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Green Defenders: A Review on Plant-Based Antioxidants Against Oxidative Injury

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Abstract:
Oxidative stress, resulting from an imbalance between endogenous antioxidant defences and reactive oxygen species (ROS), is a key driver of chronic disease onset and progression, such as cancer, cardiovascular disease, neurodegeneration, and metabolic syndromes. Plant antioxidants have become the focus of growing scientific and therapeutic attention over the past few decades because they have antioxidant properties such as scavenging ROS, chelation of pro-oxidant metals, and the modulation of redox-sensitive signalling. This review critically assesses the principal classes of plant antioxidants, flavonoids, phenolic acids, carotenoids, and alkaloids, their molecular mechanisms of action, pharmacological significance, and therapeutic potential.

Despite promising preclinical data, clinical translation is obstructed by substantial hurdles like heterogeneity in extract composition, absence of standardised dosing and dose-response information, inferior bioavailability, and regulatory disparities. These factors constrain reproducibility, efficacy, and consumer confidence. To break these obstacles, the review calls for massive-scale, placebo-controlled clinical trials, standardisation of extract preparation, use of sophisticated delivery systems (e.g., nanoencapsulation), and incorporation of omics-based platforms to decipher complex biological interactions. The potential synergistic use with standard therapies and investigation of underutilised plant sources are also suggested as avenues for the future. By filling these gaps, plant antioxidants could become effective, multi-targeted drugs in the battle against oxidative damage and its related pathologies.

Index Terms / Keywords: Plant-based antioxidants, Oxidative stress, Reactive oxygen species (ROS), Oxidative Injury, Free radical scavenging, Antioxidant mechanisms, Bioavailability

1. INTRODUCTION

Oxidative stress, an imbalance between ROS production and the effectiveness of antioxidant defence systems, is a pivotal mechanism for cellular and molecular damage in a broad range of diseases. Overproduction of ROS may result in lipid peroxidation, DNA damage, and protein oxidation, leading to chronic disease pathogenesis, including cancer, cardiovascular diseases, diabetes, neurodegenerative disorders, and premature aging.

In such cases, antioxidants have an essential function in defending against ROS and redox homeostasis. Although the organism has endogenous antioxidant mechanisms, they are usually inadequate to oppose prolonged oxidative stress and thus require extrinsic assistance via diet or supplementation. Of natural origin, plants provide a rich source of bioactive phytochemicals with antioxidant functions. Phytochemicals like flavonoids, phenolic acids, carotenoids, tannins, and alkaloids demonstrate varied mechanisms of action, viz., free radical scavenging, metal chelation, inhibition of oxidative enzymes, and modulation of redox-sensitive signal transduction pathways.

Antioxidants derived from plants have also received growing attention not only on account of their therapeutic application but also their broad safety profile and availability. Yet, their translation from bench to bedside is restricted by the limitations of poor bioavailability, heterogeneity of extract composition, absence of standardised dosages, and restricted clinical validation. As interest in phytotherapeutics increases, there is an urgent need to synthesise existing knowledge, consider existing gaps, and suggest strategic pathways towards further research and utilisation.

This review seeks to give an integrated view of the mechanistic underpinnings, therapeutic promise, and translational obstacles of plant-based antioxidants. It also brings into focus the new developments in delivery technologies, integration of omics, and regulatory aspects, along with suggestions for future research directions for clinical and pharmacological advancement.

2. OXIDATIVE STRESS: A GROWING CONCERN

Oxidative stress has emerged as a pivotal factor in the pathogenesis and development of many human disorders, receiving extensive attention during the past few years in biomedicine and clinical medicine. Oxidative stress is defined as a state of biology where the generation of reactive oxygen species (ROS) exceeds the body's antioxidant defence capacity to counteract them. This disequilibrium results in the accumulation of ROS, which are highly reactive molecules with the potential to cause damage to critical cellular constituents. Some of the most important ROS are superoxide anions (O_2^-), hydroxyl radicals (•OH), and hydrogen peroxide (H_2O_2), all of which are naturally occurring by-products of aerobic metabolism, particularly within mitochondrial respiration and oxidative phosphorylation (Sies et al., 2017).

Under normal physiological conditions, ROS serve beneficial roles as signalling molecules in a variety of cellular processes, including gene expression, immune defence, and apoptosis. However, when produced in excess or inadequately removed, ROS become detrimental, causing oxidative modifications to nucleic acids, membrane lipids, and structural and functional proteins. This oxidative damage breaks cellular integrity and function, eventually resulting in genomic instability, impaired signalling, inflammation, and cell death—pathways that are all combined to cause tissue degeneration and organ dysfunction (Liguori et al., 2018).

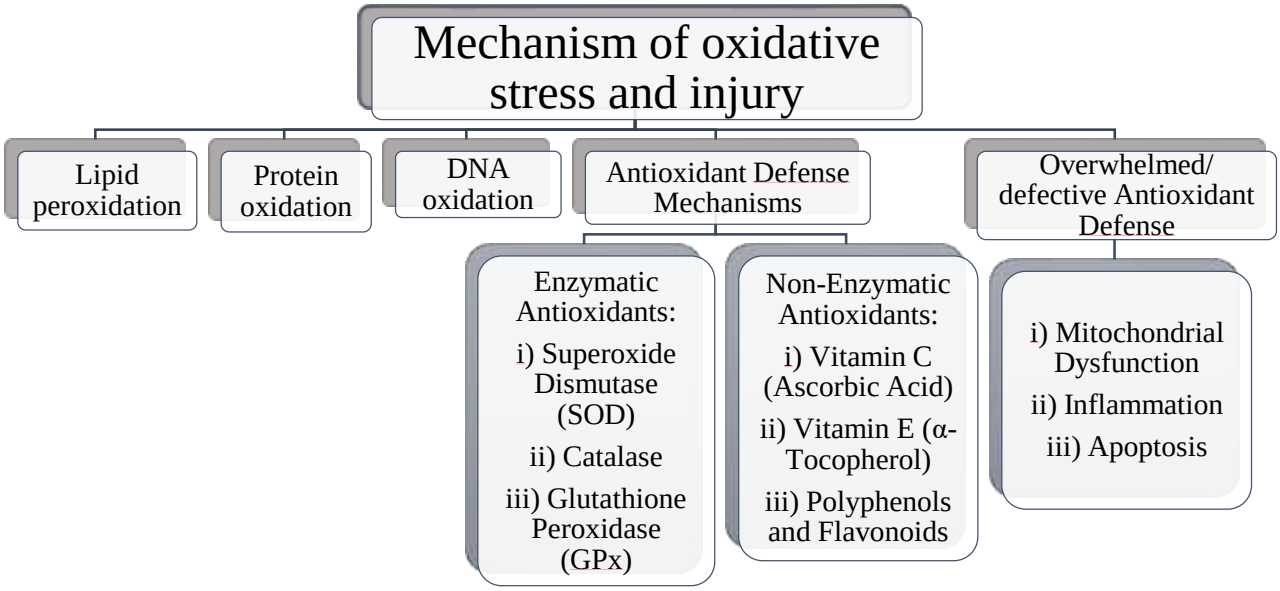
Many studies have implicated oxidative stress in the aetiology of a broad range of chronic diseases, including cardiovascular diseases (e.g., atherosclerosis and hypertension), metabolic disorders such as diabetes mellitus, neurodegenerative diseases like Alzheimer's and Parkinson's, autoimmune diseases, chronic inflammatory diseases, and many types of cancer. Oxidative stress is also a key contributor to ageing and age-related cellular deterioration, according to the free radical theory of ageing (Pham-Huy et al., 2008).

Modern lifestyle conditions have been demonstrated to strongly enhance ROS production. Environmental toxins, ultraviolet and ionising radiation, smoking tobacco, alcohol intake, processed food, fatty diets, chronic psychological stress, and a sedentary lifestyle are all known to increase oxidative load. Environment plays significant role in exerting oxidative stress for both plants and humans. In plants, environmental stressors such as high light intensity, drought, pollution, and extreme temperatures can lead to an increase in reactive oxygen species (ROS) (Munzel and Daiber, 2018). For humans, oxidative stress can be triggered by environmental pollutants, toxic metals, pesticides, and cigarette smoke. In addition, exposure to some drugs and industrial chemicals (xenobiotics) may trigger redox imbalances by inhibiting mitochondrial function or inducing ROS production. These extrinsic stressors, supplemented by intrinsic metabolic activity, generally overburden endogenous antioxidant mechanisms including superoxide dismutase (SOD), catalase, glutathione peroxidase, and non-enzymic antioxidants like glutathione, uric acid, and coenzyme Q10.

As a central factor in disease and health decline, oxidative stress is a key issue for public health worldwide. Elucidation of the molecular processes of oxidative damage and the identification of useful antioxidant strategies are essential for the design of preventive and therapeutic treatments. The increasing awareness of the limitations and possible side effects of synthetic antioxidants has led to the quest for exploring natural alternatives, especially plant-derived, that can provide efficacy and safety in combating oxidative damage.

2.1 Mechanisms of Oxidative Stress and Injury

Oxidative stress achieves its harmful action chiefly by the unrestrained accumulation of reactive oxygen species (ROS) that react with essential biomolecules—lipids, proteins, and nucleic acids—thereby impairing cellular structure and function. Molecular damage is the core of pathophysiology in many acute and chronic conditions and is in close association with ageing and tissue deterioration (Sies et al., 2017).



2.1.1 Lipid peroxidation

It is one of the best-studied effects of ROS overproduction. The cell membrane, which is polyunsaturated with fatty acids (PUFAs), is most vulnerable to ROS attack. ROS, especially hydroxyl radicals (OH•), attack PUFAs, resulting in the initiation of lipid radicals and peroxyl radicals, which continue the oxidative chain reaction. The formed lipid peroxides destabilise the lipid bilayer, changing membrane fluidity and making the membrane more permeable (Halliwell & Gutteridge, 2015). The disruption can hinder membrane-bound enzyme functions, ion transport, and receptor operation, resulting in cellular dysfunction (Beckman & Ames, 1997).

The peroxidation breakdown products of lipids, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), are very reactive and cytotoxic. The aldehydes can produce covalent adducts with proteins and nucleic acids, leading to additional damage (Steinberg et al., 1997). MDA, specifically, is a well-documented mutagenic agent that causes the formation of DNA adducts, which could result in mutations and cancer (Cadet, J., & Davies, K. J. A., 2017).

2.1.2 Protein oxidation

ROS-mediated protein oxidation includes modifications of amino acid side chains, and such modifications can lead to the development of cross-links between proteins, polypeptide chain fragmentation, and the production of carbonyl groups. These oxidative changes can adversely affect enzyme activity and cellular function. For instance, oxidation of cysteine or methionine residues in an enzyme can suppress its catalytic activity and result in decreased cellular efficiency (Davies, 2005).

One of the shared markers of oxidative protein damage is protein carbonylation, which is a process where carbonyl groups are added to proteins. Protein carbonylation has been linked to various diseases, such as Alzheimer's disease, Parkinson's disease, and cardiovascular disease (Halliwell & Gutteridge, 2015). Additionally, oxidised proteins tend to be substrates for degradation by the ubiquitin-proteasome system, but when the system is saturated, oxidised proteins accumulate, leading to cellular stress and dysfunction (Squier, 2001).

2.1.3 DNA oxidation

DNA is especially susceptible to oxidative damage because of its pivotal position in cellular function and reproduction. ROS can cause a range of DNA lesions, such as base modifications (e.g., 8-oxo-2'-deoxyguanosine), single-strand breaks, double-strand breaks, and DNA-protein cross-links (Cooke et al., 2003). These lesions can disrupt transcription and replication, causing mutations, chromosomal instability, and genomic instability, which are characteristics of cancer (Cadet et al., 2003).

DNA damage due to oxidative stress also induces the induction of the DNA damage response (DDR), a multifaceted signalling pathway that tries to repair the damage. Still, if the damage is excessive or repair

is not successful, the cell can die via apoptosis or senescence (Jackson & Bartek, 2009). These mechanisms are the cornerstone of ageing and the genesis of cancer, where mutations accumulate to lead to tumorigenesis (Vijg & Suh, 2013).

2.1.4 Antioxidant Defence Mechanisms

To counteract the deleterious effects of oxidative stress, cells depend on enzymatic and non-enzymatic antioxidant defence systems that eliminate ROS and restore redox homeostasis.

2.1.4.1 Enzymatic Antioxidants:

i) Superoxide Dismutase (SOD): Facilitates the conversion of superoxide anion ($O_2^{\bullet -}$) to hydrogen peroxide (H_2O_2), a less reactive species (McCord & Fridovich, 1969).

ii) Catalase: Additional detoxification of hydrogen peroxide by converting it to water and oxygen (Aebi, 1984).

iii) Glutathione Peroxidase (GPx): Reduces hydrogen peroxide and organic hydroperoxides with glutathione (GSH) as a substrate (Flohé & Günzler, 1984).

2.1.4.2 Non-Enzymatic Antioxidants:

Non-enzymatic antioxidants, such as vitamins C and E, glutathione, carotenoids, flavonoids, and polyphenols, also have essential roles in scavenging free radicals and protecting cellular components (Packer et al., 2001).

i) Vitamin C (Ascorbic Acid): Regenerates other antioxidants, such as vitamin E, and directly neutralises ROS (Jacob & Sotoudeh, 2002).

ii) Vitamin E (α-Tocopherol): Protects cellular membranes from lipid peroxidation by neutralising lipid peroxyl radicals (Girotti, 1998).

iii) Polyphenols and Flavonoids: These plant constituents can break lipid peroxidation chain reactions, chelate transition metals, and modulate oxidative stress pathways (Cao et al., 1997; Sun, W., & Shahrajabian, M. H., 2023). The cooperative interaction between enzymatic and non-enzymatic antioxidants guarantees a stable protection against oxidative stress. When the antioxidant defence system is lost or saturated, the accumulation of ROS results in mitochondrial impairment, inflammation, and cellular apoptosis, which are factors in the onset of degenerative diseases like Alzheimer's, Parkinson's, cardiovascular illnesses, and cancer (Sies et al., 2017; Halliwell, 2007).

2.1.5 Consequences of Overwhelmed Antioxidant Defence

During oxidative stress, in which antioxidant defences become overpowered or impaired, accumulation of oxidative damage results in multiple pivotal events during disease pathogenesis:

i) Mitochondrial Dysfunction: ROS-induced mitochondrial lipid, protein, and DNA damage can disable mitochondrial function by causing decreased ATP production, membrane potential loss, and release of pro-apoptotic factors (Wang, C. H et al., 2013).

ii) Inflammation: Oxidative stress can activate nuclear factor kappa B (NF-κB) and inflammatory pathways and can lead to the production of pro-inflammatory cytokines, which, in turn, continue to extend tissue damage and are responsible for chronic diseases including arthritis, atherosclerosis, and neurodegeneration (Sies et al., 2017).

iii) Apoptosis: Persistent oxidative damage triggers programmed cell death pathways through the activation of caspases and other apoptotic factors (Kang, H.J. et al., 2005). Apoptosis contributes to tissue degeneration and functional loss in diseases such as neurodegeneration, heart disease, and diabetes.

3. PLANT ANTIOXIDANTS: NATURE'S OWN SOLUTION

Fruits and vegetables are an extensive and varied source of phyto antioxidants, which are molecules that possess the property of neutralising reactive oxygen species (ROS) and then protecting cells against oxidative damage. The most studied classes of fruit- and vegetable-based antioxidants are polyphenols, flavonoids, carotenoids, alkaloids, tannins, lignans, and some essential vitamins such as C and E (Pietta, 2000). All of these groups of compounds possess unique structural and functional properties that enable them to act as effective free radical scavengers, metal ion chelators, and modulators of redox signalling pathways.

3.1 Important Classes of Plant Antioxidants

3.1.1 Flavonoids

Flavonoids are a highly heterogeneous group of polyphenolic compounds widely distributed in fruits and vegetables, tea, wine, and medicinal herbs. These compounds have potent antioxidant activity via a variety of mechanisms: direct reactive oxygen and nitrogen species scavenging, redox-active metal ions chelation, and regulation of antioxidant enzyme activities such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Panche et al., 2016; Pietta, 2000). Among the most researched flavonoids are quercetin, catechins, kaempferol, and epigallocatechin gallate (EGCG), which have proved to offer protective effects in models of cardiovascular disease, neurodegeneration, and cancer (Li et al., 2016).

Quercetin, for example, has been found to inhibit lipid peroxidation and DNA damage by inducing phase II detoxifying enzymes through the Nrf2 pathway (D'Andrea, 2015). Catechins, particularly in green tea, increase antioxidant defence by regulating MAPK and NF-κB signaling pathways and inhibit inflammation and apoptosis (Cabrera et al., 2006). Kaempferol and kaempferol glycosides are reported to prevent oxidative stress-mediated neuronal and hepatic injury through enhancement of mitochondrial resistance and suppression of ROS generation (Calderón-Montaño et al., 2011). Despite their high potential, the clinical application of flavonoids is often limited by low water solubility, rapid metabolism, and poor systemic bioavailability. Advanced formulations such as liposomal encapsulation and nanoemulsion systems are being explored to overcome these challenges (Yao et al., 2014).

3.1.2 Phenolic Acids

Phenolic acids, such as caffeic acid, ferulic acid, and gallic acid, are a critical subclass of plant polyphenols that play a key role in antioxidant defence systems. These phytochemicals exert their antioxidant action by direct neutralisation of free radicals, inhibition of lipid peroxidation, and modulation of redox-sensitive transcription factors like Nrf2, leading to upregulation of the expression of endogenous antioxidant enzymes (Balasundram et al., 2006; Kanski et al., 2002).

Caffeic acid has been found to inhibit ROS production and improve mitochondrial activity in neuronal cells, hence providing neuroprotection (Kelsey et al., 2010). Ferulic acid, which occurs abundantly in cereals and vegetables, manifests its antioxidant activity by stabilising free radicals and increasing nitric oxide availability and hence improving endothelial function and minimizing cardiovascular oxidative stress (Srinivasan et al., 2007). Gallic acid, which occurs in berries and tea, also exhibits high scavenging power and has proved to be neuroprotective in models of liver damage and neurodegeneration via its action upon apoptotic signalling and modulation of oxidative stress (You et al., 2010). Nevertheless, the effectiveness of phenolic acids is frequently constrained by their bioavailability and metabolic conversion in the gastrointestinal tract and liver, which can modify their antioxidant activity. Approaches like structural adjustment, encapsulation technologies, and gut microbiota-directed delivery systems are being researched to cross the barriers (Manach et al., 2005).

3.1.3 Carotenoids

Carotenoids are a family of lipid-soluble pigments with strong antioxidant activity, particularly through singlet oxygen quenching and lipid radical scavenging. Substances like beta-carotene, lutein, and lycopene incorporate into cell membranes owing to their lipophilicity, membrane structure stabilising, and lipid peroxidation protection (Krinsky & Johnson, 2005).

Beta-carotene, a vitamin A precursor, is important for immune regulation and antioxidant defence. Lutein is found densely in the eye macula, protecting retinal cells from light-induced oxidative damage.

Lycopene, which is found abundantly in tomatoes, is also a strong singlet oxygen quencher and has been shown to provide protective functions in models of oxidative cardiovascular and prostate disease (Rao & Rao, 2007). Yet, instability of carotenoids during storage and processing and bioavailability issues require formulation techniques such as emulsification and esterification to improve effectiveness and absorption.

3.1.4 Alkaloids

Alkaloids are nitrogenous secondary metabolites that are usually present in medicinal plants. They have been traditionally known to possess pharmacological activities, and some of them have also been found to exhibit antioxidant activity. Alkaloids like berberine and caffeine manifest their antioxidant activity indirectly by affecting cellular signalling pathways and by inhibiting enzymes that produce ROS.

Berberine triggers the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway, causing the transcription of antioxidant response elements (ARE) and the upregulation of detoxifying enzymes such as heme oxygenase-1 (HO-1) and NAD(P)H quinone dehydrogenase 1 (NQO1), thus preventing cells from oxidative damage (Liang et al., 2019). Additionally, it suppresses NADPH oxidase, inhibiting ROS production in endothelial and neural cells.

Caffeine, while more famously recognised as a central nervous system stimulant, has been demonstrated to possess ROS-scavenging activity and neuroprotective effects in neurodegenerative disease models. It regulates mitochondrial function, suppressing oxidative stress-evoked apoptosis and enhancing neuronal survival (Nehlig, 2016). Although the antioxidant activity of alkaloids is promising, especially by modulating redox-sensitive signalling pathways, they are less studied than other classes of phytochemicals. More studies are needed to identify their molecular mechanisms, improve delivery, and determine synergistic effects with other bioactive plant constituents.

3.1.5 Vitamins

Vitamins are vital organic substances that are involved in cellular metabolism, immune function, and oxidative stress prevention. Of these, vitamins C and E are established non-enzymic antioxidants obtained predominantly from plants. These vitamins act as the first line of defence against oxidative damage by directly neutralising reactive oxygen species (ROS), recycling other antioxidants, and stabilising free radicals (Brigelius-Flohé & Traber, 1999; Carr & Frei, 1999).

3.1.5.1 Vitamin C (Ascorbic Acid)

Vitamin C is a powerful, water-soluble antioxidant that can donate electrons to neutralise ROS like superoxide anions, hydroxyl radicals, and singlet oxygen. After being oxidised to dehydroascorbic acid, it can be reduced back to its original form inside cells without loss of activity (Carr & Frei, 1999). Besides its antioxidant function, vitamin C is crucial in collagen biosynthesis, immune modulation, and absorption of non-heme iron, thus playing a key role in many physiological processes.

Food vitamin C is rich in citrus fruits, berries, kiwi, papaya, bell peppers, broccoli, and green leafy vegetables. Certain tropical fruits, including guavas and acerola cherries, contain exceptionally high levels. Consuming regularly has been linked to decreased risk of cardiovascular diseases, cancer, and neurodegenerative diseases (Carr & Frei, 1999).

3.1.5.2 Vitamin E (Tocopherols and Tocotrienols)

Vitamin E consists of a family of lipid-soluble molecules, mostly tocopherols and tocotrienols, with the most bioactive form in humans being α-tocopherol. It is found mostly in cell membranes where it shields polyunsaturated fatty acids (PUFAs) against lipid peroxidation. By being able to break chain reactions of lipid peroxidation, vitamin E stabilises cell membranes and averts oxidative damage to phospholipids (Brigelius-Flohé & Traber, 1999).

Foods that contain vitamin E are nuts (almonds, hazelnuts), seeds, vegetable oils (sunflower and wheat germ oil), avocados, and leafy green vegetables. Besides playing an antioxidant role, vitamin E affects gene expression, immune function, and potentially has an effect in protecting against cognitive impairment and cardiovascular illness (Traber & Atkinson, 2007).

Notably, vitamin E can complement vitamin C, which is responsible for recycling the oxidised form of vitamin E, which, in turn, increases its antioxidant recycling and the length of its protective activity (Niki, 1991).

Table 1 -Major Classes of Plant-Based Antioxidants

Class	Examples	Sources	Mechanisms of Action	References
Flavonoids	Quercetin, Catechins, Kaempferol	Fruits, vegetables, tea, herbs	Radical scavenging, metal chelation, enzyme modulation	Calderón-Montaño et al., 2011; D'Andrea, 2015; Panche et al., 2016; Pietta, 2000; Vauzour et al., 2008
Phenolic Acids	Gallic acid, Ferulic acid, Caffeic acid	Berries, coffee, grains, spices	ROS neutralization, Nrf2 activation, modulation of antioxidant enzymes	Balasundram et al., 2006; Kanski et al., 2002; Srinivasan et al., 2007; You et al., 2010
Carotenoids	Beta-carotene, Lutein, Lycopene	Carrots, tomatoes, leafy greens	Singlet oxygen quenching, gene expression regulation, membrane stabilization	Krinsky & Johnson, 2005; Rao & Rao, 2007
Alkaloids	Berberine, Caffeine	Tea, coffee, Berberis spp.	Nrf2/ARE pathway activation, ROS enzyme inhibition	Kelsey et al., 2010; Liang et al., 2019; Nehlig, 2016
Vitamins	Vitamin C, Vitamin E	Citrus fruits, nuts, seeds, leafy greens	Lipid peroxidation prevention, radical scavenging, regeneration of other antioxidants	Combs, 2008; Frei, 1991

3.2 Importance in Mitigating Oxidative Stress

3.2.1. Natural Defence Against ROS

Plant-based antioxidants like polyphenols, flavonoids, carotenoids, tannins, and vitamins (E and C) are efficient free radical scavengers. These molecules suppress radical chain reactions, transfer electrons to unstable species, and hinder oxidative deterioration at the cellular level (Pietta, 2000). They can also chelate pro-oxidant metal ions (such as Fe^{2+} and Cu^{2+}), diminishing their involvement in ROS-producing reactions like the Fenton reaction.

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$ (Fenton reaction)

It occurs naturally in cells, especially in the presence of free iron and is involved in oxidative stress and cellular damage, especially when the antioxidant defence system is saturated. It is implicated in conditions like Alzheimer's, Parkinson's, cancer, and atherosclerosis because it is involved in DNA strand breaks, lipid peroxidation, and protein oxidation. Plant antioxidants can chelate metal ions such as Fe^{2+}, thus preventing the Fenton reaction and decreasing the formation of toxic hydroxyl radicals. This is one of the main ways in which natural antioxidants prevent oxidative stress.

3.2.2. Modulation of Antioxidant Enzymes

Most plant antioxidants are indirect antioxidants because they induce the body's defence mechanisms. As an illustration, polyphenols and flavonoids can induce Nrf2, a major transcription factor that stimulates endogenous antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Kwak et al., 2004). This decreases oxidative burden but also increases long-term cellular resistance.

3.2.3. Anti-Inflammatory and Cytoprotective Effects

By lowering ROS levels, plant antioxidants reduce inflammation, a primary effect and intensifier of oxidative stress. Various plant chemicals suppress NF-κB, a redox-sensitive transcription factor responsible for inducing the synthesis of pro-inflammatory cytokines (Surh, 2003). This anti-inflammatory effect is especially significant in chronic diseases like arthritis, atherosclerosis, and neurodegenerative diseases.

3.2.4. Disease Prevention and Longevity

Many studies have established that plant antioxidant-rich diets correlate with a lower occurrence of oxidative stress-related diseases. For example, Flavonoids found in tea and citrus fruits are associated with improved cardiovascular prognosis (Hertog et al., 1993). Carotenoids such as lutein and zeaxanthin shield the eyes against oxidative damage and age-related macular degeneration. Resveratrol and curcumin show neuroprotection against ROS-induced apoptosis, hinting at Alzheimer's and Parkinson's disease neuroprotective ability (Reznichenko et al., 2010; Granzotto, A., & Zatta, P., 2014).

2.1.5. Synergistic Action in Whole Foods

Importantly, the mixture of various antioxidants in whole plant foods provides synergistic effects that are stronger than individual compounds. This synergy enhances bioactivity and overall redox balance in the body (Liu, 2003). Synergistic and antagonistic action of antioxidants in food combinations can influence the total antioxidant availability in foods (Wang et al., 2011).

3.3 Mechanisms of Action of Plant-Based Antioxidants

Plant antioxidants deliver their protective action through complex and varied mechanisms. The major actions include neutralisation of reactive species, modulation of cellular signalling pathways, and regulation of genes concerning oxidative stress and inflammation. Elucidation of these mechanisms is fundamental to understanding the role of dietary antioxidants in the prevention and management of chronic diseases.

3.3.1. Neutralising Free Radicals

Free radical scavenging is the simplest and direct mode of action for plant antioxidants. They are capable of donating a hydrogen atom or an electron to reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby stabilising these and preventing chain reactions that initiate lipid peroxidation, oxidation of proteins, and DNA damage (Prior, Wu, & Schaich, 2005).

Polyphenols, flavonoids, carotenoids, and vitamins C and E are especially efficient in quenching hydroxyl radicals, superoxide anions, and peroxynitrite (Halliwell, 2007). Vitamin C decreases ROS in aqueous compartments, while vitamin E acts to protect membrane lipids against peroxidation. Carotenoids like β-carotene and lycopene scavenge singlet oxygen due to their conjugated double bond systems (Krinsky & Johnson, 2005).

This free-radical-neutralising activity minimises the cellular oxidative load to a great extent, preserving membrane integrity, defending mitochondrial function, and inhibiting the triggering of apoptosis or necrosis signalling. Therefore, these antioxidants have a significant function in protecting against oxidative stress-linked diseases, such as cardiovascular disease, neurodegeneration, and cancer (Lobo, Patil, Phatak, & Chandra, 2010).

3.3.2. Modulating Cellular Pathways

In addition to radical scavenging, plant antioxidants also regulate signalling pathways that affect oxidative stress, inflammation, and cell survival. One key target for regulation by antioxidants is the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. When in an oxidising environment, Nrf2 is released from its cytosolic inhibitor Keap1, moves into the nucleus, and induces transcription of antioxidant response element (ARE)-dependent genes. These genes express detoxifying enzymes such as glutathione S-transferase, heme oxygenase-1 (HO-1), and NAD(P)H: quinone oxidoreductase 1 (NQO1) (Surh, Kundu, & Na, 2008).

Numerous plant compounds like curcumin, resveratrol, and quercetin are well reported to cause the activation of Nrf2. For instance, curcumin increases Nrf2 nuclear accumulation, culminating in enhanced cellular antioxidant activity and oxidative insult resistance (Yang et al., 2011).

Besides, plant antioxidants also inhibit pro-inflammatory signalling by inhibition of transcription factors like nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1). Plant antioxidants inhibit transcription factors that play a role in the expression of inflammatory cytokines (e.g., TNF-α, IL-6), inducible nitric

oxide synthase (inos), and cyclooxygenase-2 (COX-2) involved in chronic inflammation and oxidative damage (Aggarwal & Harikumar, 2009).

Additionally, plant polyphenols can be demonstrated to modulate PI3K/Akt and MAPKs signalling pathways, contributing further to cell response to oxidative stress, protecting against cell loss, and alleviating apoptosis (Scalbert, Johnson, & Saltmarsh, 2005).

3.3.3. Metal Chelation: Preventing ROS Formation at the Source

Certain antioxidants derived from plants, particularly polyphenols, are capable of chelating transition metals such as iron (Fe^{2+}) and copper (Cu^{2+}), which are essential catalysts in the Haber-Weiss and Fenton reactions, producing highly reactive hydroxyl radicals from hydrogen peroxide (Perron & Brumaghim, 2009). Through the binding of these metals, antioxidants stop the initiation of radical chain reactions, thereby indirectly inhibiting the production of ROS.

For instance, flavonoids like quercetin and kaempferol are found to have high metal-chelating capacity, which makes a large contribution to their antioxidant activity (Khokhar & Magnusdottir, 2002).

3.3.4. Regeneration of Other Antioxidants: Synergistic Interactions

Plant antioxidants also facilitate the regeneration of other antioxidants by synergistic interactions. For example, vitamin C can regenerate oxidised vitamin E to its reduced form, thus maintaining its protective role in the lipid milieu (Packer, Weber, & Rimbach, 2001). In the same way, polyphenols are able to regenerate glutathione and bind with enzymes that maintain antioxidant homeostasis, upregulating the total antioxidant network.

This interdependence makes the body more resilient to coping with oxidative insult and highlights the significance of varied antioxidant consumption from diet.

3.3.5. Epigenetic Modulation and Gene Regulation

It is now indicated that plant antioxidants are capable of altering epigenetic changes, such as DNA methylation, histone acetylation, and microrna regulation, which relate to oxidative stress and chronic inflammation (Ramakrishna & Jailkhani, 2008; Rahman et al., 2021). Resveratrol and curcumin, for example, have been reported to control the expression of genes related to oxidative defence and inflammation through epigenetic pathways.

This process connects diet and long-term health outcomes, implying that plant-based antioxidants might even beneficially reprogram gene expression profiles to resist oxidative damage.

3.3.6. Mitochondrial Protection and Biogenesis

Oxidative stress generally emanates in the mitochondria, the energy-producing organelles that are ROS-sensitive. Antioxidants found in plants such as resveratrol and epigallocatechin gallate (EGCG) may stabilise mitochondrial membranes, enhance mitochondrial efficacy, and promote biogenesis through PGC-1α and SIRT1 pathway activation (Lagouge et al., 2006).

This not only decreases ROS production at the source but also improves cellular energy homeostasis, especially in ageing and neurodegenerative diseases.

3.3.7. Anti-apoptotic and Cytoprotective Effects

Some phytochemicals exhibit anti-apoptotic activities by inhibiting cell death in the presence of oxidative stress. They do so by regulating Bcl-2 family proteins, caspase cascades, and mitochondrial membrane potential. Curcumin, EGCG, and anthocyanins, for example, have been found to inhibit oxidative-stress-induced apoptosis in endothelial and neuronal cells (Scapagnini et al., 2011).

4. CHALLENGES AND LIMITATIONS

Even with a strong corpus of preclinical data highlighting the therapeutic promise of plant antioxidants, their effective translation into the clinical setting is replete with challenges. These limitations cut across several areas, such as scientific, technological, and regulatory issues:

4.1 Limited Number of Well-Designed Clinical Trials

Although it has been shown through in vitro and in vivo (animal model) experiments that plant-derived compounds have strong antioxidant activity, such effects do not easily translate to viable human use. The main reason is the limited number of well-conducted clinical trials that measure the efficacy, safety, and pharmacodynamics of such phytochemicals in human subjects.

Most of the available clinical trials are small-scale, short-term, or weakly controlled, limiting their ability to provide statistically significant or clinically meaningful conclusions. For instance, a systematic review by Li et al. (2014) of flavonoid supplementation in cardiovascular disease identified that although there were observed benefits in the short term, trials tended to have weak randomisation and standardisation, which hampered evaluation of long-term effects or cross-study comparison. In addition, heterogeneity in research design, for example, use of varying types and dose of plant extract, populations of participants, and outcome measures, makes it difficult to conduct meta-analyses or establish clinical guidelines (Manach et al., 2005). For example, curcumin, a well-studied antioxidant, has been promising in preclinical models, but human studies often provide inconsistent data because of inadequate bioavailability and absence of a standardised formulation (Gupta et al., 2013).

Another significant gap is the paucity of longitudinal trials. A chronic disease that has been shaped by oxidative stress, for example, neurodegenerative diseases or cardiovascular diseases, tends to evolve over many years. Short-term treatments, even if effective in lowering biomarkers for oxidative stress, may not indicate long-term clinical outcomes (Zhao et al., 2019).

Additionally, placebo-controlled and double-blind trials, the gold standard for clinical research, are uncommon in the field of botanical antioxidants. This creates concerns regarding bias and the placebo effect, which, being highly influential in the context of nutraceutical research where patient expectations can bias responses (Liu et al., 2013), is concerning.

Lacking strong clinical evidence, regulatory bodies are reluctant to support plant antioxidants for the prevention or treatment of disease beyond nutritional supplementation and restrict their use in conventional medicine.

4.2 Variability in Extract Composition

One of the biggest challenges in assessing and standardising plant antioxidants is the inherent heterogeneity of extract composition. In contrast to synthetic medicines that are usually made up of a single, well-characterised active component, plant extracts are intricate mixtures of many bioactive and inactive compounds. The precise composition of these constituents can differ considerably owing to several variables, each of which creates a source of variability in research as well as product development.

The causes of variation are:

i) Plant Species and Cultivar: Varying species and even cultivars of the same species can show large differences in phytochemical composition. For example, flavonoid composition in various cultivars of Camellia sinensis (tea plant) is quite different, influencing both antioxidant activity and health effects (Gulati et al., 2009).

ii) Geographical Position and Climate: Environmental factors like altitude, temperature, soil type, and rainfall are crucial in phytochemical biosynthesis. Lee et al. (2014) reported that ginsenoside content varied significantly between Korean and Chinese-grown Panax ginseng, demonstrating the influence of terroir on chemical composition.

iii) Plant Part Used and Harvest Time: The content of bioactive compounds may also vary with plant maturity or time of harvest. For instance, the level of anthocyanins in berries reaches a maximum at full maturity but decreases dramatically thereafter (Skrovankova et al., 2015). Leaves, roots, bark, and seeds in a single plant may even have completely different types of antioxidants.

iv) Post-Harvest Treatment and Storage: Drying operations, temperature manipulation, and duration of storage all affect phytochemical stability and concentration. Careless handling might result in oxidation, hydrolysis, or volatilisation of such important antioxidant components (Azmir et al., 2013).

v) Extraction Solvents and Methods: The extraction method—aqueous, alcoholic, supercritical fluid, or ultrasonic—may have a dramatic influence on yield and composition of compounds recovered. Solvent polarity is important in selectively recovering specific classes of antioxidants (Dai & Mumper, 2010). Absence of standardised extraction procedures results in extreme variability even when the same plant material is employed.

This multifactorial heterogeneity detracts from reproducibility and makes dose-response evaluation more challenging, since different studies may be evaluating substantially different chemical entities under the name of the same extract. In addition, it slows down regulatory approval and clinical translation, since regulatory agencies need to have consistent and well-characterised formulations for therapeutic application.

4.3 Lack of Standardised Dosages and Dose-Response Relationships

One of the long-standing shortcomings in the clinical use of plant antioxidants is the lack of standardised doses and undefined dose-response relationships. Few preclinical and clinical trials derive an apparent dose-therapeutic effect correlation, thus, it is challenging to define optimal, safe, and effective human dosage ranges.

This variation in phytochemical concentration between plant extracts is one of the crucial complicating factors. For example, research into quercetin showed that even pharmaceutical preparations can contain widely different amounts of active ingredient, depending on source and preparation method (Chen et al., 2013). Furthermore, some bioactive substances may show biphasic or hormetic dose-response profiles, such that low and high doses have opposite biological impacts (Calabrese, 2005), making dosage advice even more complex.

Without established dosing paradigms, interventions risk being subtherapeutic, incapable of achieving the desired biological effect or toxic, particularly when ingested in concentrated or supplement form. This shortfall impedes regulatory approval and threatens consumers ingesting over-the-counter herbal preparations without the oversight of medical professionals.

4.4 Potential Bioavailability and Stability Challenges

Most phytochemicals, even if they exhibit high antioxidant activity in vitro, possess low bioavailability in vivo and thus reduce their therapeutic potential. The key pharmacokinetic challenges are: Poor aqueous solubility, Low intestinal permeability, Heavy metabolism by gut and liver enzymes and High systemic clearance.

For example, curcumin, a polyphenol from Curcuma longa, has very low systemic bioavailability because of its poor absorption, rapid metabolism, and excretion (Anand et al., 2007). Even flavonoids such as epigallocatechin gallate (EGCG) from tea are subject to quick degradation and conjugation in the liver and gastrointestinal tract (Manach et al., 2005).

Additionally, most phytochemicals are chemically unstable. Light, heat, oxygen, or acidic conditions, such as in the stomach, can degrade active constituents before systemic circulation. Stability problems not only diminish efficacy but also complicate product formulation, shelf life, and storage.

To overcome these shortcomings, new delivery systems, including nanoencapsulation, liposomes, and solid lipid nanoparticles, are being investigated to improve absorption and avoid degradation (Patel et al., 2013).

4.5 Regulatory and Quality Control Barriers

The regulatory environment surrounding botanical antioxidants is dispersed and not uniform between nations. Plant substances in most areas are sold as dietary supplements or traditional remedies, which do not receive the same degree of scrutiny as pharmaceuticals. It means that there are loose approval processes, frequently lacking rigorous efficacy or safety trials (Marcus & Grollman, 2002).

Additionally, the absence of standardised quality control measures results in product quality inconsistencies, such as contamination, adulteration, mislabeling, and improper dosing. In a research by Gafner and Blumenthal (2017), many commercially sold herbal products contained undetectable amounts of active constituents or undeclared synthetic medications, which raised major concerns regarding product integrity.

These inconsistencies threaten consumer confidence and are a challenge for health care practitioners interested in using phytotherapeutics in practice. Regulatory authorities such as the FDA (USA), EMA (Europe), and AYUSH (India) have proposed standards for evaluating herbal products, but, as yet, there is a lack of harmonisation at an international level.

5. FUTURE DIRECTIONS:

To close the translational gap between promising preclinical findings and effective clinical use, several strategic steps need to be taken:

5.1 Large-Scale, Placebo-Controlled Clinical Studies

Well-designed, randomised, double-blind, placebo-controlled clinical trials (RCTs) are needed to determine the safety, efficacy, and therapeutic thresholds of plant antioxidants. Existing evidence is compromised by small sample sizes and methodological variability. Carefully powered RCTs with extended follow-up and standardised endpoints can generate the high-quality evidence necessary for clinical efficacy and regulatory approval (Ioannidis, 2005). Large-scale trials such as the PREDIMED trial on polyphenol-abundant Mediterranean diets, for example, provide a template for upcoming antioxidant-based interventions (Estruch et al., 2013).

5.2 Standardising Plant Extract Preparation and Characterisation

Uniform methodologies for extraction, processing, and harvesting are paramount to ensure a consistent phytochemical makeup. Standardisation would allow more comparable and reproducible studies from varied laboratories and populations (Kaufman et al., 2011). Bioactive compound fingerprinting and quantification using advanced techniques such as high-performance liquid chromatography (HPLC) and mass spectrometry can be utilized as the basis for formulation and quality control development (Bilia et al., 2014).

5.3 Use of Advanced Delivery Systems

Advanced drug delivery systems such as nanoencapsulation, liposomes, micelles, and solid lipid nanoparticles have the potential to significantly enhance the bioavailability, stability, and targeted delivery of poor solubility phytochemicals (Sharma et al., 2016). Nano-formulations of curcumin and resveratrol, for instance, have shown improved absorption and therapeutic activity in animal and early clinical models (Yallapu et al., 2012).

5.4 Integrating Omics-Based Approaches

Genomics, proteomics, and metabolomics can reveal molecular pathways impacted by antioxidant compounds and aid in the identification of efficacy and toxicity biomarkers. These technologies also

facilitate personalised phytotherapy by matching treatments to genetic or metabolic profiles (Hasin et al., 2017). As an example, metabolomics research has clarified flavonoids' impact on lipid metabolism and oxidative stress responses at a systems biology level (Scalbert et al., 2009).

5.5 Investigating Synergy with Conventional Therapies and Man-made Drugs

Antioxidants derived from plants could also increase the effectiveness of current therapies by synergistic or additive interactions, permitting lower dosing and decreased side effects. For instance, quercetin potentiates the action of chemotherapeutic drugs without increasing toxicity (D'Andrea, 2015). This synergy can be investigated systematically by applying network pharmacology and combinatorial screening methods.

5.6 Exploring Underutilised or New Plant Sources

A huge inventory of native and unexplored plants has undiscovered antioxidant capacity. Ethnobotanical knowledge, in tandem with high-throughput screening and bioassay-guided fractionation, may assist in identifying new bioactive compounds (Fabricant & Farnsworth, 2001). High-diversity bioregions like the Amazon, Indian subcontinent, and African tropics are hotspots for phytochemical discovery.

6. CONCLUSION

Plant antioxidants are a promising armamentarium against oxidative stress and its related pathologies. Their polypharmacological mechanisms, such as ROS scavenging, metal ion chelation, and redox signalling pathway modulation, provide a comprehensive strategy for preventing cellular damage and preserving physiological homeostasis. The rich phytochemical diversity of plants offers a treasure trove of therapeutic leads with potential uses in a wide range of chronic diseases.

Yet, in spite of robust support from in vitro and in vivo research, clinical translation is still limited. Major hurdles like heterogeneity in extract composition, absence of standardised dosing, low bioavailability, and poor clinical trials need to be addressed systematically. Standardisation of extract preparation, use of sophisticated delivery platforms, and stringent regulatory guidelines are essential steps toward ensuring consistency, safety, and efficacy.

In the future, integration of omics technologies, systems biology, and personalised medicine will improve our understanding of plant-based antioxidants at a molecular level and allow for targeted interventions. Further investigation of synergistic combinations with traditional therapies and under-exploited botanical sources could reveal new opportunities for innovation.

Essentially, closing the gap between ancient knowledge and contemporary science will be central to creating the next generation of antioxidant therapeutics—sustainable, efficient, and deeply grounded in nature's pharmacy.

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