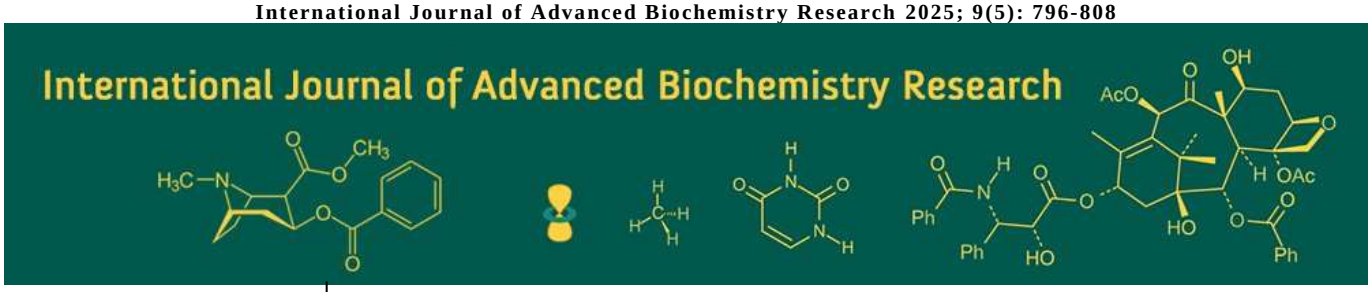

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Combating disease with diet: The role of antioxidants against reactive oxygen species

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Abstract
Reactive oxygen species (ROS) are highly reactive molecules that play a dual role in cellular physiology, acting as signaling molecules at low concentrations while contributing to oxidative stress and cellular damage at elevated levels. This review explores the formation, regulation, and biological effects of ROS, emphasizing their implications in various pathologies, including cancer, diabetes, and neurodegenerative diseases. Mitochondria and NADPH oxidases are identified as primary sources of ROS, with superoxide dismutase (SOD) and other antioxidant enzymes playing crucial roles in mitigating oxidative damage. The balance between ROS production and antioxidant defenses is critical for maintaining cellular homeostasis and preventing disease progression. Furthermore, the review discusses emerging therapeutic strategies aimed at modulating ROS levels, such as gene therapy, stem cell therapy, and personalized medicine approaches that tailor antioxidant treatments based on individual metabolic profiles. The potential of probiotics in reducing inflammation and oxidative stress in gastrointestinal disorders is also highlighted. Understanding the intricate relationship between ROS and cellular signaling pathways, particularly the NF-κB pathway, is essential for developing effective interventions against ROS-related diseases. This comprehensive overview underscores the importance of maintaining redox balance and presents avenues for future research focused on harnessing the beneficial aspects of ROS while minimizing their detrimental effects. Furthermore, this review provides a foundation for innovative therapeutic strategies targeting oxidative stress and its associated disorders by integrating knowledge from various fields, including molecular biology and clinical medicine.

Keywords: Reactive oxygen species, oxidative stress, antioxidants, disease pathogenesis, therapeutic strategies

1. Introduction
The human body is a complex entity composed of organs, systems, and various cellular responses that combine to fulfill specific functions necessary to sustain life (Grzegorz *et al*. 2024) [28]. Several types of reactive species participate in cellular responses and have attracted interest. These species are named according to the nature of reactive atoms such as oxygen (reactive oxygen species), nitrogen (reactive nitrogen species) or sulfur (reactive sulphur species) (Sies and Jones, 2020) [91]. Oxygen has a unique molecular structure (Fig.1) and is prevalent in cells. It readily accepts free electrons generated by normal oxidative metabolism within the cell, forming reactive oxygen species (ROS) (Richard and Davis, 2009) [82]. ROS are chemically reactive molecules containing oxygen that play a dual role in biological systems. These are molecules that contain at least one oxygen atom and exhibit greater reactivity compared to molecular oxygen and encompass both free radical species (such as singlet oxygen, hydroxyl radical, and superoxide) and non-radical species (such as hydrogen peroxide, H_2O_2) (Cheng; Rauf).

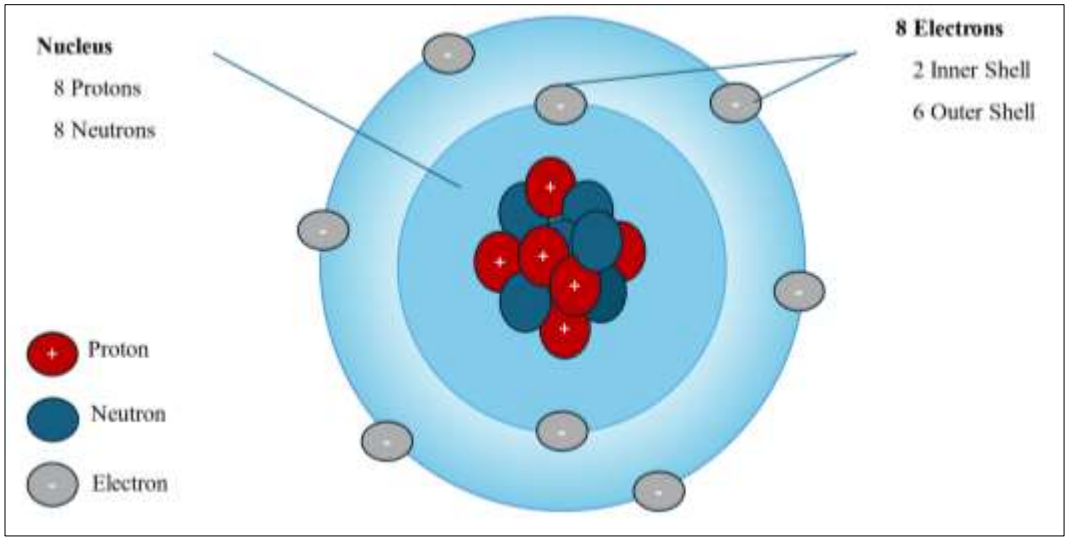

Fig 1: Oxygen atom

In physiological contexts, reactive oxygen species (ROS) are typically generated as a byproduct of normal cellular metabolism during oxidative reactions in the mitochondrial respiratory chain. Additionally, ROS are produced through various intra- and extracellular processes that regulate cellular homeostasis, including cell division, differentiation, and apoptosis. Elevated ROS levels can lead to cellular damage also activate specific signaling pathways involved in ROS scavenging to mitigate their detrimental effects. The balance between the generation of reactive oxygen species (ROS) and the antioxidant defense mechanisms is essential for preserving cellular homeostasis. Oxidative stress, stemming from an overabundance of ROS, is implicated in the pathogenesis of various diseases, including neurodegenerative disorders such as Alzheimer's (Czapski *et al.* 2016) [18] and Parkinson's diseases (Thomas *et al.* 2007) [98], cardiovascular diseases (Knock *et al.* 2019; Handy and Loscalzo, 2017) [50, 31] like atherosclerosis (Incalza *et al.* 2018) [38], cancer (Srinivas *et al.* 2019; Hemple and Trebak, 2017) [95, 33], diabetes, and inflammatory conditions (Lugrin *et al.* 2014; Tschopp, 2011) [58, 99]. ROS can instigate oxidative harm by interacting with cellular constituents, thereby disturbing normal cellular processes and advancing disease states. This review emphasizes the sources, pathways associated with the production of ROS, the role of antioxidants along the strategies for ROS management.

2. Sources and Production of ROS

Various cellular sources contribute to ROS generation. Sources can be either endogenous (produced within the body) or exogenous (Outside the body) (Schieber and Chandel, 2014) [86] Fig.2. These ROS molecules originate from oxygen which is utilized in various metabolic responses. Mitochondria are the primary cellular organelles responsible for ROS generation, particularly through the electron transport chain (ETC) embedded in the inner mitochondrial membrane during oxidative phosphorylation (OXPHOS) for ATP production (Liguori *et al.* 2018) [54]. Around 2% of the oxygen is utilized through mitochondria to generate O2-. Therefore, mitochondria are considered the utmost source of ROS (Phaniendra *et al.* 2015) [72]. To counteract the harmful effects of ROS, cells are equipped with antioxidant defense systems comprising enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, as well as non-enzymatic antioxidants like vitamins C and E, glutathione, and flavonoids (Brand, 2016) [12] (Fig.3).

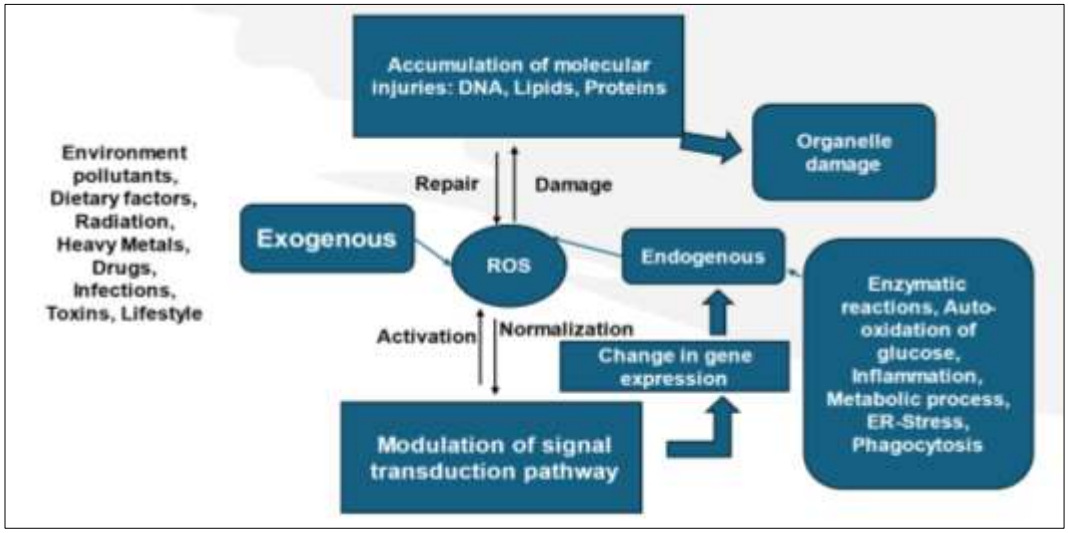

Fig 2: Sources and Production of ROS

3. Pathways associated with the production of ROS

Understanding the pathways through which ROS exert their effects and identifying potential inhibitors to regulate ROS levels are active areas of research in the field of oxidative stress biology. Targeting these pathways and developing effective ROS inhibitors shows potential for therapeutic interventions in diseases linked to oxidative stress. Researchers aim to uncover novel strategies by understanding the complex interaction between ROS and cellular signaling pathways, crucial for mitigating oxidative damage and maintaining cellular health.

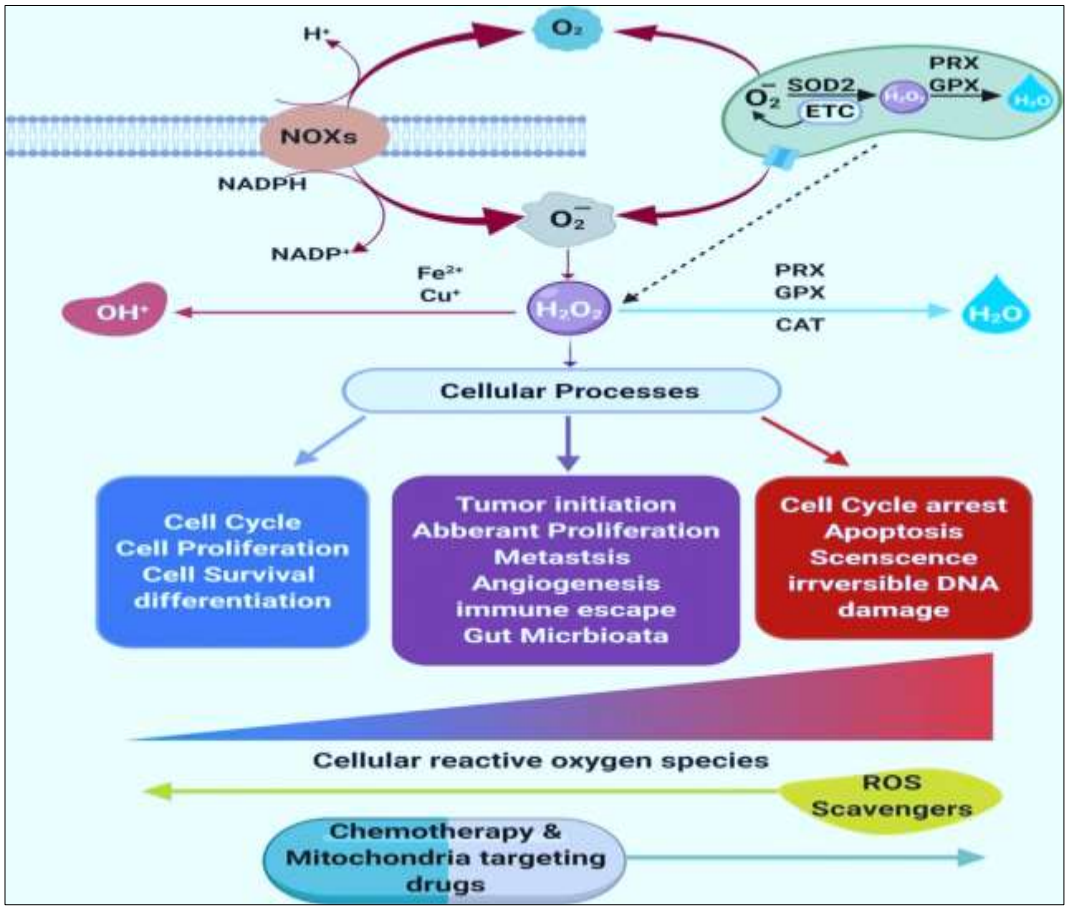

Fig 3: Generation and regulation of reactive oxygen species (ROS) and their impact on cellular functions.

Mitochondria and NADPH oxidases are primary sources of the formation of reactive oxygen species (ROS), including superoxide (O2−), hydroxyl radicals (HO•), and hydrogen peroxide (H2O2). Superoxide dismutase (SOD1 or SOD2) converts O2− into H2O2, which can then be converted into water (H2O) by peroxiredoxin (PRX), glutathione peroxidase (GPX), and catalase (CAT) in both mitochondria and cytosol. ROS are generated during normal cellular processes, with homeostasis maintained by cellular antioxidants. Low levels of ROS (green) are essential for maintaining normal cellular proliferation, survival, and differentiation. Moderate to high levels of ROS (light red) promote increased cellular proliferation, survival, tumor initiation, immune escape, genomic instability, metastasis, invasion, and angiogenesis. Extremely high levels of ROS (dark red), often induced by chemotherapeutic agents, are detrimental to cells, leading to cell cycle arrest, apoptosis, senescence, and irreparable DNA damage. (Kirtonia *et al.* 2020) [49].

3.1 Nuclear factor- Kappa B pathway

The nuclear factor-kappa B (NF-κB) pathway regulates various cellular processes, including inflammation, immunity, cell survival, and proliferation. In the context of reactive oxygen species (ROS), the NF-κB pathway plays a significant role in responding to oxidative stress and maintaining cellular homeostasis (Pajares *et al.* 2018) [68]. When cells are exposed to ROS, they activate signaling pathways that can activate NF-κB (Garda and Brink, 2014) [26] (Fig 4). ROS can directly influence the NF-κB pathway by modulating the activity of key proteins involved in its activation. This pathway is activated by two distinct pathways namely canonical and non-canonical pathways (Bonizzi and Karin, 2004) [9]. Non-canonical ROS can activate NF-κB through the phosphorylation of a protein called p65, which is a subunit of the NF-κB complex (Hayes *et al.* 2020) [32]. This phosphorylation event is essential for p65 to engage with other proteins and activate the transcription of specific genes involved in the cellular response to oxidative stress. On the other hand, NF-κB can also be inhibited by ROS under certain conditions (Khan *et al.* 2021) [47]. The relationship between ROS and NF-κB is complex and context-dependent, with ROS being able to both activate and inhibit NF-κB-mediated transcription (Vallabhapurapu and Karin, 2009) [102]. The balance between pro-inflammatory processes regulated by NF-κB and the antioxidative conditions within cells is crucial for maintaining cellular health and responding to oxidative stress effectively (Lingappan, 2018) [56]. Overall, the NF-κB ROS pathway represents a dynamic interplay between ROS

signaling and the cellular response mediated by NF-κB. Understanding how ROS influences the NF-κB pathway can provide insights into the mechanisms underlying oxidative stress-related diseases and potential therapeutic strategies for modulating NF-κB activity in response to ROS-induced damage (Morgan, 2011) [65].

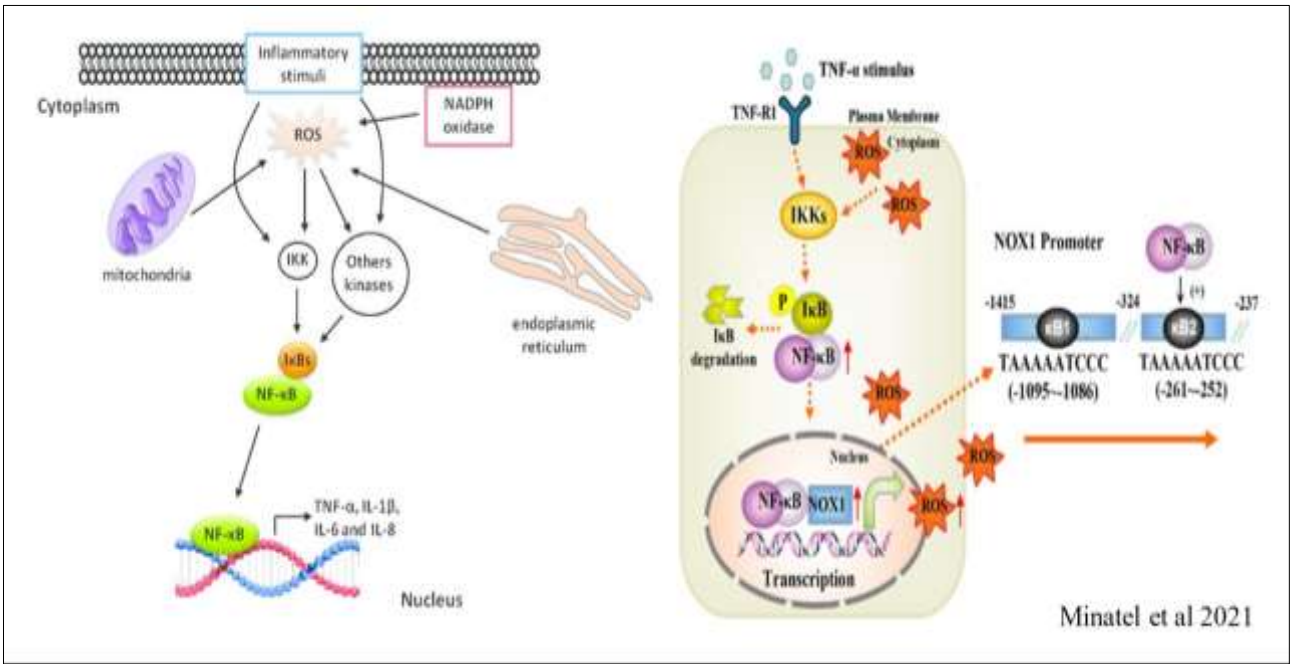

Fig 4a: Signaling Mechanism of ROS- Mediated Nuclear Factor Kappa-B (NF-kB) Activation. b. Mechanism of NF-kB activation by TNF-ά stimulus and translocated into the nucleus, binds to NOX1 promoter region and activates oxidative stress leading to inflammation and ROS production. (Wu and Li, 2021) [21].

3.2. MAPK`s Pathway

Mitogen-Activated Protein Kinases (MAPKs) pathway is a crucial signaling cascade that regulates various cellular processes in response to external stimuli, including stress, growth factors, and cytokines (Smalley, 2003) [92]. The MAPK pathway consists of a series of protein kinases that relay signals from the cell surface to the nucleus, ultimately leading to changes in gene expression and cellular responses (Sato *et al.* 2004) [84].

MAPK signaling pathway, also referred to as the Ras-Raf-ERK-MAPK pathway, comprises seven transduction families in mammals (Grosch *et al.* 2003) [27]. These families share a basic structure involving two serine/threonine kinases (Kanojia *et al.* 2017) [43] and one dual-specificity threonine/tyrosine kinase (Soh *et al.* 2000) [93]. ERK, a key member of the MAPK family which includes MEK1 and MEK2 genes, plays a pivotal role in signaling cascades, transmitting extracellular signals to intracellular targets (Kim *et al.* 2002) [48]. The MAPK signal transduction pathway is central to the regulation of cellular growth, development, and differentiation, and is crucial in processes such as cell proliferation, differentiation, apoptosis, and autophagy (Zhu *et al.* 2004) [119]. In eukaryotic cells, four main MAPK cascades have been identified: ERK, JNK/stress-activated protein kinase, p38 MAPK, and ERK5. Signal transmission in this pathway follows a three-stage enzyme-linked reaction involving MAP3K, MAP2K, and MAPK (Finlay *et al.* 2000) [23]. Within this pathway, Ras functions as an upstream activator, Raf as MAP3K, MEK as MAP2K, and ERK as MAPK, forming the Ras-Raf-MEK-ERK pathway (Hilger *et al.* 2002) [34]. Ras, the upstream protein of the Raf-MEK-ERK pathway, is a small G protein with an active GTP-bound form and an inactive GDP-bound form (Fan *et al.* 2019) [22]. It transmits signals by binding MAP3K and Raf kinases to the cell membrane, subsequently activating these kinases. The MAPK/ERK pathway conveys extracellular information from cell surface receptors to DNA in the nucleus (Cuadrado and Nebreda, 2010) [17]. Ligand binding to the dimer transmembrane tyrosine kinase receptor initiates intracellular signaling along the Ras-Raf-MEK-ERK pathway (Aggarwal *et al.* 2019) [2]. Activation of this cascade results in the phosphorylation of ERK1/2, leading to the transcriptional induction of target genes in the nucleus and cytoplasm (Sidhanth *et al.* 2018) [89] (Fig 5).

3.3 Phosphoinositide 3-kinase (PI3K)-Akt signaling pathway

The Phosphoinositide 3-kinase (PI3K)-Akt signaling pathway is a crucial intracellular signaling pathway that plays a fundamental role in regulating various cellular processes, including cell growth, proliferation, survival, and metabolism (Innocenti *et al.* 2003; Qiu *et al.* 2014) [39, 78]. In the context of ROS, the PI3K-Akt pathway interacts with ROS signaling through multiple mechanisms (Pimienta and Pascual, 2007) [73]. ROS can directly activate PI3K by oxidizing and inhibiting PTEN, a negative regulator of PI3K, thereby activating Akt. Akt, in turn, regulates cellular responses to oxidative stress by phosphorylating and modulating downstream targets involved in cell survival and apoptosis, such as BAD and FOXO transcription factors. Conversely, ROS can indirectly influence the PI3K-Akt pathway by activating signaling cascades like MAPK, which can interact with the PI3K-Akt pathway to regulate cell growth and proliferation in response to oxidative stress (Xu *et al.* 2023) [112]. Moreover, ROS-induced oxidative modifications of proteins within the PI3K-Akt pathway can affect its activity and downstream signaling (Wang *et al.* 2016) [105]. The interplay between ROS and the PI3K-Akt pathway is crucial for cellular adaptation to oxidative stress

(Sies and Jones, 2020) [91]. While moderate ROS levels can activate signaling pathways like PI3K-Akt to enhance cell survival and antioxidant defenses, excessive ROS production can overwhelm cellular antioxidant mechanisms, leading to oxidative damage (Almeida *et al.* 2020). Understanding the complex interactions between ROS and the PI3K-Akt pathway is essential for deciphering cellular responses to oxidative stress and how dysregulation of these pathways contributes to diseases such as cancer, neurodegenerative disorders, and metabolic conditions (Kerins and Ooi, 2018) [46]. Targeting components of the PI3K-Akt pathway and redox signaling presents potential therapeutic avenues for managing diseases associated with oxidative stress.

4. Reactive Oxygen Species (ROS) and Associated Diseases

ROS are essential for normal cellular functions, excessive ROS production can lead to oxidative stress, which is implicated in the pathogenesis of numerous diseases mainly due to three reasons: Lipid oxidation, protein damage, and DNA damage (Fig 6). The role of ROS in disease pathogenesis underscores the importance of maintaining redox balance within the body (Kirtonia *et al.* 2020) [49]. A few of the diseases along with the mechanisms is mentioned below.

a. Cancer: ROS are known to contribute to cancer development through several mechanisms. i) DNA Damage-High levels of ROS can cause oxidative DNA damage, leading to mutations and genomic instability, which are hallmarks of cancer (Karin, 2009; Uehara and Tanaka, 2018) [44, 101]. ii) Tumor Microenvironment-ROS can influence the tumor microenvironment by promoting inflammation and altering the behavior of immune cells, such as tumor-associated macrophages and myeloid-derived suppressor cells, which can enhance tumor growth and metastasis (Srinivas *et al.* 2019; Hempel and Trebak, 2017) [95, 33]. iii) Cell proliferation-ROS can activate signaling pathways that promote cell proliferation and survival, contributing to tumorigenesis (Salminen *et al.* 2019) [83].

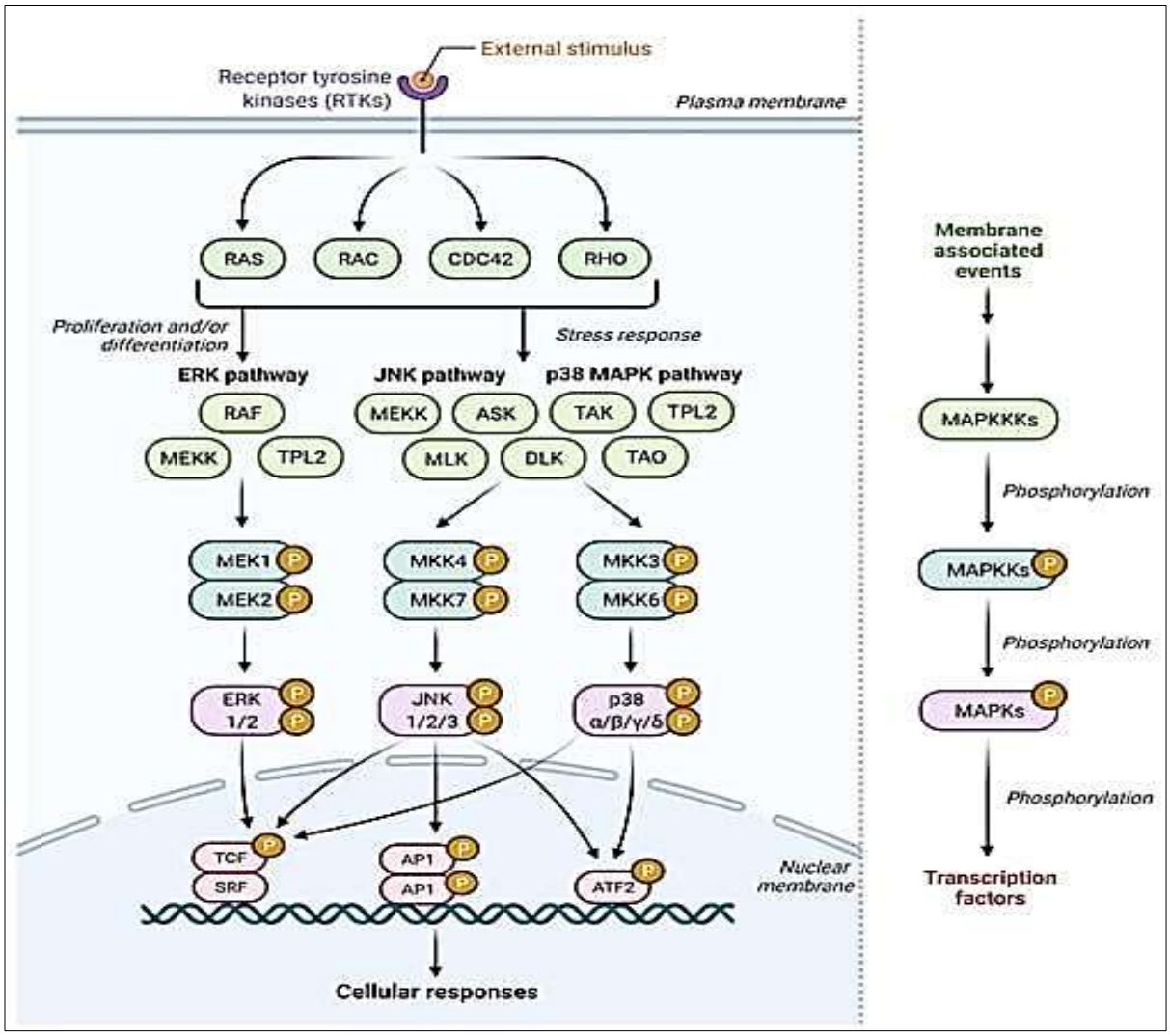

Fig 5: Activation of MAPK pathway. External stimulation activates three transcription factors through sequential protein phosphorylation and translocate to the nucleus leading to cellular response (Pua *et al.* 2022)

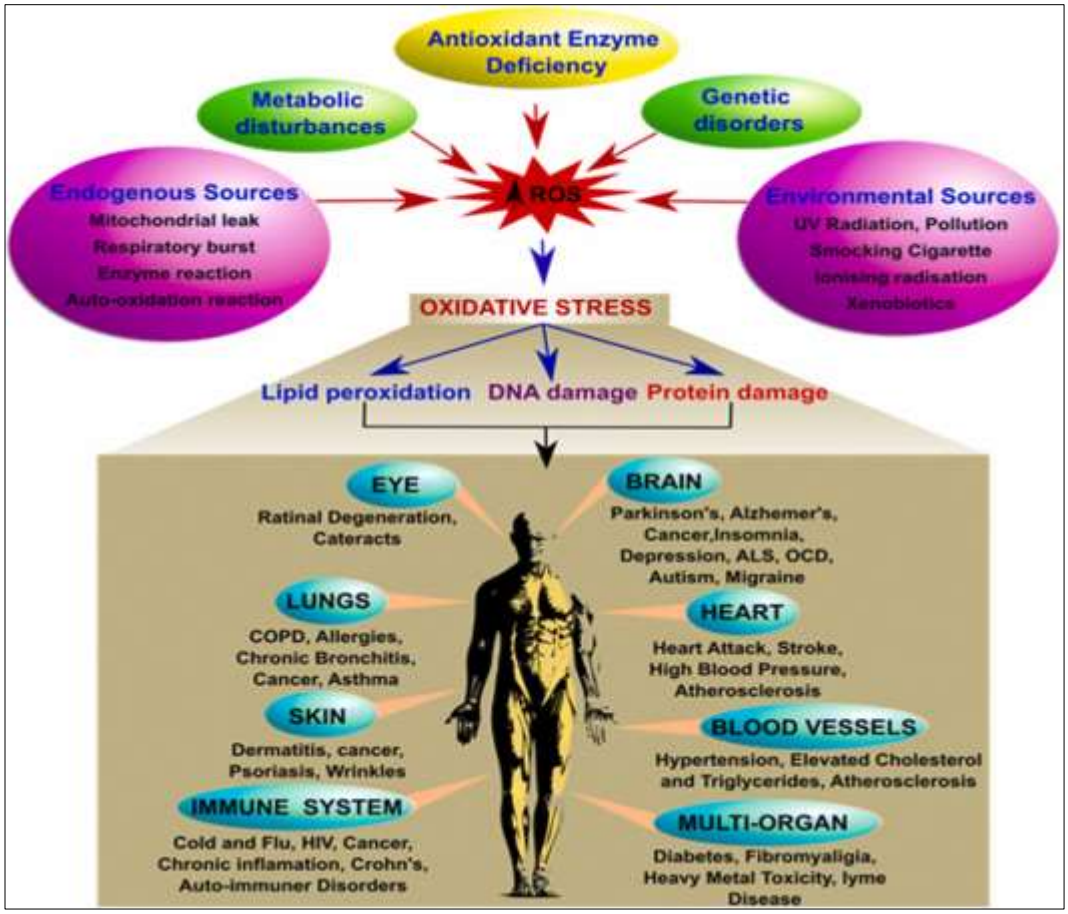

Fig 6: Effect of oxidative Stress on human Body (Atala *et al.* 2023)

b. Cardiovascular Diseases: Oxidative stress plays a critical role in the development of cardiovascular diseases: i. Endothelial Dysfunction- ROS can damage endothelial cells, leading to impaired vasodilation and increased vascular permeability, which are precursors to atherosclerosis. ii. Inflammation: ROS activate inflammatory pathways, resulting in the recruitment of immune cells to the vascular wall, further exacerbating atherosclerotic plaque formation (Puddu *et al.* 2005) [76]. iii. Myocardial Injury: In conditions such as ischemia-reperfusion injury, excessive ROS production can lead to cardiomyocyte death and heart failure (Wenzel *et al.* 2008) [106].

c. Neurodegenerative Disorders: ROS are implicated in the pathogenesis of several neurodegenerative diseases, including Alzheimer's and Parkinson's diseases (Qin *et al.* 2006) [77]: i. Oxidative Damage-Neurons are particularly vulnerable to oxidative stress due to their high metabolic activity and lipid-rich membranes (Tucci *et al.* 2012) [100]. ROS can damage proteins, lipids, and DNA, leading to neuronal dysfunction and death (Taradar and Pula, 2018) [97]. ii. Inflammation-ROS can activate microglia, the resident immune cells in the brain, leading to chronic neuroinflammation, which is associated with neurodegeneration (Sbodio *et al.* 2019) [85].

d. Diabetes: In diabetes, ROS contributes to various complications: a. Insulin Resistance-Elevated ROS levels can interfere with insulin signaling pathways, leading to insulin resistance and impaired glucose uptake (Panahi *et al.* 2017) [69]. B. Beta-Cell Dysfunction- Pancreatic beta cells are susceptible to oxidative stress, which can impair insulin secretion and exacerbate hyperglycemia (Yoon *et al.* 2006; Kanikarla and Jain, 2015) [113, 42]. C. Vascular Complications- ROS promotes endothelial dysfunction and inflammation, contributing to complications such as diabetic retinopathy (Rendra *et al.* 2019) [81], nephropathy (Volpe *et al.* 2018) [104], and neuropathy (Gandhi *et al.* 2014) [25].

e. Inflammatory Diseases: Chronic inflammation is often associated with increased ROS production. Inflammatory Bowel Disease (IBD)- In conditions like IBD, ROS can perpetuate inflammatory responses and contribute to tissue damage (Chong *et al.* 2017; Bourreille *et al.* 2013) [16, 11]. Rheumatoid Arthritis-ROS is involved in the activation of inflammatory pathways and the destruction of joint tissues (Escames *et al.* 2012; Lin *et al.* 2005) [20, 55].

f. Respiratory Disease: Oxidative stress is a key factor in respiratory diseases (Wyche *et al.* 2004) [111]. Chronic Obstructive Pulmonary Disease (COPD)- ROS contributes to airway inflammation, mucus hypersecretion, and lung tissue damage in COPD (Young *et al.* 2015) [114]. Asthma- Increased ROS levels can exacerbate airway hyperresponsiveness and inflammation in asthmatic patients Chio and Tuveson, 2017) [15].

5. Role of Antioxidant

Antioxidants act as radical scavengers, hydrogen donors, electron donors, peroxide decomposers, singlet oxygen quenchers, enzyme inhibitors, synergists, and metal-chelating agents and can neutralize oxidants and counteract

free radicals (Han *et al.* 2021) [30]. These can be categorized into exogenous and endogenous according to their source of production (Fig 7). Antioxidants regulate the level of reactive oxygen species (ROS) by influencing gene expression and related signalling pathways to uphold redox equilibrium and preserve cellular integrity. Consequently, therapeutic approaches targeting antioxidants present a promising strategy for preventing and managing diseases resulting from excessive ROS exposure (Shen *et al.* 2019) [88]. Role of dietary antioxidants on human diseases is mentioned in Table 1.

6. Strategies for ROS Management

It is crucial to follow management strategies for reactive oxygen species (ROS) to prevent oxidative stress and associated cellular damage that can disrupt normal cellular function and contribute to the development of various diseases. By managing ROS effectively, one can help maintain cellular health and mitigate the risk of oxidative damage-related diseases. Several strategies such as

Antioxidant therapy: Involves the use of substances like Vitamin C, Vitamin E, and glutathione to neutralize ROS, restore redox balance, protect cellular components from oxidative damage, and modulate inflammatory responses (Nishino *et al.* 2017) [67]. These therapies help prevent mutations and maintain cell membrane integrity, which are crucial for proper cell function (Kawata *et al.* 2018) [45]. They also enhance the body's antioxidant defenses, such as Nrf2 activators (Ismail *et al.* 2020) [40] and dietary antioxidants. Furthermore, antioxidant therapy can prevent disease progression by improving endothelial function, slowing the progression of neurodegenerative disorders, and reducing diabetes complications (Song *et al.* 2017) [94]. Further research is needed to explore the efficacy of antioxidant compounds and their potential clinical applications.

Lifestyle and Dietary Modifications: ROS can be managed through lifestyle and dietary modifications. A balanced diet rich in antioxidants, including fruits, vegetables, whole grains, nuts, and seeds, can help neutralize ROS and reduce oxidative stress (Martinez *et al.* 2005) [61]. Regular exercise can enhance antioxidant defences and prevent increased ROS production. Limiting exposure to environmental pollutants and toxins, such as pollution, tobacco smoking, and alcohol consumption, can also help lower ROS levels. Ensure adequate sleep, maintain a restful environment, and practice relaxation techniques to restore the body (Chainy and Sahoo, 2020) [13]. Stress management techniques like meditation and physical activity can help reduce stress levels and lower ROS production (Hosseini *et al.* 2020) [36]. Hydration is crucial for overall health and can help flush out toxins. Some dietary supplements, such as antioxidant supplements, may be beneficial, but consult a healthcare professional before starting. Hormesis, such as calorie restriction and intermittent fasting, can enhance antioxidant defenses and improve metabolic health, potentially reducing ROS levels. These strategies not only help manage ROS but also contribute to improved well-being and disease prevention (Ezerina *et al.* 2018) [21].

Pharmacological Interventions: Pharmaceutical interventions can help in mitigating oxidative stress-related damage. Strategies such as supplementations with antioxidants such as Coenzyme Q-10 Alpha-lipoic acid neutralize and reduce oxidative stress (Laleu *et al.* 2010) [52]. Mitochondrial-targeted antioxidant compounds such as Mito Q and SS-31, reduce ROS production. Anti-inflammatory medications reduce inflammation and indirectly reduce ROS production (Augsburger *et al.* 2019) [6].

Enhancing Endogenous antioxidant defenses: Nrf2 (Nuclear factor erythroid 2- related factor2) pathway plays a pivotal role in regulating the expression of antioxidant enzymes. (Zeng *et al.* 2019) [115] Activating this pathway can significantly boost the body`s endogenous antioxidant defenses. Sulforaphane found in cruciferous vegetables such as broccoli and brussels sprouts is a potent Nrf2 activator that enhances the expression of various antioxidant enzymes (Joo *et al.* 2016) [41]. Curcumin from turmeric has also been shown to activate the pathway leading to increased production of endogenous antioxidants (Kwon *et al.* 2017) [51]. Hormesis a mild stressor, such as caloric restriction or intermittent fasting, stimulates the body`s adaptive stress response, enhancing its antioxidant defences (Dao *et al.* 2020) [19].

Maintaining Mitochondrial Health: Mitochondrial biogenesis (production of new mitochondria) through exercise and calorie restriction can enhance cellular efficiency and reduce ROS production. Supplementing with nutrients like CoQ-10, carnitine and B vitamins improves mitochondrial health (Wind *et al.* 2010) [107].

Gene Therapy and Advanced Interventions: Gene editing, an emerging technology uses CRISPR (Clustered regularly interspaced short palindromic repeats) that allows for modification of the DNA and corrects genetic defects that produce excessive ROS (Perillo *et al.* 2020) [71]. Stem cell therapy is used to repair or replace damaged tissues and reduces oxidative stress in chronic diseases (Zhou *et al.* 2014) [117].

Monitoring and Diagnostics: Personalizing antioxidant therapies based on individual genetic and metabolic profiles can optimize ROS production. Regularly monitoring the oxidative stress biomarkers such as malondialdehyde and 8-oxo-dG can assist in evaluating the effectiveness of interventions.

By integrating these approaches, individuals can effectively manage ROS levels, mitigate oxidative stress, and reduce the susceptibility to ROS-associated diseases.

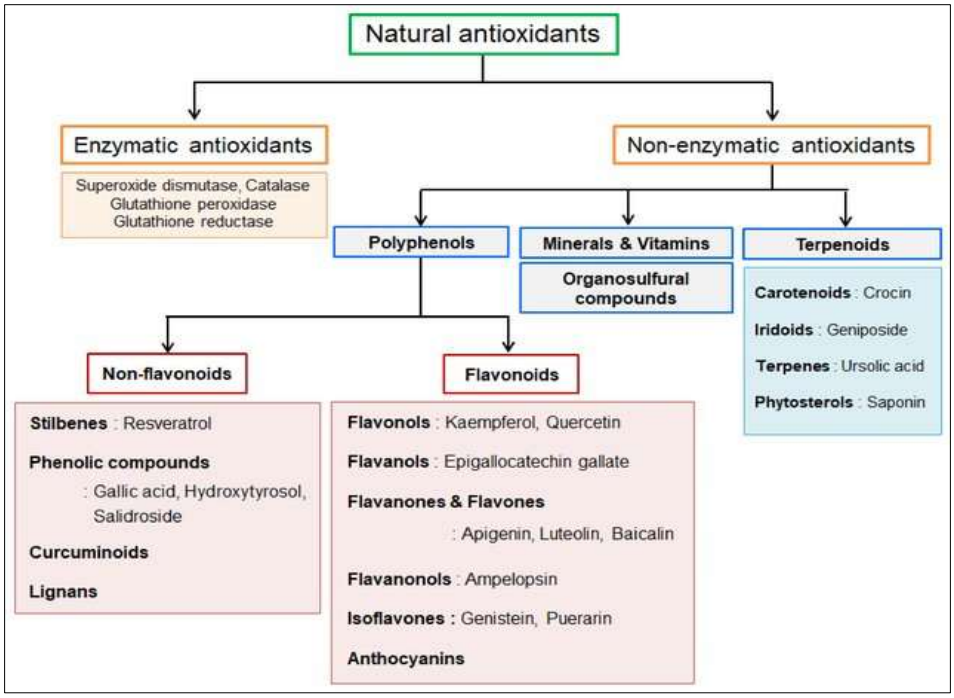

Fig 7: Classification of antioxidants based on the source of production (Lee and Im, 2021)

Table 1: Effect of antioxidants on diseases

Antioxidant	Dietary Source	Effect on diseases	References
Anthocyanin	Strawberries, Black rice	Reduced astrogliosis and maintained neuromuscular junctions and muscle function in ALS, prolonged lifespan in animal models.	Winter *et al.* 2017 Peng *et al.* 2014 [108, 70]
Lipoic acid	Muscle meats, kidney, liver, and heart	Shielded neurons from oxidative stress-induced mitochondrial dysfunction	Shay *et al.* 2009; Moreira *et al.* 2010; Zuo and Motherwell, 2013 [87, 64, 120]
Lycopene	Tomatoes, watermelon, papaya, apricot, and pink grapefruit	Enhanced clinical outcomes in asthma by reducing airway inflammation. Decreased LDL oxidation in the blood. Lycopene intake was negatively associated with the incidence of cardiovascular disease.	Wood *et al.* 2012 Rao and Agarwal 2000 [109, 79].
Melatonin	White mustard (seed), black mustard (seed), almond (seed), celery, walnuts, sweet corn, rice	Mitigated oxidative stress-related lung damage in respiratory diseases	Gumral *et al.* 2019; Bonnefont and Collin, 2010 [29, 10]
Phytochemicals	Fruits	Possibly prevent or postpone the onset of Parkinson's disease	Mazo *et al.* 2017 [62]
Polyphenols	Fruits, Vegetables, coffee, tea and Cereals	Increased intake of polyphenols was associated with a lower risk of cardiovascular disease. Exhibited anti-cancer effects against lung, breast, tongue, stomach, laryngeal, colon, and prostate cancers. Prolonged lifespan in animal models.	Vita, 2005 Manikandan *et al.* 2012. Ignarro *et al.* 2017; Peng *et al.* 2014 [103, 59, 37, 70].
Theaflavins	Black Tea	Increased longevity in animal models	Peng *et al.* 2014 [70]
Resveratrol	Purple wine and peanuts	Protected neurons against oxidative stress-induced toxicity	Anekonda, 2008; Bellaver *et al.* 2014 [4, 7]
Selenium	Tuna, oysters, salmon, eggs, green peas, pepper, onion, pork, Beef	A combination of selenium and vitamin E provided protection against oxidative damage in the colons of rats with ulcerative colitis.	Bitiren *et al.* 2010 [8]
Vitamin E	Wheatgerm oil, sunflower oil, hazelnut and almonds	Lowered the rates of cardiovascular disease-related mortality and non-fatal myocardial infarction. Mitigated functional decline related to Alzheimer's disease. A combination of vitamin E and coenzyme Q10 enhanced energy production in certain cases of Friedreich ataxia.	Navarro *et al.* 2008 [66]
Vitamin A	Eggs, dairy products, orange-colored fruits, green leafy and yellow-colored vegetables	Consumption of vitamins A and C was negatively correlated with the occurrence of asthma.	Tang *et al.* 2010; Allen *et al.* 2019 [96]
Vitamin C	Strawberry, Grapefruit, broccoli, and orange	Decreased airway inflammation and exercise-induced bronchoconstriction in asthma. Consumption of vitamins A and C was negatively correlated with the development of asthma.	Proteggente *et al.* 2002 [74]
Vitamin D	Fatty ocean fish, sunlight	Enhanced respiratory muscle function and exercise capacity in COPD. Boosted bone mineral density and lowered the risk of hip and other fractures in older adults.	Holick *et al.* 2011. Lips *et al.* 2020 [35, 57]

7. Conclusion

Reactive oxygen species (ROS) are highly reactive molecules that can cause oxidative stress, leading to cellular damage and contributing to various diseases, including neurodegenerative disorders, cardiovascular diseases, and cancer. The body has both endogenous and exogenous sources of ROS, and maintaining a balance between ROS production and antioxidant defenses is crucial for cellular health. Endogenous antioxidants, such as enzymes (e.g., superoxide dismutase, catalase, glutathione peroxidase) and non-enzymatic antioxidants (e.g., vitamins C and E, glutathione), play a vital role in neutralizing ROS. Strategies to enhance these defenses include activating the Nrf2 pathway, consuming a balanced diet rich in antioxidants, engaging in regular moderate exercise, ensuring adequate sleep, and utilizing pharmacological agents like N-acetylcysteine (NAC) to boost glutathione levels. Additionally, mild stressors such as caloric restriction and intermittent fasting can stimulate the body's adaptive stress response, further enhancing antioxidant defenses.

Enhancing endogenous antioxidant defenses is essential for managing ROS and preventing oxidative stress-related cellular damage. Individuals can significantly improve their body's ability to counteract oxidative stress by adopting dietary modifications, lifestyle changes, and pharmacological interventions. This proactive approach helps reduce the risk of various diseases and promotes overall health and longevity. Continued research into effective strategies for boosting antioxidant defenses will be crucial in developing therapeutic interventions for oxidative stress-related conditions.

Credit authorship contribution statement

Cherukuri Anusha: Writing original draft, conceptualization, review & editing. Manisha Patil: Writing, reviewing, and editing. Renuka Aggarwal: Reviewing and Supervision. Kiran Grover: Supervision and Conceptualization.

Ethical Approval

There was no need for ethical approval as this was a literature paper and the data used was already available to the public.

Consent for Publication

We have given the journal the right to publish this work.

Declaration of conflicting interests

The author (s) declared no potential conflicts of interest for the research, authorship, and/or publication of this article.

Data Availability statement

Since the study was a literature review, all the articles used in the study can be accessed online.

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