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Superoxide Dismutase (SOD): A Promising Enzyme in the Area of Biopharmaceuticals in Its Native and Immobilized Form: A Review

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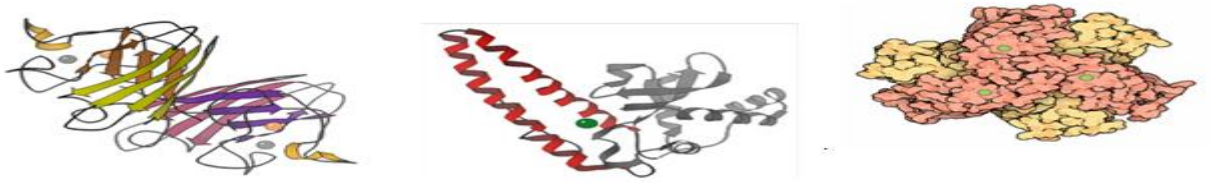
Abstract: ***Super Oxide Dismutase (SOD) an ubiquitous potent antioxidant enzyme primarily scavenges reactive oxygen species (ROS) like superoxide radicals, which causes oxidative damage to a living organism's essential proteins, lipids and its DNA. The accumulation of ROS in the body is a major inductive factor aging related diseases. It is important to maintain ROS at an appropriate level to prevent these diseases. SOD is a vital enzyme in defending against oxidative damage in vivo. The SOD enzyme promises to be a good therapeutic agent against ROS. The present review describes the therapeutic effects of SOD in some physiological and pathological conditions. Because of the defects in the direct application of SOD or SOD mimics, different mounting delivery systems (immobilization enzyme systems) have been developed for the efficient applications of SOD to realize antioxidant treatment.***

Keywords: ROS, anti-oxidant enzyme, SOD, anti-aging therapeutics, immobilized enzyme.

I. INTRODUCTION

Senescence, which enhances susceptibility for stimulation and increases rate of death, is a gradual physiological deterioration with age. Biological mechanism of aging is still unknown [1]. Nowadays, a number of research studies have found that reactive oxygen species (ROS) have a close relationship with ageing and homeostasis in organisms [2]. ROS, which is frequently mentioned in the field of biology and medicine, refers to oxygen-containing substances with high reactivity, specifically superoxide anion (O_2^-), hydroxyl radical (OH^-), singlet oxygen ($^1O_2$), peroxide free radical (LOO^-), hydrogen peroxide lipid (LOOH), peroxynitro group ($ONOO^-$), hypochlorous acid (HOCl), hydrogen peroxide (H_2O_2) and ozone (O_3) [3]. Although ROS generated in the process of oxygen metabolism are essential for cell signaling and immune response, superfluous ROS could oxidize lipids, proteins and nucleic acid, thus triggering various diseases such as inflammation, stroke, cancer, Alzheimer's disease and Parkinson's disease [4].

Superoxide Dismutases (SODs) are a group of metalloenzymes that are found in all kingdoms of life. SODs form the frontline of defense against ROS-mediated injury[5]. Different forms of SODs are found and are distinguished based on the metal co-factors present at the active site of the enzyme. Copper and Zinc SOD (Cu/Zn-SOD), Manganese SOD (Mn-SOD), Iron SOD (Fe-SOD) and Nickel SOD (Ni-SOD) are the common forms of SODs [6]. Cu/Zn-SODs are known as SOD 1, Mn-SODs and Fe-SODs together are known as SOD 2 and Ni-SODs are known as SOD 3. Cu/Zn-SODs (SOD 1) are most commonly found in eukaryotes including humans. The cytosols of virtually all eukaryotic cells contain an SOD enzyme with Cu and Zn. For example, commercially available Cu/Zn-SOD is normally purified from bovine red blood cells. The bovine Cu/Zn-SOD is a homodimer of molecular weight 32,500 [7] (Fig. 1 (a)). Fe-SODs and Mn-SODs (SOD 2) are used by prokaryotes and in mitochondria and chloroplasts. Structure of human mitochondrial Mn-SOD is shown in Fig. 1 (a) [8]. Ni-SOD (SOD 3) is found in prokaryotic cells. This has a hexameric (6-copy) structure (Fig. 1 (c)), built from right handed 4-helix bundles, each containing N-terminal hooks that chelate a Ni ion [9]. SOD is commercially obtained from marine phytoplankton, bovine liver, horseradish, cantaloupe and certain bacteria.



. Fig.1 (a) Structure of Cu/Zn-SOD (b) Structure of Mn-SOD (c) Structure of Ni-SOD

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The SODs catalyze the dismutation of superoxide anion free radical into molecular free oxygen(O_2) and hydrogen peroxide (H_2O_2) as shown in Fig. 2 and decreases superoxide radical level. This reaction is accompanied by alternative oxidation-reduction of metal ions present in the active sites of SODs [10]. Generally, the SOD enzyme converts 2 molecules of superoxide anion (O_2^-) into one molecule each of hydrogen peroxide (H_2O_2) and oxygen(O_2). Followed by the decomposition of H_2O_2 into water and oxygen is carried out by enzymes like catalase and peroxidase.

$$2O_2^- + 2H^+ \longrightarrow H_2O_2 + O_2$$

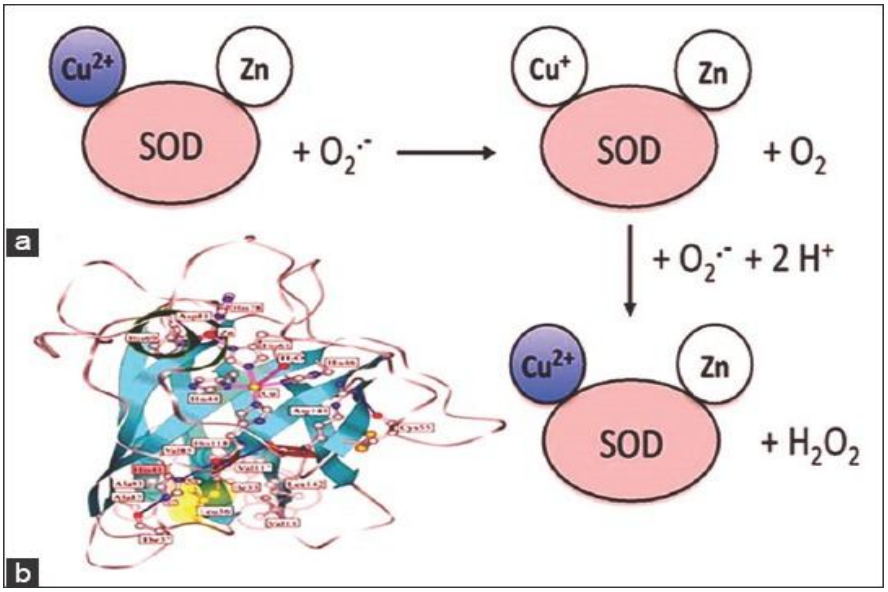

Figure 2: (a) Mechanism of dismutation of O_2^-radical by SOD.
(b) Sub unit structure of Bovine Cu/Zn-SOD.

Immobilized enzyme was in 1916 [11]. It was demonstrated that activity of invertase enzyme does not get hampered when it is adsorbed on a solid matrix, such as charcoal or aluminum hydroxide. This aspect led to the development of currently available enzyme immobilization techniques. Initially immobilization techniques used to have very low enzyme loadings, with respect to the available surface areas. In late 1990s various covalent methods of enzyme immobilization were developed. While enzyme immobilization has been studied for many years, the appearance of recent published research and review papers indicate a continued interest in the area [12]. Currently commercial application of immobilized enzymes have been enhanced as they are highly efficient [13]. Further, resistance to various environmental changes such as pH or temperature has been increased during immobilization of enzyme on solid surface [14]. Presently different immobilization techniques are applied for immobilization of enzymes like – adsorption, covalent binding, entrapment and cross linking (Fig. 3). Choosing a suitable solid support is very important for enhanced efficiency of immobilized enzymes [15]. For therapeutic enzymes like SOD, immobilization on nanoparticles is suitable for their application as biopharmaceuticals [16].

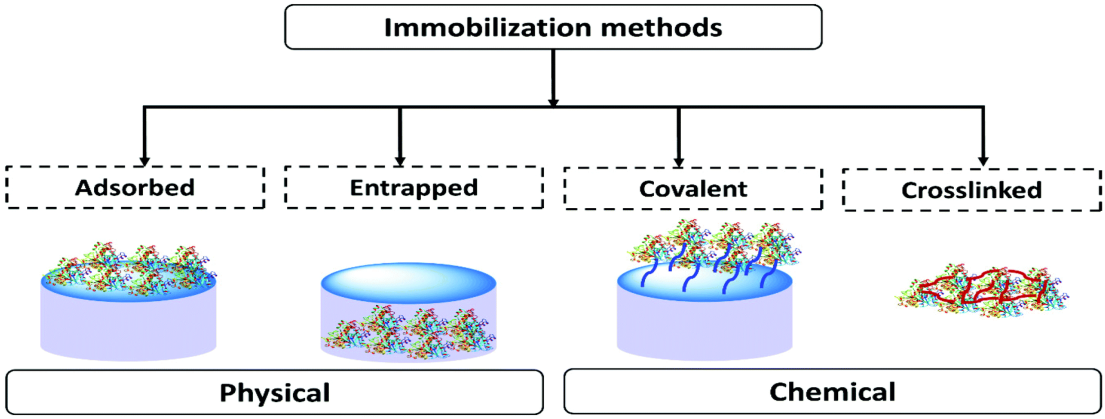

Figure 3: Immobilization techniques of enzymes

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II. THERAPEUTIC APPLICATIONS OF SOD

Mutations in SOD 1 enzyme can cause familial amyotropic lateral sclerosis (ALS, a form of motor neuron disease) [17]. The other two SODs have not been linked to any human diseases. In patients with thalassemia, SOD will increase as a form of compensation mechanism. However, in the chronic stage, SOD does not seem to be sufficient and tends to decrease due to the destruction of proteins from the massive reaction of oxidant-antioxidant [18]. From extensive study on small animals, SOD enzymes and SOD mimics are found to offer high potential for treating diseases resulting from oxidative stress. This review discusses in brief the various therapeutic potentials of SOD.

A. SOD And Cancer

Many studies have revealed the critical role of oxidative stress in carcinogenesis. Indeed, there are several clear evidences indicating that ROS work as endogenous class of carcinogens by inducing mutations in cells [19]. It has been reported that SOD may regulate cancer progression and, hence, can be used as novel target for cancer treatment [20]. Furthermore, it has been shown that Cu/Zn-SOD can be used as a novel therapeutic target for the treatment of multiple myeloma [21]. SOD liposome/mimetics have experimentally shown promising results in cancer prevention in animal models. They have also been shown to be safe during the early phase of clinical trials. Dietary supplement-based SOD cancer prevention provides another opportunity for antioxidant-based cancer prevention[22].

B. SOD And Inflammatory Diseases

Neutrophils play a central and essential role in the pathogenesis of inflammation. Activated neutrophils adhere to vascular endothelium and transmigrate to the extravascular space, release ROS, protease enzyme and large amounts of chemokines [23]. ROS and proteases damage normal tissue and extracellular matrix proteins. O_2^-serves to activate endothelial cells and enhance neutrophil infiltration. Studies have shown that inhibition of O_2^- can prevent the infiltration of neutrophils at the site of damage [24]. SOD may serve as an inhibitory agent of neutrophil-mediated inflammation and may stand for a novel therapeutic approach for the ROS-dependent tissue damage induced by neutrophils through several mechanisms. Preclinical studies with bovine Cu/Zn-SOD showed encouraging results for its use as a human therapeutic agent in acute and chronic inflammatory conditions, including dematosis due to burn and wound injury [25].

C. SOD And Cystic Fibrosis (CF)

Cystic fibrosis is characterized by the chronic inflammation and the recruitment of activated neutrophils. In the plasma of patients with CF, SOD activity was significantly lower as compared with the healthy individuals [26]. It has been found that the antifibrotic action of Cu/Zn-SOD is mediated by TGF-β1 repression followed by phenotypic reversion of myofibroblasts. Radiation-induced fibrosis of breast was significantly reduced by Cu/Zn-SOD [27]. These findings indicate new therapeutic possibilities targeting antioxidant pathways including SOD, so that oxidative stress can be reduced in CF cells, and proinflammatory response can be limited.

D. SOD And Ischemia

ROS including O_2^- and its reaction product peroxynitrite has a significant role in endothelial and tissue injury associated with ischemia and reperfusion. Overexpression of Cu/Zn-SOD reduces ischemic damage resulting from ischemia/reperfusion [28].

E. SOD And Aging

SOD is considered to be an anti-aging enzyme. The free radical theory of aging was proposed by Derham Harman [29]. It is postulated that oxygen free radicals generated in metabolic pathways result in age-related deterioration through oxidative damage to biomolecules, with mitochondria being the main target of attack. Accumulation of oxidative damage is considered to be one of the key mechanisms of aging. It has been suggested that novel SOD mimetics may be useful in attenuating aging-induced cognitive impairments and other aspects of physiological decline with aging[30].

F. SOD And Rheumatoid Arthritis

Rheumatoid arthritis is a systemic disease and is characterized by a chronic inflammation reaction in the synovium of joints leading to degeneration of cartilage and erosion of juxta-articular bone.

It was found that SOD activity is less is low in patients suffering from rheumatoid arthritis and the administration SOD through liposomes had a positive effect in the treatment of experimental arthritis [31].

G. SOD And Neurodegenerative Diseases

Oxidative stress has been shown to be involved in the pathophysiology of several neurodegenerative diseases. The affected regions of patients having Alzheimer's disease (AD) have reduced activity of reduced activity of antioxidant enzymes such as SOD, catalase and glutathione peroxidase [32]. Several mutations in Cu/Zn-SOD gene are found to be associated with Familial Amyotrophic Lateral Sclerosis (FALS), which is a fatal neurodegenerative disease that leads to the selective loss of motor neurons [33]. It has been experimentally demonstrated that overexpression of SOD 2 reduces hippocampal superoxide and hence prevents memory deficits in a mouse model [34]. SOD/catalase mimetic EUK-207 exhibited protection against and interruption of progression of amyloid and tau pathology and cognitive decline in a mouse model of AD [35].

H. SOD And Diabetes

In diabetes, persistent hyperglycemia stimulates the production of ROS from various sources [36]. As a result, diabetes usually leads to increased formation of ROS and weakened antioxidant defenses [37]. Treatment with SOD has experimentally been shown to reduce liver oxidative stress in diabetic animals [38]. It has been demonstrated that extracellular SOD can act as a therapeutic agent to protect the progression of diabetic nephropathy [39].

I. Industrial And Cosmetic Applications Of SOD

SOD formulations are being used along with the production of tobacco based products to minimize the free radical damage that occurs in respiratory tract [40] and which can reduce the hangover after consumption of alcohol [41]. SOD plays an important role in pathogens to scavenge the extracellular ROS derived from the host defense mechanism. Due to this activity many research works have been carried out as a target for drugs to the host against the pathogens like Plasmodium falciparum [42], Brucella abortus, Schistosoma mansoni etc. The application of SOD extended to cosmetic and manufacturing other supplementary products to protect from free radical damages. Nelson [43] investigated and reported that SOD prolongs the survival of organs for transplantation. SOD is also used to develop biosensors to detect superoxide anions [44]. Studies also showed that SOD may reduce free radical damage to skin, for example to reduce fibrosis following radiation for breast cancer. Now a days the formulations of SOD are widely used commercially as moisturizes, sunscreens, skin-lightening creams, eye creams, nail polish and anti-hair fall sprays and available in prestigious brands such as such as Paula's Choice, Bioelements, Rachell Perry, Revitol Corporation, The Herbarie, Dabao Cosmetics Co. Ltd., Supplement Spot LLC, Nature's Drugstore, Avenue, Phytomer, Pevonia Botanica Skin Care and Estee Lauder [45]. SOD from marine source is being used in cosmetics by Loreal and different formulations and manufacturing processes were patented by the same company [46]. Various sources of SOD from both native and recombinant are now commercially available in the form of biochemical reagents from different companies such as Roche, Sigma, Wako, Jena, Bioscience, AMS Biotechnology Ltd., Worthington and Calzyme [47].

III. SOD-MODIFIED & IMMOBILIZED AND ITS ADVANTAGES

Enzymes are catalysts that catalyze many biochemical and chemical reactions. As these biocatalysts are present universally in plants and animals and due to their ease of production, substrate specificity and green chemistry they are widely used in diverse applications such as food industry, textile industry, health care & pharmaceuticals, chemical manufacturing and waste management. However, all these desirable characteristics of enzymes and their widespread industrial applications are often obstructed by their lack of long-term operational stability, shelf life and by their recovery and reusability. Enzyme modifications and immobilization are some of the strategies to overcome these problems. Compared to their free form, modified or immobilized enzymes are generally more stable and easier to handle. In addition, the reaction products are not contaminated with the enzyme which is useful in food and pharmaceutical applications

The administration of SOD it its free form has some disadvantages, most importantly, the low accumulation in inflamed areas due to its reduced half-life in the blood stream and its rapid renal excretion. To overcome this, SOD can be incorporated either in highly loaded conventional liposomes or long-circulating liposomes (PEG-liposomes). Many SOD mimetics have been synthesized that can be used as pharmaceutical agents in large number of diseases in which the native SOD is ineffective. Potent SOD mimetics such as metalloporphyrins, Mn cyclic polyamines, Mn salen derivatives, and nitroxides have been developed for treating various diseases resulting from increased oxidative stress [48].

Isocell Pharma has developed an oral supplement SOD product Glisodin in combination with Gliadin which not only prevent degradation of SOD in the gastrointestinal tract and also improved its uptake in intestine [49].

The characteristics of solid support (matrix) are important in determining the performance of the immobilized enzyme systems. Several natural polymer materials like cellulose, alginate, chitin, collagen, carrageenan, chitosan, starch etc are commonly used as support materials. Besides, natural polymers various synthetic polymeric materials are also used as support materials as they posses good mechanical stability, moreover they can be modified easily [50]. A variety of inorganic supports like alumina, silica, zeolites and mesoporous silicas are also used for immobilization of enzymes [51]. For therapeutical enzymes like SOD, nanoparticles act as very efficient support for immobilization, because of their ideal characteristics for balancing the key factors that determine biocatalysts efficiency [52]. Different techniques of immobilization of enzymes on nanoparticles are shown in Fig.4. Several techniques are developed to enhance the stability and cellular delivery ability of SOD such as PEGylation or encapsulating proteins in vesicles, liposomes and mesoporous nanoparticles (MSN).

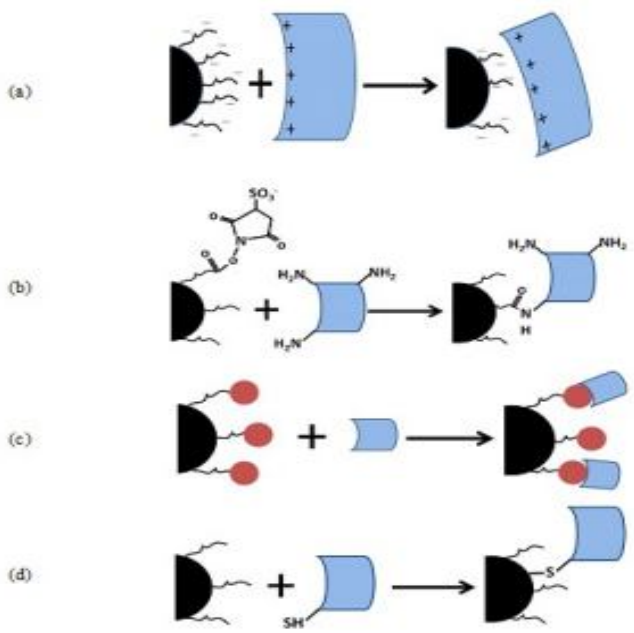

Figure 4: Approaches to link enzymes to nanoparticles: (a) Electrostatic adsorption
(b) Covalent attachment (c) Conjugation using specific affinity of protein
(d) Direct conjugation to the nanoparticles surface.

IV. CONCLUSIONS

SOD can be used as pharmaceutical in treating various diseases resulting from oxidative stress. SOD conjugates and mimetics have improved performance and overcome some of the limitations of the free enzyme. Antioxidant-based mimetics may potentially be the future of oxidative stress targeted therapies in chemoprevention. Immobilization process has been used for enhancing enzyme activity and stability in aqueous and non-aqueous media. Selecting and designing the support matrix are important in enzyme immobilization. Recently, the use of nanoparticles has emerged as a versatile tool for generating excellent support material for enzymes like SOD to increase the enzyme stability due to their small size and large surface area. The nanoparticles are key components in future for better performance of pharmaceutical enzymes like SOD.

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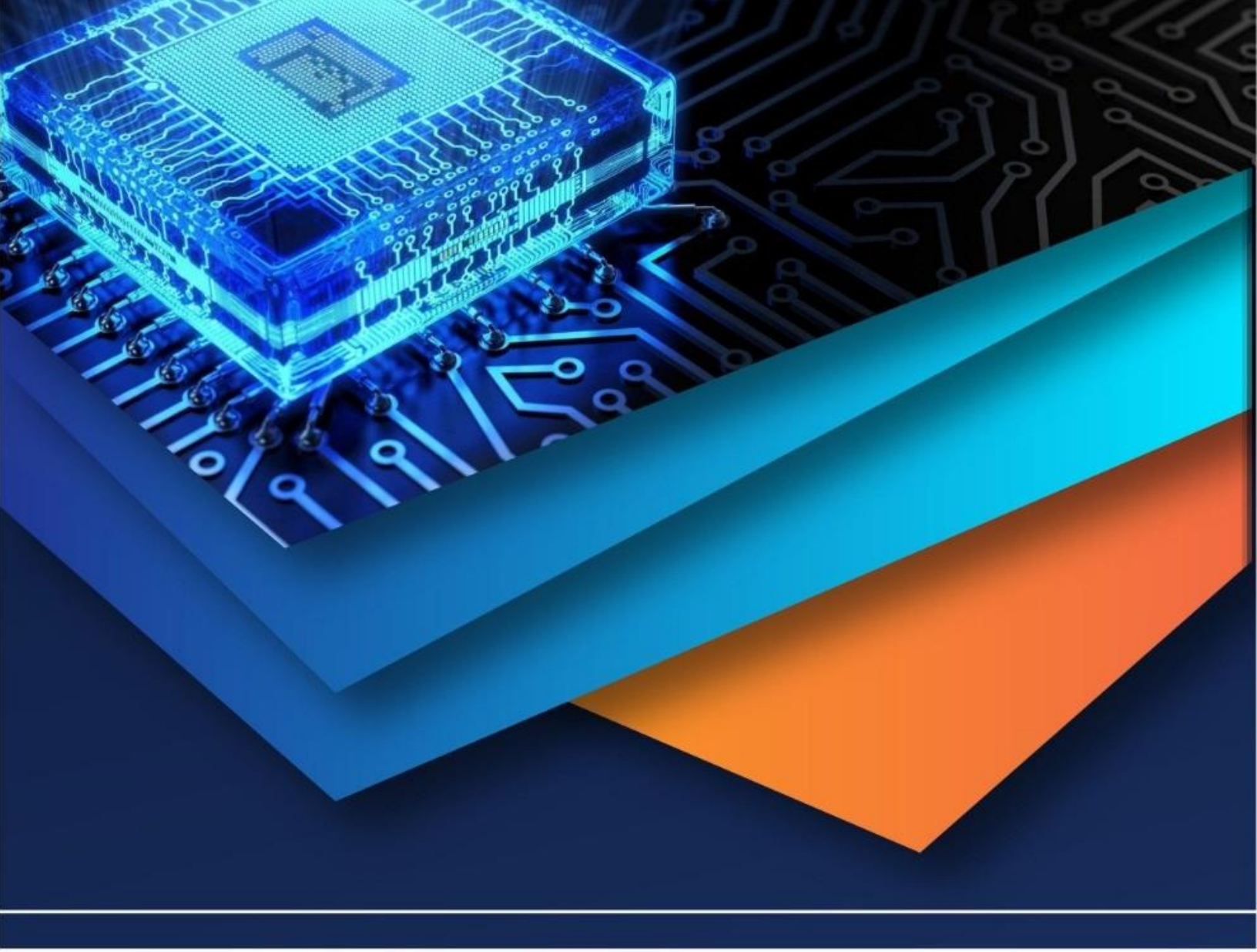

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