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# Oxidative Stress Lipid Peroxidation and Cell Death Pathways: A Survey

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## Abstract

This survey paper provides a comprehensive analysis of the interconnected biological processes involving oxidative stress, lipid peroxidation, and cell death pathways, emphasizing their significance in cellular damage and disease progression. The paper begins with an exploration of oxidative stress, defined by an imbalance between reactive oxygen species (ROS) and antioxidants, and its implications for cellular components and diseases such as neurodegenerative disorders, cancer, and cardiovascular diseases. Lipid peroxidation, a critical consequence of oxidative stress, is examined for its role in disrupting membrane integrity and contributing to regulated cell death pathways like ferroptosis. The survey further delves into various cell death modalities, including apoptosis, necroptosis, and pyroptosis, highlighting their distinct mechanisms and roles in maintaining cellular homeostasis and responding to pathological stimuli. The interconnections between these processes are analyzed for their implications in disease pathophysiology, with a focus on potential therapeutic targets and interventions. The paper suggests novel diagnostic and therapeutic approaches, such as the modulation of ferroptosis and the use of antioxidants, to mitigate oxidative stress-related damage. Concluding with a synthesis of key findings, the survey underscores the importance of understanding these processes for developing targeted strategies to improve health outcomes across diverse pathological contexts.

## 1 Introduction

### 1.1 Structure of the Survey

This survey is structured to provide a thorough examination of the interconnected biological processes of oxidative stress, lipid peroxidation, and cell death pathways. It begins with an **Introduction** that outlines the significance of these processes in cellular damage and disease progression. The subsequent **Background** section explores fundamental aspects of oxidative stress, lipid peroxidation, and cell death pathways, emphasizing their biological relevance and interconnections, including the roles of free radicals and antioxidants in cellular homeostasis [1].

The survey then details **Oxidative Stress**, defining its mechanisms, causes, and effects on cellular components, while highlighting diseases linked to oxidative stress, as noted by [2] and [3]. The next section, **Lipid Peroxidation**, discusses the mechanisms involved, its role in cellular damage, and implications in disease contexts, including ferroptosis.

Following this, the survey examines **Cell Death Pathways**, providing an overview of various pathways such as apoptosis and necrosis, with a focus on how oxidative stress and lipid peroxidation induce cell death. This section also investigates regulated cell death pathways and their potential impact on disease progression.

In the **Interconnections and Implications** section, the survey analyzes the relationships between oxidative stress, lipid peroxidation, and cell death pathways, emphasizing their implications for

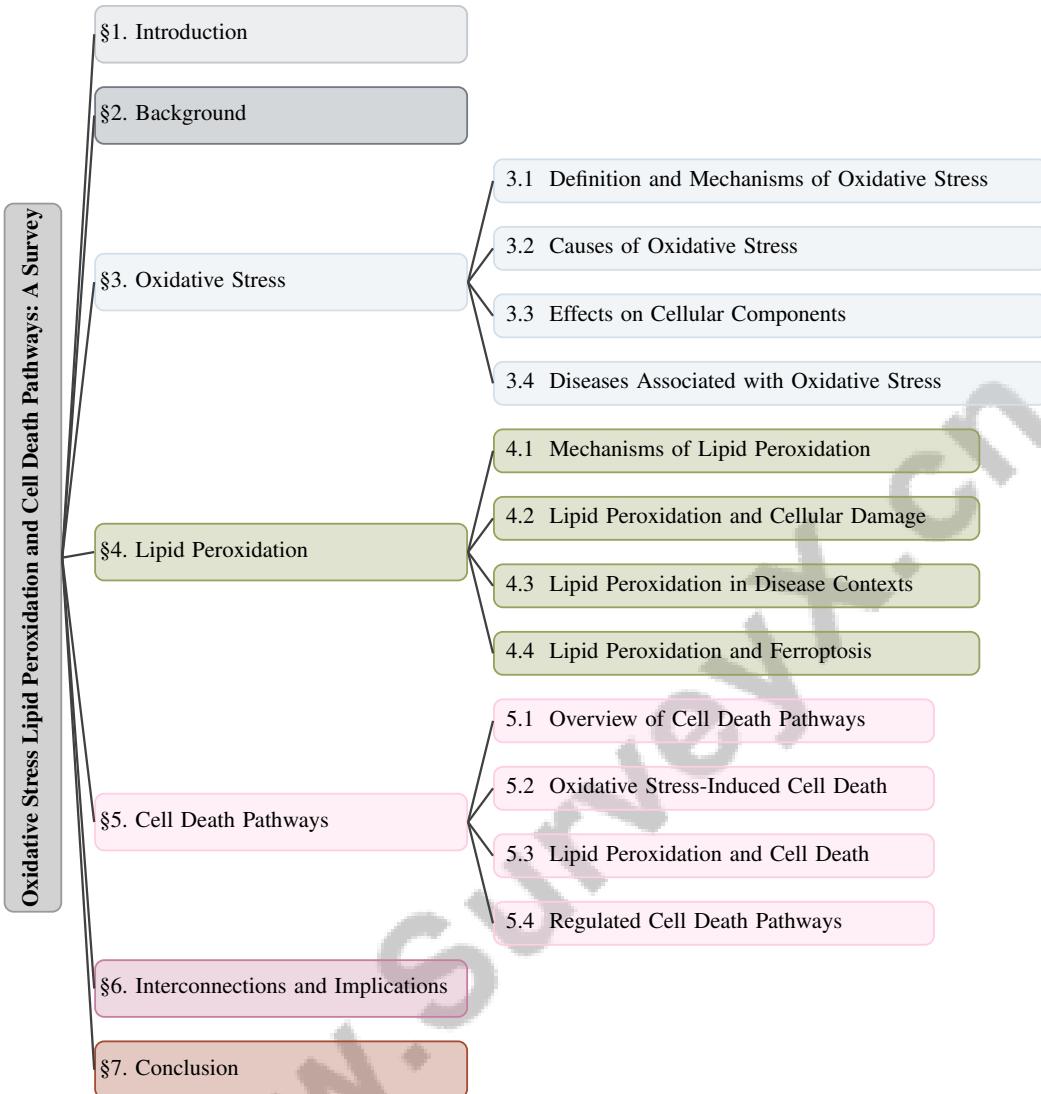


Figure 1: chapter structure

disease pathophysiology and progression. It explores potential therapeutic targets and interventions, alongside innovative diagnostic and therapeutic approaches [4, 5].

The survey concludes with a comprehensive **Conclusion** that synthesizes key points, highlighting the critical roles of oxidative stress and protein aggregation in disease progression, particularly in neurodegenerative disorders like Parkinson's disease. It underscores the importance of understanding these biological processes for developing potential therapeutic strategies, including targeted interventions to mitigate lipid peroxidation and restore normal cellular functions [2, 6]. The following sections are organized as shown in Figure 1.

## 2 Background

### 2.1 Role of Free Radicals and Antioxidants in Cellular Homeostasis

Maintaining cellular homeostasis requires a delicate balance between reactive oxygen species (ROS) and antioxidants. ROS, often generated during normal metabolic processes, are typically counteracted by antioxidants. However, excessive ROS can surpass antioxidant defenses, resulting in oxidative stress that damages lipids, proteins, and nucleic acids [7]. This imbalance is associated with various pathological conditions, highlighting the importance of effective antioxidant systems.

Antioxidants not only neutralize free radicals but also bolster endogenous defense mechanisms. Compounds such as 'Sylimevit' have shown effectiveness in reducing oxidative stress in biological systems [8]. Additionally, antioxidants influence cellular signaling pathways, affecting redox homeostasis and modulating oxidative stress responses. Toll-like receptors (TLRs) play a significant role in the interaction between pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), illustrating the intricate link between oxidative stress and inflammation [9].

The relationship between oxidative stress and cellular homeostasis is further influenced by factors like chirality, which impacts energy transfer efficiency in photosynthetic complexes, suggesting that structural dynamics can affect oxidative stress responses [10]. Moreover, the low sensitivity of current diagnostic methods for conditions such as myasthenia gravis complicates the management of oxidative stress-related diseases, underscoring the need for enhanced diagnostic techniques [5].

### 3 Oxidative Stress

In order to comprehensively understand the implications of oxidative stress, it is essential to first define the phenomenon and explore the underlying mechanisms that contribute to its occurrence. This foundational knowledge will provide insight into how oxidative stress disrupts cellular homeostasis and contributes to various health conditions. As depicted in Figure 2, this figure illustrates the hierarchical structure of oxidative stress, detailing its definition, mechanisms, causes, effects on cellular components, and associated diseases. It emphasizes the production of reactive oxygen species (ROS), their impact on lipids, proteins, and DNA, and their role in various diseases, highlighting the complexity and significance of oxidative stress in health and disease management. The subsequent subsection will delve into the definition and mechanisms of oxidative stress, elucidating its role in cellular dysfunction and the intricate interplay of biological systems involved in this process.

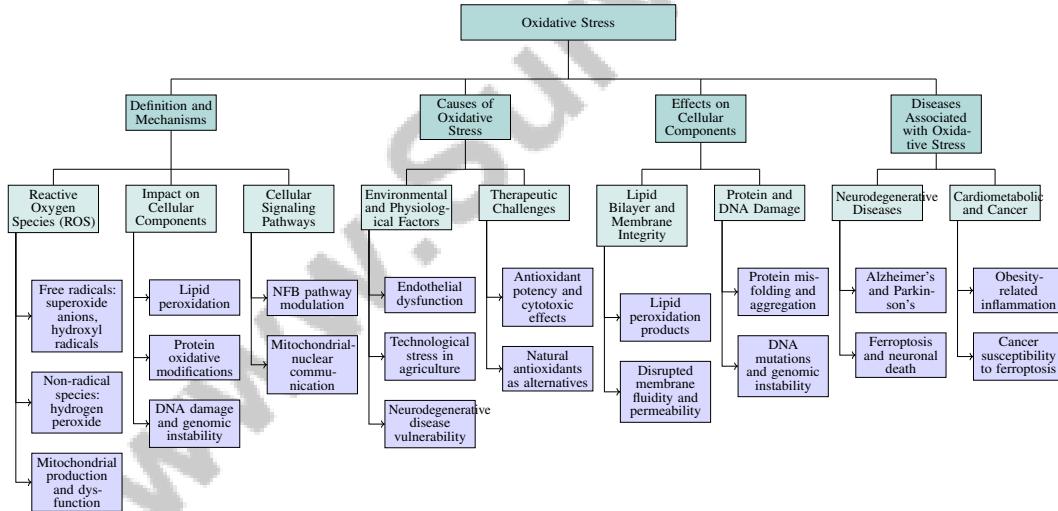


Figure 2: This figure illustrates the hierarchical structure of oxidative stress, detailing its definition, mechanisms, causes, effects on cellular components, and associated diseases. It emphasizes the production of reactive oxygen species (ROS), their impact on lipids, proteins, and DNA, and their role in various diseases, highlighting the complexity and significance of oxidative stress in health and disease management.

#### 3.1 Definition and Mechanisms of Oxidative Stress

Oxidative stress is defined as a state where the production of reactive oxygen species (ROS) surpasses the capacity of biological systems to detoxify these reactive intermediates or to repair the resulting damage. This imbalance is crucial in altering cellular functions and structures, thereby influencing health and disease dynamics [11]. The mechanisms of oxidative stress are complex, involving the interaction of various cellular components and signaling pathways.

The generation of ROS, including free radicals like superoxide anions and hydroxyl radicals, as well as non-radical species such as hydrogen peroxide, is central to oxidative stress. These ROS are predominantly produced in mitochondria, where they can disrupt electron transport chains, leading to mitochondrial dysfunction. The mitochondrial dynamics, particularly fission and fusion processes, are critical in understanding oxidative stress mechanisms, as they affect mitochondrial network complexity and cellular responses [12]. Furthermore, mitochondrial-nuclear communication pathways play a significant role in regulating nuclear transcription in response to mitochondrial stress, emphasizing the intricate interplay between cellular organelles [13].

The impact of oxidative stress extends to various cellular components, including lipids, proteins, and DNA. Lipid peroxidation, for example, disrupts lipid homeostasis and affects cell viability by altering lipid compositions, potentially leading to regulated cell death [14]. Proteins undergo oxidative modifications, resulting in altered function and aggregation, as demonstrated by proteomic changes in response to oxidative stress [2]. Additionally, oxidative stress can induce DNA damage, contributing to mutations and genomic instability. Advanced techniques such as Surface Enhanced Raman Spectroscopy (SERS) have been utilized to detect and quantify oxidized nucleotides, providing insights into molecular damage during oxidative stress [5].

Oxidative stress also plays a dual role in cellular signaling pathways, notably influencing the activation or inhibition of the NFB pathway, which is vital for mediating cellular responses to stress [15]. The modulation of this pathway underscores the complexity of oxidative stress as both a signaling and damaging entity. Moreover, the challenges in understanding how ROS mediate lipid accumulation in oleaginous microorganisms under environmental stresses highlight the intricate roles of ROS in cellular processes [16]. The difficulties in measuring ROS and the inconsistent correlations between oxidative stress and pathological states further complicate the understanding of oxidative stress [3].

Oxidative stress is a critical process in cellular physiology and pathology, characterized by an imbalance between reactive oxygen species (ROS) and antioxidants, leading to disruptions in redox signaling and cellular homeostasis. This phenomenon arises from the excessive production of ROS, which can overwhelm the antioxidant defense mechanisms, resulting in molecular damage across various biomolecular classes, including proteins, lipids, carbohydrates, and DNA. The brain, due to its high oxygen consumption and lipid-rich composition, is particularly vulnerable to oxidative stress, which is implicated in numerous neurodegenerative diseases and can significantly impair neuronal function and plasticity. Understanding the intricate dynamics of oxidative stress is essential for elucidating its role in health and disease, as well as for developing potential therapeutic strategies. [2, 17, 18, 11]. Understanding the mechanisms of oxidative stress is essential for developing strategies to mitigate its detrimental effects and improve health outcomes.

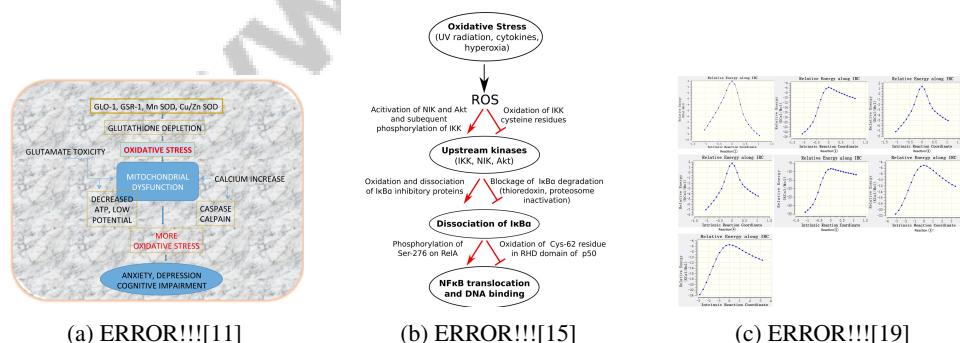


Figure 3: Examples of Definition and Mechanisms of Oxidative Stress

As shown in Figure 3, Oxidative stress is a pivotal concept in understanding the imbalance between the production of free radicals and the ability of the body to counteract their harmful effects through neutralization by antioxidants. This phenomenon is integral to the pathophysiology of numerous diseases and aging processes. The accompanying figure illustrates various definitions and mechanisms underlying oxidative stress, drawing from multiple sources to provide a comprehensive overview. The subfigures, though currently marked with errors, are intended to visually represent the complex interplay of factors involved in oxidative stress, as cited from recent studies. This example aims to elucidate the multifaceted nature of oxidative stress, highlighting its

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significance in scientific research and its implications for health and disease management. [? Jsalim2017oxidative,lingappan2018nf,cao2024study)

### 3.2 Causes of Oxidative Stress

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defenses of biological systems, leading to potential cellular damage. Various factors contribute to this imbalance, including environmental, physiological, and pathological conditions. Endothelial dysfunction, for instance, is intricately linked with systemic inflammation and oxidative stress, posing significant challenges in understanding the complex interactions involved [20]. This complexity is further exemplified by the increase in lipid peroxidation processes observed in piglets subjected to technological stress from early weaning, highlighting the role of stress-induced oxidative mechanisms in agricultural settings [8].

As illustrated in Figure 4, the causes of oxidative stress can be categorized into environmental and physiological factors, health and disease implications, and therapeutic approaches. This figure highlights key contributors to oxidative stress, such as endothelial dysfunction and technological stress, as well as its impact on diseases like neurodegenerative and reproductive health issues, and potential therapeutic strategies involving natural antioxidants.

In the brain, high oxygen consumption and a lipid-rich environment render it particularly vulnerable to oxidative damage, which can impair central nervous system functions. This vulnerability is evident in neurodegenerative diseases such as Alzheimer's, where oxidative stress contributes to disease progression and current treatments fail to adequately mitigate oxidative damage. This underscores the need for novel therapeutic compounds that can effectively address oxidative stress in neurodegenerative contexts [21]. Similarly, oxidative stress is a significant factor in reproductive health, where the interplay between oxidative stress and sperm DNA damage presents measurement challenges, complicating our understanding of its impacts [22].

In agriculture, oxidative stress can severely affect plant growth and yield. For instance, tomato plants under heat stress experience disrupted photosynthesis and exacerbated oxidative damage, illustrating the broader ecological implications of oxidative stress [23]. The variability in oxidative stress markers across different ecological conditions further complicates the interpretation of oxidative stress benchmarks, potentially leading to misinterpretations [24].

The therapeutic potential of antioxidants is often limited by their potency and potential cytotoxic effects, posing challenges in effectively mitigating oxidative stress. However, natural antioxidants, such as phenolic compounds from *Suillus* sp, offer a promising alternative to synthetic compounds, providing a potential avenue for addressing oxidative stress through natural means [25]. In neurological disorders like Parkinson's disease, energy deficiency and excitotoxicity, exacerbated by oxidative stress, are central to levodopa-induced toxicity in neurons [26].

These diverse causes of oxidative stress underscore its multifaceted nature and the need for comprehensive strategies to manage its impact on cellular health. A comprehensive understanding of the multifaceted factors contributing to oxidative stress is essential for the development of targeted interventions aimed at mitigating oxidative damage, particularly in neurodegenerative diseases and other oxidative stress-related conditions. This knowledge can enhance clinical outcomes by addressing the underlying biochemical mechanisms, such as the imbalance between reactive oxygen species and antioxidants, which plays a critical role in cellular dysfunction and disease progression [3, 2, 18, 17, 11].

### 3.3 Effects on Cellular Components

Oxidative stress exerts profound effects on various cellular components, leading to structural and functional alterations that compromise cellular integrity. One of the primary targets of oxidative stress is the lipid bilayer of cell membranes, where the accumulation of reactive oxygen species (ROS) initiates lipid peroxidation. This process results in the formation of lipid peroxidation products, which disrupt membrane fluidity and permeability, ultimately compromising membrane integrity and cell viability [27].

The impact of oxidative stress is particularly evident in the context of heat stress, where the excessive accumulation of ROS damages chloroplasts, impairing the photosynthetic process in plants. This

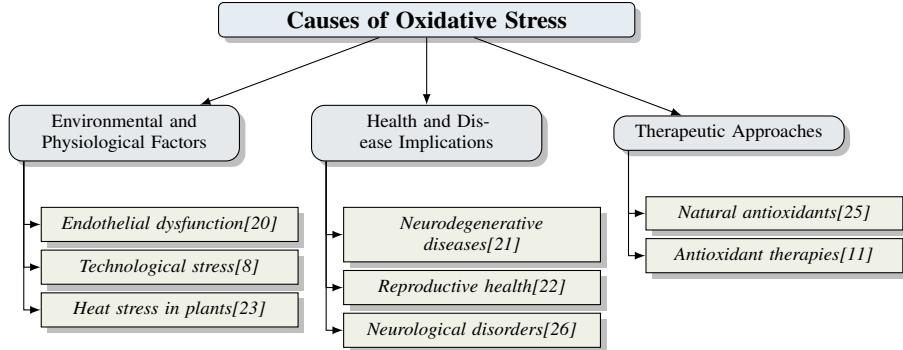


Figure 4: This figure illustrates the causes of oxidative stress, categorized into environmental and physiological factors, health and disease implications, and therapeutic approaches. It highlights key contributors to oxidative stress, such as endothelial dysfunction and technological stress, its impact on diseases like neurodegenerative and reproductive health issues, and potential therapeutic strategies involving natural antioxidants.

impairment is critical, as it affects the plant's ability to convert light energy into chemical energy, thus hindering growth and productivity [23]. In the animal kingdom, oxidative stress contributes to the pathophysiology of neurological disorders such as migraines. The desensitization or excessive activation of the sympathetic nervous system (SNS) leads to hyperexcitability of baroreceptors, which in turn triggers oxidative stress and activates pain pathways, exacerbating migraine symptoms [28].

Proteins are also susceptible to oxidative modifications, which can alter their structure and function. These modifications may lead to protein misfolding, aggregation, and degradation, thereby affecting cellular processes such as enzyme activity and signal transduction. The damage inflicted on cellular proteins by oxidative stress highlights the critical necessity for robust proteostasis mechanisms, which are vital for preserving cellular homeostasis and mitigating the molecular alterations caused by oxidative imbalances, as evidenced by recent advancements in proteomic studies that reveal the extensive impact of oxidative stress on protein expression and modifications. [2, 17]

Moreover, oxidative stress can induce DNA damage, resulting in mutations and genomic instability. The oxidative modifications of nucleic acids can interfere with replication and transcription processes, potentially leading to carcinogenesis and other genetic disorders. The complex relationship between oxidative stress and cellular components underscores the critical need for effective antioxidant defenses. These defenses are essential to counteract the harmful effects of reactive oxygen species (ROS), which, when produced in excess, can lead to significant molecular damage across various cellular structures, including proteins, lipids, carbohydrates, and DNA. Maintaining a delicate balance between oxidants and antioxidants is vital for preserving cellular function and preventing the biochemical impairments associated with oxidative stress, particularly in vulnerable tissues such as the brain, which is highly susceptible to oxidative damage due to its high oxygen consumption and lipid-rich composition. [17, 11]

### 3.4 Diseases Associated with Oxidative Stress

Oxidative stress is implicated in a myriad of diseases, where the imbalance between reactive oxygen species (ROS) production and antioxidant defenses leads to cellular damage and dysfunction. Neurodegenerative diseases, such as Alzheimer's and Parkinson's, are prominently associated with oxidative stress, as evidenced by literature correlating oxidative damage with these conditions [18]. In Parkinson's disease, ferroptosis driven by alpha-synuclein aggregation contributes to neuronal death, highlighting the role of oxidative stress in disease pathogenesis [6].

Cardiometabolic diseases, including obesity-related inflammation, are significantly influenced by oxidative stress. The ineffective treatment options for NLRP3-related inflammation underscore the need for novel therapeutic strategies to mitigate oxidative damage in metabolic dysfunction [29]. In connective tissues, collagen mechanoradicals generated under mechanical load serve as a source of oxidative stress, linking mechanical stress to redox processes and tissue damage [30].

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The role of oxidative stress extends to cancer, where the regulation of ferroptosis—a form of regulated cell death—is not fully understood. The variability in cancer susceptibility to ferroptosis presents challenges in therapeutic targeting, necessitating further exploration of the molecular mechanisms involved. Furthermore, proteomic studies have identified oxidative modifications that affect cellular functions, providing insights into the proteotoxic stress associated with cancer progression [2].

In the context of metal-induced toxicity, silver nanoparticles (AgNPs) and silver ions (Ag<sup>+</sup>) demonstrate distinct pathways of oxidative stress-induced cell death. AgNPs primarily cause necrotic cell death via lipid peroxidation, while Ag<sup>+</sup> induces apoptosis through hydrogen peroxide-mediated oxidative stress [31]. These findings highlight the diverse mechanisms by which oxidative stress contributes to disease pathology across different biological systems. Understanding these mechanisms is crucial for developing targeted interventions to mitigate the impact of oxidative stress in various diseases.

## 4 Lipid Peroxidation

Lipid peroxidation is a critical aspect of oxidative stress, significantly impacting cellular integrity and function. This process involves the oxidative degradation of lipids, particularly polyunsaturated fatty acids (PUFAs), leading to a cascade of reactions that can result in cellular damage and disease progression. Understanding the mechanisms of lipid peroxidation is essential for elucidating its role in various biological contexts. The following subsection delves into the intricate biochemical pathways of lipid peroxidation and their implications for cellular health.

### 4.1 Mechanisms of Lipid Peroxidation

Lipid peroxidation is characterized by the oxidative degradation of lipids, primarily targeting PUFAs within cellular membranes. It is initiated by reactive oxygen species (ROS), such as hydroxyl and carbonate radicals, which abstract hydrogen atoms from PUFAs, forming lipid radicals. These radicals subsequently react with molecular oxygen to generate peroxy radicals, propagating a chain reaction that produces lipid hydroperoxides. Recent studies indicate that carbonate radicals, which can form rapidly from hydroxyl radicals in biological systems, exhibit heightened reactivity towards PUFAs, particularly through hydrogen abstraction from diallyl carbon atoms. This understanding emphasizes the complex interplay between various ROS in mediating lipid peroxidation and its implications for cellular damage and neurodegenerative diseases like Parkinson's disease [32, 17, 6, 19].

NADPH oxidase enzymatic activity is closely linked to lipid peroxidation initiation, significantly contributing to ROS production. Additionally, the conversion of hydroxyl radicals to carbonate radicals within the carbonate–bicarbonate buffering system *in vivo* adds complexity to this process [33]. Antioxidant defenses, including glutathione peroxidase (GPx) and superoxide dismutases (MnSOD, Cu/ZnSOD), mitigate lipid peroxidation by neutralizing ROS and repairing oxidative damage. Nonetheless, detecting and quantifying oxidative modifications in proteins and lipids poses challenges. Advanced methodologies, such as micro-Raman spectroscopy combined with Surface Enhanced Raman Spectroscopy (SERS), have been developed to detect oxidized nucleotides in small sample volumes, enhancing our understanding of lipid peroxidation processes [5].

Lipid peroxidation is implicated in neurodegenerative diseases, where oxidative stress promotes the formation of neurotoxic protein aggregates, exacerbating disease progression. It also functions as a spatial relay mechanism, enhancing immune cell detection of wound signals over greater distances [34]. A comprehensive understanding of lipid peroxidation mechanisms is crucial for developing therapeutic strategies against oxidative stress-related pathologies.

As illustrated in Figure 5, the study of lipid peroxidation is vital for understanding the oxidative degradation of lipids, impacting cell membrane integrity and function. The figure visually explores the mechanisms underlying lipid peroxidation, focusing on various aspects of this complex biochemical phenomenon. One subfigure, titled "Distance from Bilayer Center and Hydrogen Bonding Dynamics in a Membrane System," tracks temporal changes in the distance from the bilayer center, emphasizing the role of -tocopherol's OH group in membrane stability. However, placeholders marked as "ERROR!!!" indicate missing visual data that could further elucidate other mechanisms of lipid peroxidation, underscoring the need for comprehensive data visualization to capture its multifaceted nature [32, 35, 36].

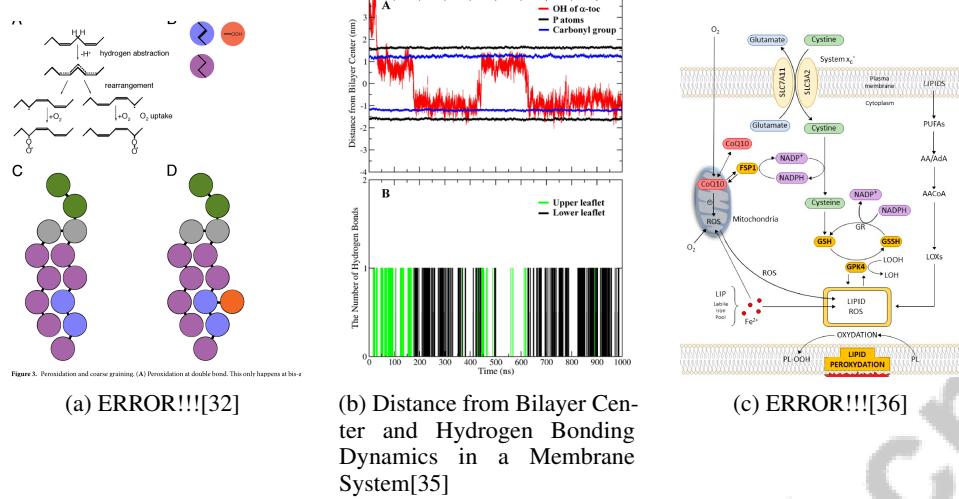


Figure 5: Examples of Mechanisms of Lipid Peroxidation

## 4.2 Lipid Peroxidation and Cellular Damage

Lipid peroxidation critically contributes to cellular damage through the oxidative degradation of lipids within cell membranes, compromising membrane integrity and leading to dysfunction and cell death. This oxidative stress-induced pathway involves lipid radical formation that propagates a chain reaction, generating toxic aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE). These highly reactive aldehydes can form adducts with proteins and DNA, exacerbating cellular damage and disrupting signaling pathways [7].

The implications of lipid peroxidation for cellular health are profound, as it compromises membrane stability and disrupts critical signaling pathways, potentially triggering regulated cell death mechanisms like ferroptosis. This form of cell death is characterized by lipid hydroperoxide accumulation, further contributing to cellular dysfunction and neurodegenerative diseases. Interactions between oxidized lipids and membrane proteins can alter membrane conductance and calcium signaling, leading to neuronal death and the progression of conditions such as Parkinson's disease [6, 3, 32, 17, 11]. Notably, interventions like -tocopherol administration can inhibit pore formation in oxidized lipid bilayers, enhancing membrane stability under oxidative stress.

Moreover, lipid peroxidation modulates immune responses by establishing gradients at wound sites that enhance leukocyte recruitment, facilitating long-range detection of early wound signals through ROS mechanisms [37, 35, 38, 17, 3]. This underscores the importance of lipid peroxidation in both pathological and physiological contexts.

Advanced detection methods enable the early identification of oxidative stress biomarkers, including lipid peroxidation products, which are crucial for understanding the initial phases of oxidative damage, particularly in diseases like diabetes and atherosclerosis. These biomarkers provide insights into mechanisms of cellular damage and the pathophysiological processes underlying chronic inflammatory conditions [2, 17, 3]. High-sensitivity techniques allow for detecting oxidized nucleotides at minimal concentrations, essential for early intervention strategies.

The cellular damage resulting from lipid peroxidation has significant health implications, potentially activating various cell death pathways, including necrosis and apoptosis. Real-time monitoring of living cells to distinguish different cell death pathways offers a non-destructive approach to understanding the consequences of lipid peroxidation. Insights gained are vital for developing therapeutic strategies aimed at reducing oxidative stress and preserving cellular function. Compounds like 'Sylimavit' have shown significant reduction in lipid peroxidation compared to control groups, emphasizing the potential of specific antioxidants to mitigate oxidative damage [8].

### 4.3 Lipid Peroxidation in Disease Contexts

Lipid peroxidation is intricately involved in the pathogenesis and progression of various diseases, primarily through its detrimental effects on cellular structures and functions. The oxidative degradation of lipids results in reactive aldehydes, such as MDA, which can modify proteins and nucleic acids, exacerbating cellular dysfunction and disease progression. Elevated MDA levels have been observed in children with early childhood caries (ECC), suggesting a link between lipid peroxidation and the carious process [39].

In neurodegenerative diseases, lipid peroxidation is implicated in oxidative stress marker accumulation within amyloid-beta (A) plaques, characteristic of Alzheimer's disease. These oxidative modifications, particularly cholesteryl ester accumulation, contribute to neurotoxicity in various neurodegenerative conditions. Elevated ROS levels from oxidative stress lead to extensive cellular damage, particularly detrimental to the lipid-rich neuronal membranes. The interaction of aggregated proteins, such as -synuclein, with neuronal membranes exacerbates oxidative damage and triggers forms of cell death like ferroptosis, highlighting the intricate relationship between oxidative stress, lipid metabolism, and neurodegeneration [6, 40, 18, 17, 11].

Lipid peroxidation also plays a significant role in cardiovascular diseases, where oxidative stress is a critical factor in endothelial dysfunction and atherosclerosis. The protective role of endothelial BRCA2 against atherosclerosis emphasizes the relationship between genetic factors and oxidative stress in maintaining vascular health. Endothelial BRCA2 is crucial for DNA damage repair; its deficiency leads to increased oxidative stress, contributing to endothelial dysfunction and atherogenesis. Research indicates that loss of endothelial BRCA2 exacerbates atherosclerosis, particularly under hypercholesterolemic conditions, disrupting lipid metabolism and protein folding pathways. Individuals with BRCA2 mutations may face an elevated risk of developing atherosclerosis, indicating a need for further investigation into BRCA2 as a potential therapeutic target for cardiovascular diseases [3, 41].

In cancer, lipid peroxidation contributes to tumor progression by modulating cellular signaling pathways and inducing oxidative damage. The role of catechins and other antioxidants in mitigating oxidative stress-related damage offers potential therapeutic avenues for preventing cancer progression. Lipid peroxidation is intricately involved in regulating ferroptosis, characterized by the iron-dependent accumulation of lipid peroxides. This process is crucial in various pathological conditions, including cancer, where ferroptosis modulation may provide novel therapeutic strategies. The mechanisms underlying ferroptosis involve a balance between lipid peroxide formation and detoxification, with factors like glutathione peroxidase 4 (GPX4) inhibition and cysteine availability serving as significant triggers. Understanding these interactions is essential for developing targeted cancer therapies that exploit ferroptosis [42, 36].

The therapeutic potential of antioxidants in mitigating lipid peroxidation and its associated damage is highlighted by studies comparing different antioxidant strategies. For example, 'Sylimevit' has been shown to reduce lipid hydroperoxides by 52

Lipid peroxidation plays a critical role in the pathophysiology of various diseases, influencing disease progression through oxidative damage and modulation of cellular pathways. A comprehensive understanding of lipid peroxidation's biochemical mechanisms, including its biomarkers and associated antioxidant responses, is crucial for elucidating its significant role in various disease processes, such as inflammation, diabetes, and atherosclerosis. This insight is essential for developing targeted therapeutic strategies aimed at mitigating the harmful effects of lipid peroxidation and improving clinical outcomes [37, 3].

### 4.4 Lipid Peroxidation and Ferroptosis

Ferroptosis is a newly recognized form of regulated cell death characterized by its dependence on iron and the accumulation of lipid peroxides, particularly from PUFAs. Distinct from apoptosis and necrosis, ferroptosis is marked by specific cellular changes, including alterations in mitochondrial morphology and membrane integrity due to intense oxidative stress and lipid peroxidation. This process plays a significant role in various physiological and pathological conditions, including cancer, where it may eliminate nutrient-deficient or damaged malignant cells. Understanding ferroptosis regulation, particularly the roles of glutathione peroxidase 4 (GPX4) and the interplay between lipid metabolism and iron homeostasis, offers potential therapeutic avenues for cancer treatment and other diseases associated with dysregulated cell death [42, 36, 43, 44]. The lipid peroxidation

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process, initiated by ROS and propagated by iron-catalyzed Fenton reactions, is pivotal in ferroptosis, underscoring lipid peroxidation's importance in executing this form of cell death.

The initiation of lipid peroxidation in ferroptosis involves hydrogen atom abstraction from specific carbon sites within PUFAs, potentially facilitated by carbonate radicals [19]. The resultant lipid radicals react with molecular oxygen to form lipid peroxides, accumulating and disrupting cellular membranes, ultimately leading to cell death. This mechanism highlights the critical role of lipid composition and oxidative stress in ferroptosis [14].

Iron homeostasis is central to regulating ferroptosis, as iron catalyzes lipid peroxide formation. Disruption of iron homeostasis, such as with doxorubicin-induced cardiotoxicity, exacerbates lipid peroxidation and ferroptosis, illustrating the interplay between iron metabolism and cell death pathways [45]. Non-coding RNAs (ncRNAs) further modulate ferroptosis, indicating a complex regulatory network integrating lipid metabolism and cell death signals [43].

Lipid peroxidation is intricately linked to ferroptosis in various disease contexts. For instance, in neurodegenerative diseases, alpha-synuclein aggregation is associated with increased lipid peroxidation, triggering ferroptosis and contributing to neuronal cell death [6]. This connection underscores the potential for therapeutic interventions targeting lipid peroxidation and iron metabolism to mitigate ferroptosis-related pathologies.

Understanding the mechanisms of lipid peroxidation and its role in ferroptosis is crucial for developing targeted therapies aimed at regulating this form of cell death. Exploring lipid-based therapies and modulating iron homeostasis presents significant potential for treating diseases linked to ferroptosis, characterized by iron-dependent lipid peroxide accumulation and oxidative stress. Research indicates that lipid peroxidation and iron metabolism are crucial in the ferroptotic process, with mechanisms such as the xCT-GSH-GPX4 pathway and ferritinophagy playing vital roles in regulating cellular responses. Continued investigation into these biochemical pathways and therapeutic strategies is essential for developing effective interventions against conditions associated with ferroptosis, including various cancers and neurodegenerative diseases [43, 42, 36].

## 5 Cell Death Pathways

### 5.1 Overview of Cell Death Pathways

Cell death pathways are integral to biological regulation, affecting development, homeostasis, and disease. These pathways are categorized into apoptotic and non-apoptotic forms, each with distinct mechanisms and outcomes [46]. Apoptosis, a programmed cell death process, is caspase-dependent and involves morphological changes such as cell shrinkage and DNA fragmentation. It maintains cellular homeostasis by removing damaged cells without causing inflammation [47]. Necrosis, traditionally seen as unregulated, involves cell swelling and membrane rupture leading to inflammation. However, regulated necrosis forms, like necroptosis, are mediated by specific signaling pathways and contribute to immune responses [48].

Specialized regulated cell death (RCD) forms, including ferroptosis, pyroptosis, and NETosis, have unique implications. Ferroptosis, driven by iron-dependent lipid peroxidation, is significant in cancer therapy [49]. Pyroptosis, linked to inflammasome activation, releases cytokines critical for host defense against infections [50]. NETosis involves neutrophil traps that neutralize pathogens, emphasizing innate immunity [47]. These modalities are classified into caspase-dependent and independent pathways [46], essential for developing therapeutic strategies, especially in cancer, where tumor microenvironment interactions are crucial [49].

### 5.2 Oxidative Stress-Induced Cell Death

Oxidative stress contributes significantly to cell death by disrupting the balance between reactive species and antioxidants, leading to molecular damage. This imbalance often results in mitochondrial dysfunction and excessive ROS production, damaging DNA, lipids, and proteins, especially in high-energy tissues like the brain, contributing to neurodegenerative diseases and diabetes complications [51, 17, 18, 11]. ROS overproduction activates cell death pathways, including apoptosis, necrosis, and ferroptosis, essential for cellular homeostasis but potentially pathological when dysregulated.

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Oxidative stress-induced cell death mechanisms are complex. JNKs play a crucial role in regulating pro-apoptotic gene expression and mitochondrial events [52]. Oxidative stress also modulates immune functions, affecting disease outcomes, particularly in neurodegenerative diseases where it exacerbates neuronal damage, as seen in Alzheimer's disease [53]. In cancer, oxidative stress-induced cell death contributes to treatment resistance, prompting exploration of alternative RCD pathways like pyroptosis [54]. Oxidative stress impacts the cardiovascular system, contributing to endothelial dysfunction and atherosclerosis, with endothelial BRCA2 deficiency exacerbating disease under hypercholesterolemic conditions [33].

Understanding oxidative stress-induced cell death is crucial for addressing diseases like Alzheimer's, Parkinson's, and diabetes complications. Insights into the signaling pathways and molecular mechanisms involved are vital for developing targeted therapies to mitigate oxidative stress's adverse effects [2, 18, 51, 17, 11].

### 5.3 Lipid Peroxidation and Cell Death

Lipid peroxidation significantly influences cell death pathways by degrading lipids within membranes, particularly in ferroptosis, characterized by iron dependency and lipid peroxidation. This disrupts membrane integrity, increasing permeability and leading to cell death [32, 42, 43, 36]. JNKs may link lipid peroxidation to cell death pathways, highlighting the oxidative stress-cell fate interplay. Lipid peroxidation affects membrane stability and signaling, exacerbating dysfunction and death in neurodegenerative diseases through protein aggregation like alpha-synuclein [6].

In cancer, lipid peroxidation contributes to variability in cell death responses across cancer types, complicating therapeutic targeting. It enhances immune cell recruitment during tissue injury, indicating a role in immune responses and inflammation [49]. Different agents induce distinct cell death pathways, such as necrotic death by silver nanoparticles versus apoptosis by silver ions via oxidative stress [31]. Therapeutic agents with strong free radical scavenging properties, like TCH derivatives, underscore the need to understand lipid peroxidation in disease contexts [1].

Lipid peroxidation is crucial in cell death pathways, impacting membrane integrity, signaling pathways, and immune responses. Understanding its mechanisms and implications for RCD is essential for developing targeted therapies to alleviate its harmful effects, improving health outcomes in diseases like autoimmune disorders and conditions with defective cellular clearance. Research in ferroptosis linked to lipid peroxidation may lead to innovative lipid-based therapies to modulate metabolism and enhance cellular function [14, 44].

### 5.4 Regulated Cell Death Pathways

Regulated cell death (RCD) pathways maintain cellular homeostasis and respond to pathological stimuli, including apoptosis, necroptosis, ferroptosis, and pyroptosis. Each is defined by unique molecular mechanisms, significantly impacting disease progression, particularly in cancer, and informing therapeutic interventions. JNKs regulate various programmed cell deaths, crucial for tumorigenesis and resistance. The 14-3-3 protein family integrates signaling pathways governing apoptosis, cell cycle, and stress responses. Understanding these interactions is vital for manipulating cell death mechanisms in diseases like neurodegeneration and cancer [55, 56, 57, 58].

Apoptosis involves caspase activation leading to non-inflammatory cellular dismantling, essential for removing damaged cells and maintaining tissue homeostasis. Necroptosis, a caspase-independent RCD form, features plasma membrane rupture and inflammation, often acting as a backup when apoptosis is inhibited [48]. The apoptosis-necroptosis interplay underscores RCD complexity and its implications for diseases, including cancer and neurodegeneration.

Ferroptosis, driven by iron-dependent lipid peroxidation, requires ROS and lipid hydroperoxides. It is relevant in cancer therapy, targeting tumor cells resistant to apoptosis-inducing treatments. Ferroptosis regulation involves genes and proteins modulating iron homeostasis and lipid metabolism, presenting therapeutic targets for cancer treatment [46].

Pyroptosis, mediated by inflammasome activation, releases pro-inflammatory cytokines, bridging innate and adaptive immunity. Targeting pyroptosis in cancer therapy is explored for modulating immune responses and enhancing treatment effectiveness [46]. Understanding RCD pathway regulation and interactions is crucial for developing therapeutic strategies for diseases with inappropriate

cell death or survival, such as cancer, neurodegeneration, and autoimmune disorders [46]. The complex RCD pathway interplay, including roles in inflammation and tissue repair, offers potential for therapeutic interventions to improve disease outcomes [48].

## 6 Interconnections and Implications

### 6.1 Disease Implications and Pathophysiology

Method Name	Pathophysiological Mechanisms	Therapeutic Targets	Disease Applications
NT[7]	Oxidative Stress	Cyclooxygenase-2	Neurodegenerative Disorders
PENACC:ES[33]	Lipid Metabolism	Lipid Mediators	Metabolic Syndrome
MDA-TBARS[39]	Oxidative Stress	Lipid Peroxidation	Early Childhood Caries

Table 1: Summary of pathophysiological mechanisms, therapeutic targets, and disease applications associated with various methods. The table highlights the roles of oxidative stress and lipid metabolism in neurodegenerative disorders, metabolic syndrome, and early childhood caries, along with their respective therapeutic targets.

The intricate relationship between oxidative stress, lipid peroxidation, and cell death pathways plays a pivotal role in the pathophysiology of numerous diseases. Table 1 provides a comprehensive overview of the pathophysiological mechanisms, therapeutic targets, and disease applications pertinent to oxidative stress and lipid metabolism, emphasizing their significance in diverse medical conditions. In neurodegenerative disorders like Alzheimer’s and Parkinson’s, oxidative stress exacerbates neuronal damage, with the unfolded protein response in mitochondria (UPRmt) providing a potential therapeutic target by counteracting mitochondrial dysfunction [13]. Cyclooxygenase-2-derived reactive metabolites further link oxidative stress to neurotoxicity and neuronal cell death [7].

In oncology, the regulation of cell death pathways, notably ferroptosis and pyroptosis, is increasingly recognized for its potential to overcome drug resistance and enhance therapeutic efficacy. Ferroptosis, driven by iron-dependent lipid peroxidation, is a promising target in cancer treatment [43], while pyroptosis offers a strategy to improve the effectiveness of immune therapies like checkpoint inhibitors and CAR-T cells [54]. Emerging antioxidant classes also show potential in mitigating oxidative stress in cancer [34].

Cardiovascular diseases are heavily influenced by oxidative stress, impacting endothelial dysfunction and atherosclerosis. The role of endothelial dysfunction in exacerbating sepsis severity demands further investigation [20], while oxidative stress’s varied effects in metabolic syndrome highlight its broad impact [33].

Oxidative stress’s influence extends to dental health, with lipid degradation implicated in early childhood caries (ECC). Future research should explore the connections between malondialdehyde (MDA), salivary biomarkers, diet, and antioxidants in ECC [39].

In infectious diseases, immunogenic cell death is critical for host defense, with insights into regulatory mechanisms of immune responses informing therapeutic strategies [59]. Toll-like receptor (TLR) research offers pathways for developing therapies for inflammatory diseases [9].

Understanding the interconnections among oxidative stress, lipid peroxidation, and cell death pathways is essential for elucidating disease mechanisms. By focusing on regulated cell death (RCD) pathways like necroptosis, pyroptosis, ferroptosis, and cuproptosis, researchers can identify therapeutic targets and develop diagnostic tools to improve treatment efficacy, address cancer resistance, and enhance health outcomes across various diseases [58, 60, 43, 49, 61].

### 6.2 Regulation and Therapeutic Targeting

Modulating oxidative stress, lipid peroxidation, and cell death pathways offers promising therapeutic avenues to reduce cellular damage and disease progression. Key to these interventions is regulating reactive oxygen species (ROS), which play critical roles in diseases like neurodegenerative disorders, cancer, and diabetes. While excessive ROS cause cellular damage, balanced ROS levels are crucial for normal signaling [15, 60, 18, 51, 11]. Understanding ROS production and regulation is vital for developing therapies to mitigate oxidative damage. Hydrogen sulfide (H<sub>2</sub>S), for instance, has shown promise in activating protective pathways against oxidative stress.

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Advancements in RCD pathways, especially ferroptosis, present strategies to overcome cancer treatment resistance by targeting resistant cells [53]. The link between lipid peroxidation and alpha-synuclein aggregates offers a therapeutic target in neurodegenerative diseases, where modulating lipid peroxidation may prevent harmful protein aggregation.

In neurotoxicity, targeting specific pathways with drugs like nimesulide, a selective cyclooxygenase-2 inhibitor, could alleviate oxidative damage [7].

Targeting oxidative stress and lipid peroxidation in cardiovascular diseases has identified multiple therapeutic targets, enhancing our understanding of cardiotoxic mechanisms. Strategies include boosting antioxidant defenses and targeting lipid peroxidation to improve cardiovascular health [6, 17, 3]. Natural extracts from fungi also offer safer alternatives to synthetic antioxidants for therapeutic use.

Future research should delve into the regulatory mechanisms of cell death pathways and explore therapeutic interventions that modulate these processes in diseases [48]. Developing therapies that induce pyroptosis in cancer cells while sparing normal tissues is a promising research direction.

Regulating oxidative stress, lipid peroxidation, and cell death pathways is crucial for improving outcomes in diseases like cancer, diabetes, and neurodegenerative disorders. ROS play dual roles in tumor progression and cell death, with manipulation of ROS levels in cancer affecting cell survival and apoptosis. Hyperglycemia-induced oxidative stress in diabetes links to cellular damage and complications. Novel RCD pathways, such as necroptosis, pyroptosis, ferroptosis, and cuproptosis, are being explored as therapeutic targets to enhance anti-tumor responses and overcome resistance. Understanding the balance of oxidative stress and lipid metabolism is essential for developing interventions to mitigate disease progression [36, 60, 18, 49, 51]. Advancing our understanding of these processes will enable innovative interventions addressing the causes of cellular damage and disease.

### 6.3 Innovative Diagnostic and Therapeutic Approaches

Emerging diagnostic and therapeutic approaches targeting oxidative stress, lipid peroxidation, and cell death pathways are evolving rapidly, driven by advances in molecular understanding. The exploration of RCD pathways, such as ferroptosis and pyroptosis, has opened new therapeutic avenues, particularly in cancer treatment. Small molecules and nanomaterials have shown potential in inducing pyroptosis in cancer cells, suggesting promising clinical applications [54]. Traditional Chinese medicine and natural compounds targeting RCD pathways offer novel strategies, leveraging their pharmacological properties to modulate cell death [58].

Modulating ferroptosis, characterized by iron-dependent lipid peroxidation, presents significant therapeutic opportunities in cancer. Studies of various ferroptosis inducers and inhibitors elucidate their mechanisms and potential applications, providing a framework for future research [36]. Clinical trials on RCD modulators highlight their potential in disease management, though many are in early stages [49].

Future research should refine models to incorporate detailed interactions and explore strategies targeting oxidative stress and related pathways [62]. The dynamic interactions involving 14-3-3 proteins and their isoform-specific functions offer therapeutic targeting opportunities, particularly in cancer [55]. Understanding nucleoredoxin (NXN) interactions may provide insights into its therapeutic potential in redox imbalance diseases, suggesting avenues for targeted interventions [63].

Combination therapies targeting multiple pathways are emerging as a promising trend, emphasizing the need to consider epigenetic factors and cell therapies in future research [53]. Modulating excitonic transport in tauopathies represents a novel therapeutic target, warranting further exploration [64]. These innovative approaches hold significant promise for advancing the management of diseases associated with oxidative stress, lipid peroxidation, and cell death pathways, paving the way for more effective and targeted treatments.

## 7 Conclusion

The intricate relationship between oxidative stress, lipid peroxidation, and cell death pathways is crucial for understanding the mechanisms underlying various diseases. An imbalance in reactive

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oxygen species and antioxidant defenses triggers oxidative stress, leading to lipid peroxidation and activating cell death pathways such as apoptosis, necroptosis, and ferroptosis. These interconnected processes are key contributors to disease progression, affecting neurodegenerative disorders, cancer, and cardiovascular diseases.

This survey highlights the significant role of mitochondrial dynamics in cellular function and their association with diseases related to mitochondrial dysfunction. The regulation of cell death pathways, particularly ferroptosis and pyroptosis, offers promising therapeutic targets for overcoming drug resistance in cancer treatment. Additionally, the potential of natural antioxidants, like phenolic compounds from *Suillus* sp, in mitigating oxidative stress underscores their therapeutic promise.

Advanced methodologies, such as FMGM, provide valuable insights into complex biological interactions within disease contexts, enhancing the development of therapeutic strategies. Future research should focus on optimizing current interventions, such as Spd-CD concentrations to improve crop stress resilience, while ensuring the safe use of nano-fertilizers to preserve ecological balance.

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