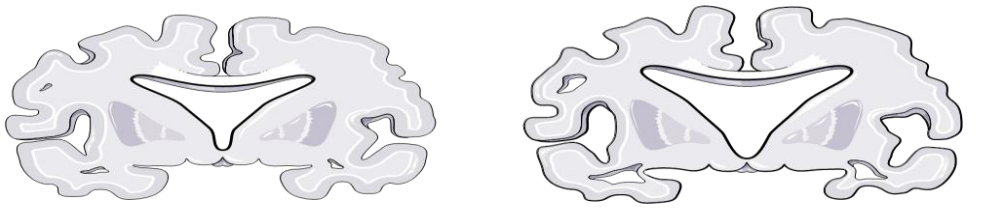


Figure: 3 different stage of Alzimer's disease

The β-amyloid peptide senile plaques were a hallmark of Alzheimer's disease, which develops in the brain . It has been shown that protein-protein adducts occur in all cases of Alzheimer's disease, switching soluble β-amyloid to insoluble fibrils in senile plaques [9]. One of the *in vitro* studies demonstrated that the emerging form of β-amyloid was not harmful, but the aging form has been toxic to neurons [17]. Later has been responsible for synthesizing hydrogen peroxide in neuroblastoma and hippocampal neurons. Moreover, β-amyloid was directly bound to catalase, diminishing enzyme activity [15]. Accordingly, the catalase β-amyloid interaction may play an essential role in developing oxidative stress by increasing hydrogen peroxide in cells [15]. Consequently, one of the hypotheses about how β amyloid triggers oxidative damage in cells is that β amyloid directly interacts with catalase by interacting with the enzyme and inhibiting its catalytic activity, leading to oxidative stress. As a result, catalase, directly and indirectly, affects Alzheimer's disease pathogenesis.

- **Parkinson's Disease**

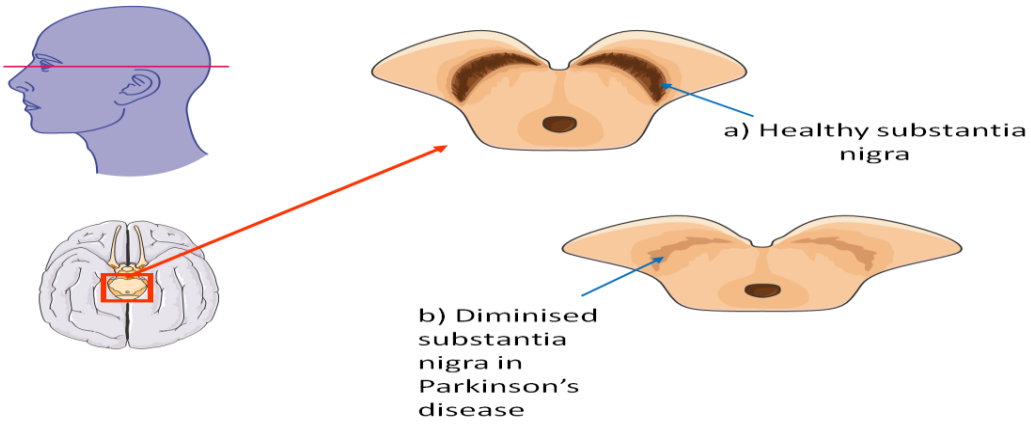


Figure: 4 Parkinson's disease a) normal substantia nigra b) Diminised substantia nigra

Parkinson's disease is an age-associated neurological disorder that starts as a simple tremor in hand and affects the entire body's movement. It gradually deteriorates the quality of life significantly as the disease progresses. During rest or sleep, the limbs were characterized by rhythmic tremors. Early in the disease's progression, patients struggle to control their movements and become rigid in their muscles. The disease was diagnosed as dopamine insufficiency caused by damage to dopamine-producing neurons in the substantia nigra pars compacta (SNpc) [16]. Later pathogenesis was influenced by various factors, including mitochondrial dysfunction, oxidative stress, inherited genetic traits, and environmental pollutants. The α-synuclein, a protein, was intimately associated with Parkinson's disease [13]. One of the research revealed that a mutation in a gene that makes α-synuclein had been the development of a mutant protein that can trigger the accumulation of dopamine in the cytoplasm of neurons [11]. It undergoes auto-oxidation, producing hazardous dopamine-quinone species. Catalase production and activity have been inhibited by mutant α-synuclein protein.

Based on numerous studies, it is possible to conclude that the low catalase activity and high hydrogen peroxide production in Parkinson's disease has been caused by mutant α-synuclein.

- **Vitiligo**

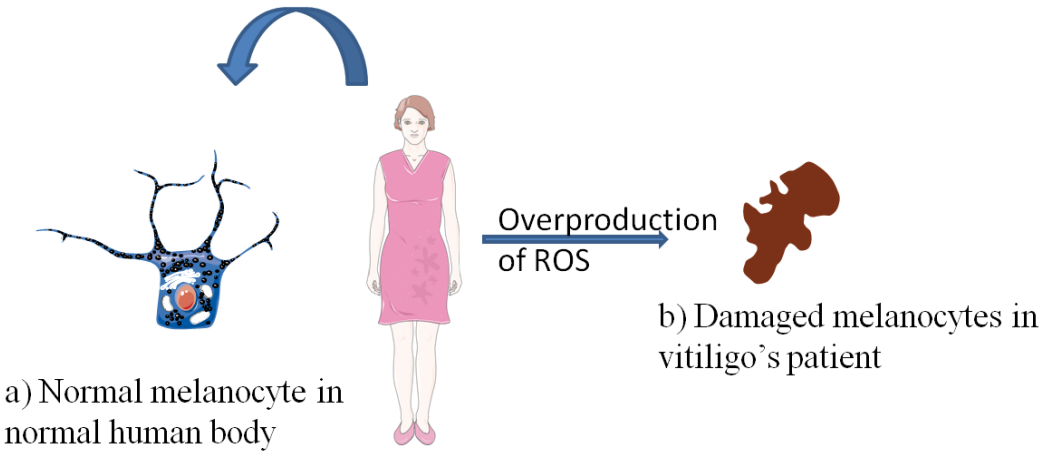


Figure: 5 a) shows the normal melanocytes in healthy human body which contaning normal level of reactive oxygen species (ROS), b) shows the Damaged melanocytes in vitiligo's patients because of overproduction of reactive oxygen species

Vitiligo is one of the idiopathic and pigmentary disorders in which melanocyte cells of the skin are damaged or can no longer produce melanin. Various studies have shown that the catalase levels in Vitiligo patients were lower than in the healthy control [19] Hydroxyl radicals can be produced spontaneously from hydrogen peroxide by photochemical reduction, i.e., the Haber-Weiss reaction [6]. These hydroxyl radicals were capable of oxidizing lipids in the cell membrane. Later could cause damage to melanocytes in the epidermal layer of the skin in such patients [12]. In addition, the inhibitory effect of hydrogen peroxide or an allelic alteration of the CAT gene results in low catalase activity. One more study reported that a mutation in the CAT gene could alter the expression of a gene and be responsible for structural changes in the melanocytes [7]. Although the results of population studies were contradictory, a linkage between pathogenesis and catalase may still be possible. Further studies are mandatory to understand the link is necessary.

V. Conclusion:

Various oxidants are produced during cellular metabolism that are harmful to the body. Luckily, our body adapts an antioxidant system that protects cells from the oxidant. An antioxidant is catalase, a crucial enzyme that breaks down hydrogen peroxide and maintains the cellular redox balance. Several diseases are becoming common in the modern world, including diabetes, Alzheimer's, and Parkinson's. Catalase has been shown to relate to the pathogenesis of these diseases, despite the fact that there are many factors involved. Some scientists are conducting research in this area at different laboratories, but aging is causing many challenges to be overcome. However, catalase is not yet fully developed as a therapeutic drug for the treatment of several oxidative stress-related diseases. Research is needed to confirm whether catalase can be used to treat age-related disorders.

VI. Future Perspective

The etiology of some severe disorders, including diabetes, Parkinson's disease, vitiligo, and Alzheimer's disease, is reviewed in this article. It is mandatory to analyze catalase's function in the etiology of disorders linked to oxidative stress and its therapeutic strategy. As a crucial regulator, catalase substantially impacts the metabolism of hydrogen peroxide. One of the study revealed that catalase is involved in regulating the concentration of hydrogen peroxide, which is essential for the signaling process. More experimental validation is required for the catalase-based treatment approaches before clinical trials. Catalase as a drug or therapy could be a brand-new and vast area of investigation. Positive results may indicate that it could be used to treat many disorders linked to oxidative stress.

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