Oxidative Stress, Free Radicals, Antioxidants: A Critical Review with Emphasis on Plant-Derived Antioxidants

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***Abstract*—Oxidative stress occurs when the body's production of free radicals and reactive oxygen species (ROS) exceeds its antioxidant capacity, causing progressive damage to lipids, proteins, and DNA. This imbalance is now recognised as a central driver of major chronic diseases including cardiovascular disease, diabetes, cancer, Alzheimer's disease, chronic kidney disease, and accelerated ageing. Synthetic antioxidants such as BHA, BHT, and TBHQ carry serious limitations - carcinogenic potential, prooxidant behaviour, allergenicity, and consistent failure in large-scale clinical trials (SELECT, HOPE, CARET, ATBC) - directing scientific attention toward safer, plant-derived alternatives.**

This review comprehensively analyses free radical biology, oxidative stress mechanisms, endogenous antioxidant defences (including the Nrf2 master regulator), and the pharmacology of polyphenols, flavonoids, tannins, terpenoids, and carotenoids. The documented toxicological limitations of synthetic antioxidants and the scientific superiority of multi-mechanism plant antioxidants are critically evaluated.

Systematic evaluation of sixty botanically diverse medicinal and food plant species using DPPH, ABTS, FRAP, CUPRAC, ORAC, and metal chelation assays consistently demonstrated strong to very strong antioxidant activity. Traditional Indian medicinal plants - Curcuma longa, Phyllanthus emblica, Ocimum sanctum, and Moringa oleifera - alongside global species including Punica granatum peel, Syzygium aromaticum, and Rubus occidentalis showed potency equal to or exceeding synthetic antioxidant standards. Plant antioxidants are superior due to multi-mechanism action, Nrf2 activation, pleiotropic bioactivities, and an excellent safety profile, making them the rational choice for antioxidant-based disease prevention and pharmaceutical development.

***Index Terms*—Oxidative stress; free radicals; reactive oxygen species; plant-derived antioxidants; polyphenols; flavonoids; Nrf2; DPPH; FRAP; synthetic antioxidants; lipid peroxidation; chronic disease; nutraceuticals**

I. LIFESTYLE AND ENVIRONMENTAL FACTORS: THE PRIMARY TRIGGERS OF FREE RADICAL GENERATION

The trajectory of human health in the twenty-first century has been profoundly shaped by the interplay between modern lifestyle choices and environmental exposures. Urbanisation, industrialisation, dietary transitions towards ultra-processed foods, physical inactivity, tobacco use, excessive alcohol consumption, psychological stress, sleep deprivation, and chronic exposure to environmental pollutants collectively constitute a milieu that is inherently pro-oxidant in nature [1]. These factors act in concert to overwhelm the body's natural capacity to maintain redox homeostasis, thereby initiating a cascade of molecular events that culminate in the pathogenesis of a broad spectrum of chronic and degenerative diseases [1, 9].

Dietary patterns constitute one of the most critical determinants of the body's redox status. Diets characterised by high intakes of refined carbohydrates, saturated and trans-fats, red and processed meats, and low intakes of fresh fruits, vegetables, and whole grains are consistently associated with elevated circulating biomarkers of oxidative stress including malondialdehyde (MDA), 8-hydroxydeoxyguanosine (8-OHdG), and oxidised low-density lipoprotein (oxLDL) [1, 5]. Conversely, adherence to Mediterranean-type dietary patterns rich in polyphenols, carotenoids, and other phytochemical antioxidants is associated with lower oxidative stress burden and reduced incidence of non-communicable diseases [2, 4]. The recognition that dietary antioxidants can substantially modulate the oxidative stress load has driven intense scientific interest in characterising and harnessing plant-derived bioactive

molecules for therapeutic and preventive applications [3, 43].

Beyond dietary factors, environmental pro-oxidants represent a growing and increasingly recognised public health concern. Exposure to fine particulate matter (PM2.5), ground-level ozone, polycyclic aromatic hydrocarbons (PAHs), heavy metals (lead, cadmium, mercury, arsenic), pesticides, industrial chemicals, and ultraviolet (UV) radiation all directly generate reactive oxygen species (ROS) within biological tissues or deplete endogenous antioxidant defences [5, 16]. Occupational exposures (mining, agriculture, manufacturing), indoor air pollution from cooking fuels, and the accumulation of persistent organic pollutants in the food chain further compound the oxidative burden at the population level. It is therefore evident that both modifiable lifestyle behaviours and environmental exposures are fundamental upstream determinants of the degree of free radical generation and resulting oxidative stress in human populations [1, 6].

Psychological stress is an often-underappreciated source of oxidative stress. Activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system during chronic psychological stress leads to elevated catecholamine levels, which undergo auto-oxidation to generate superoxide radicals. Cortisol-mediated immunosuppression further compromises antioxidant defences by reducing GSH synthesis and suppressing catalase expression. Epidemiological studies have documented significantly elevated levels of oxidative stress biomarkers in individuals experiencing chronic occupational stress, anxiety, and depression [1, 16]. Tobacco smoking is perhaps the most potent single lifestyle source of exogenous free radicals, with a single puff of cigarette smoke estimated to contain more than 10^{15} free radical molecules, including nitrogen oxides, semiquinone radicals, and various reactive carbonyl species [5, 7].

Fig.1. Lifestyle and Environmental sources of Free Radical Generation

II. FREE RADICALS: DEFINITION, GENERATION, AND BIOLOGICAL SIGNIFICANCE

2.1 Definition and Chemical Nature of Free Radicals

A free radical is defined as any chemical species that contains one or more unpaired electrons in its outermost atomic or molecular orbital. This electronic configuration renders free radicals thermodynamically unstable and highly reactive, as they possess a strong tendency to achieve electronic stability through the acquisition of an electron from, or donation of an electron to, adjacent molecules [7, 8]. The resulting chain reactions can propagate rapidly through biological macromolecules, causing widespread structural and functional damage. Free radicals may carry a positive charge, negative charge, or be electrically neutral; their defining characteristic is the

presence of the unpaired electron, not their charge state [5, 11].

The concept of free radicals in biological systems was first substantiated by Rebeca Gershman and Daniel Gilbert in the 1950s and subsequently formalised by Denham Harman in his landmark free radical theory of ageing (1956), which proposed that the progressive accumulation of oxidative damage from endogenously generated free radicals is the fundamental molecular driver of biological ageing and age-associated disease [8, 41]. Since then, the field of redox biology has evolved dramatically, revealing that free radicals occupy a central and nuanced position in both physiological regulation and pathological processes, with their biological impact depending critically on the species involved, the cellular compartment, the concentration, and the temporal context [10, 11].

2.2 Classification and Sources of Reactive Species

Reactive oxygen species (ROS) comprise both radical and non-radical oxygen-containing molecules that are chemically more reactive than molecular oxygen (O_2). The major physiologically relevant ROS include: (i) Superoxide anion radical ($O_2^{\bullet -}$), generated primarily by the one-electron reduction of O_2 catalysed by NADPH oxidase (Nox) enzymes, mitochondrial electron transport chain (ETC) complexes I and III, xanthine oxidase, and cytochrome P450 enzymes. While superoxide itself has limited reactivity with most biological molecules, it is the progenitor of most other ROS; (ii) Hydrogen peroxide (H_2O_2), produced by the spontaneous or SOD-catalysed dismutation of superoxide. Though non-radical, H_2O_2 is a critical redox signalling molecule and can cross cell membranes to act at distant sites; (iii) Hydroxyl radical (•OH), the most reactive and damaging of all ROS, generated by the Fenton reaction between H_2O_2 and redox-active Fe^{2+} or Cu^{+} ions. Its extreme reactivity means it reacts at near diffusion-limited rates with virtually any biological molecule within a few molecular diameters of its site of formation; (iv) Singlet oxygen ($^1O_2$), an excited non-radical form of molecular oxygen generated primarily during UV irradiation and photosensitisation reactions; (v) Peroxyl radicals (ROO•) and alkoxyl radicals (RO•), generated during lipid peroxidation chain reactions; (vi) Hypochlorous acid (HOCl), generated by myeloperoxidase in activated neutrophils during the oxidative burst [5, 7, 11].

Reactive nitrogen species (RNS) constitute an equally important class of reactive molecules in biological redox chemistry. Nitric oxide (NO•), synthesised from L-arginine by nitric oxide synthase (NOS) isoforms (nNOS, eNOS, iNOS), is itself a radical but at physiological concentrations serves critical roles in vasodilation, neurotransmission, and immune defence. However, NO• rapidly reacts with superoxide at near-diffusion-limited rates to form peroxynitrite ($ONOO^-$), a potent oxidant and nitrating agent capable of nitrating tyrosine residues in proteins (forming 3-nitrotyrosine, a validated biomarker of nitrosative stress), oxidising GSH, and initiating lipid peroxidation [6, 11, 12]. Other important RNS include nitrogen dioxide (NO_2•), dinitrogen trioxide (N_2O_3), and nitroxyl (HNO). The combined concept of reactive oxygen and nitrogen species (RONS) is now widely employed to encompass the full spectrum of reactive intermediates generated in biological systems [11].

2.3 Endogenous Sources of Free Radical Generation

Under physiological conditions, the mitochondrial electron transport chain is quantitatively the most significant intracellular source of ROS. As electrons flow through Complexes I (NADH: ubiquinone oxidoreductase) and III (ubiquinol: cytochrome c oxidoreductase), a small percentage (estimated at 0.2–2% of total O_2 consumed under normal conditions) undergoes one-electron reduction to form superoxide, primarily at the flavin mononucleotide (FMN) site of Complex I and the ubi semiquinone site of Complex III [13]. The mitochondrial matrix, which contains Mn-SOD as its primary superoxide-scavenging enzyme and has abundant iron available for Fenton chemistry, is therefore a hotspot for oxidative damage, particularly to mitochondrial DNA (mtDNA), which lacks the protective histone coating of nuclear DNA and has limited repair mechanisms [13].

NADPH oxidases (Nox enzymes) represent the second major enzymatic source of superoxide in biological systems. The Nox family comprises seven isoforms (Nox1-5 and Duox1-2), each with distinct tissue distribution, subcellular localisation, and regulatory mechanisms. Nox2 (gp91phox), the prototypic phagocyte NADPH oxidase, generates superoxide as a deliberate antimicrobial mechanism during the 'respiratory burst' of activated neutrophils and macrophages, producing the high localised ROS concentrations required for pathogen killing [12].

However, inappropriate or chronic activation of Nox enzymes in vascular endothelial cells, cardiomyocytes, neurons, and renal tubular cells under pathological conditions including hypertension, hyperglycaemia, ischaemia, and angiotensin II stimulation contributes substantially to disease-associated oxidative stress [12, 24].

Additional important endogenous sources of ROS include: xanthine oxidase, which generates both superoxide and H_2O_2 during the catabolism of hypoxanthine and xanthine to uric acid, and is particularly activated during ischaemia-reperfusion; cytochrome P450 (CYP) enzymes in the endoplasmic reticulum, which generate ROS as by-products of xenobiotic and drug metabolism; monoamine oxidases (MAO-A and MAO-B) in the outer mitochondrial membrane, which produce H_2O_2 during the oxidative deamination of monoamine neurotransmitters; cyclooxygenases (COX-1 and COX-2) during prostaglandin biosynthesis; lipoxygenases; and nitric oxide synthase enzymes when uncoupled due to substrate or cofactor (BH4) deficiency [5, 16]. The cellular generation of ROS is therefore not confined to any single compartment or enzyme but represents a complex, multi-source network whose dysregulation under pathological conditions can rapidly escalate to systemic oxidative stress.

III. REACTIVE OXYGEN AND NITROGEN SPECIES: THE FORMATION OF OXIDATIVE STRESS

3.1 Definition and Pathophysiology of Oxidative Stress

Oxidative stress is defined as a disruption of the balance between the generation of reactive oxygen and nitrogen species (RONS) and the capacity of the biological antioxidant defence system to neutralise these reactive intermediates and repair the resulting damage. First formally conceptualised by Helmut Sies in 1985 and subsequently refined in collaboration with Dean Jones in 2020, the contemporary definition of oxidative stress emphasises disruption of redox signalling and control rather than merely quantitative imbalance [8, 10]. This distinction is important because it recognises that ROS serve essential physiological functions at low to moderate concentrations - including regulation of cell proliferation, differentiation, migration, apoptosis, and immune activation - and that it is the qualitative and quantitative dysregulation of redox chemistry, rather than the mere presence of ROS, that constitutes pathological oxidative stress [9, 11].

At the cellular level, oxidative stress triggers the activation of multiple redox-sensitive transcription factors and signalling cascades. Nuclear factor kappa B (NF-κB), a master regulator of the inflammatory response, is activated by ROS through IκB kinase (IKK)-dependent phosphorylation and degradation of its inhibitor IκBα, leading to the transcriptional upregulation of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), adhesion molecules (ICAM-1, VCAM-1), and additional pro-oxidant enzymes [36]. Activator protein-1 (AP-1), comprising Jun and Fos family members, is similarly activated by ROS through the JNK and p38 MAPK pathways, driving the expression of genes involved in proliferation and matrix degradation. Conversely, the Nrf2/Keap1 pathway represents the primary adaptive cytoprotective response to oxidative stress, activating the transcription of a battery of antioxidant and detoxification genes through antioxidant response element (ARE) binding [43, 45].

Mitochondrial dynamics - the processes of mitochondrial fusion and fission regulated by dynamin-related GTPases (MFN1, MFN2, OPA1 for fusion; DRP1, FIS1 for fission) - are critically regulated by the cellular redox environment and profoundly influence the cellular response to oxidative stress [13]. Under mild oxidative stress, increased mitochondrial fusion promotes the dilution and complementation of damaged mitochondrial components, preserving bioenergetic capacity. Under severe or chronic oxidative stress, excessive DRP1-mediated mitochondrial fission generates small, dysfunctional mitochondria with reduced membrane potential, impaired ATP synthesis, and increased ROS generation, creating a vicious cycle of escalating oxidative damage that ultimately triggers apoptotic and necrotic cell death pathways [13].

3.2 Dual Role of ROS: Physiological Versus Pathological

It is essential to appreciate that not all ROS generation is deleterious. At sub-toxic concentrations, ROS function as indispensable second messengers in cellular signalling networks. H_2O_2, generated at the plasma membrane by growth factor receptor-activated

NADPH oxidases, reversibly oxidises regulatory cysteine residues in protein tyrosine phosphatases (PTPs) and kinases, modulating their activity and transmitting proliferative and survival signals [9, 11]. NO• generated by eNOS in vascular endothelial cells diffuses into vascular smooth muscle cells where it activates soluble guanylate cyclase, elevates cGMP, and mediates vasodilation - a process fundamental to blood pressure regulation and cardiovascular homeostasis [6]. Phagocyte-generated ROS constitute a critical arm of the innate immune response against bacterial and fungal pathogens, where deficiency (as in chronic granulomatous disease, CGD) leads to life-threatening recurrent infections [12].

The threshold between beneficial and deleterious ROS effects is context-dependent and regulated by the concentration, duration, subcellular localisation, and chemical identity of the specific reactive species involved. Redox biology has thus evolved from a simple 'ROS = damage' paradigm towards a nuanced understanding of redox homeostasis as a dynamically regulated system essential for normal cellular function, whose disruption - in either direction (excessive ROS or excessive antioxidant suppression) - can have pathological consequences [10, 11]. This understanding has important implications for the design of antioxidant therapies: indiscriminate, non-targeted antioxidant supplementation that globally suppresses all ROS may paradoxically impair beneficial signalling and immune function, an insight that helps explain the disappointing results of several large-scale antioxidant supplementation trials [43].

IV. OXIDATIVE DAMAGE TO BIOLOGICAL MACROMOLECULES: LIPIDS, PROTEINS, AND DNA

4.1 Lipid Peroxidation

Lipid peroxidation (LPO), the oxidative degradation of polyunsaturated fatty acids (PUFAs) in cellular membranes and lipoproteins, is one of the most extensively studied and clinically significant consequences of oxidative stress. The process proceeds through a self-propagating chain reaction consisting of three phases: initiation, propagation, and termination [14]. During initiation, a reactive radical (typically •OH) abstracts a bisallylic hydrogen atom from a PUFA side chain (particularly arachidonic acid, linoleic acid, or docosahexaenoic acid), generating a carbon-centred lipid radical (L•) that rapidly rearranges to form a conjugated diene structure. During propagation, L• reacts with molecular oxygen to form a lipid peroxyl radical (LOO•), which in turn abstracts hydrogen from an adjacent PUFA molecule to form a lipid hydroperoxide (LOOH) and a new carbon-centred radical, thereby propagating the chain [14, 5].

The major end-products of lipid peroxidation are highly cytotoxic aldehydic compounds including malondialdehyde (MDA), 4-hydroxynonenal (4-HNE), acrolein, and isoprostanes. MDA is the most widely measured lipid peroxidation biomarker, typically quantified by the thiobarbituric acid reactive substances (TBARS) assay. 4-HNE is considered the most biologically active lipid peroxidation product, forming covalent adducts (via Michael addition to cysteine, histidine, and lysine residues and via Schiff base formation with lysine) with proteins, lipids, and nucleic acids, thereby impairing protein function, inducing mitochondrial dysfunction, activating apoptotic pathways, and causing genotoxic DNA damage [14]. The oxidative modification of LDL to form oxLDL - occurring primarily through apolipoprotein B-100 modification by lipid peroxidation products - is a pivotal event in atherosclerosis initiation, as oxLDL is avidly internalised by macrophage scavenger receptors, promoting foam cell formation and plaque development [26].

4.2 Protein Oxidation

Proteins, which constitute the primary functional molecules of living cells, are major targets of oxidative attack. ROS-mediated protein oxidation can occur through direct radical attack on amino acid side chains or through secondary reactions with lipid peroxidation products and reactive carbonyl compounds. The most common forms of oxidative protein modification include: (i) carbonylation - the introduction of carbonyl (aldehyde or ketone) groups into amino acid side chains (particularly Pro, Arg, Lys, Thr), typically via metal-catalysed oxidation; protein carbonyls are widely used as biomarkers of protein oxidation and accumulate with ageing and disease; (ii) methionine and cysteine oxidation — the reversible oxidation of methionine to methionine sulphoxide (repaired by methionine sulphoxide reductases) and the reversible oxidation of cysteine thiol groups to disulphides,

sulphenic acid, sulphinic acid, or sulphonic acid - these modifications serve important regulatory roles at low levels but impair protein function when excessive [10, 16]; (iii) tyrosine nitration by peroxynitrite, forming stable 3-nitrotyrosine adducts that disrupt tyrosine phosphorylation-dependent signalling; (iv) cross-linking and aggregation of proteins, reducing their functional activity and targeting them for proteasomal degradation [6, 16].

4.3 DNA and RNA Oxidative Damage

DNA, the repository of genetic information, is a critical target of oxidative damage. The major oxidative DNA lesion is 8-hydroxy-2'-deoxyguanosine (8-OHdG), formed by the hydroxyl radical-mediated oxidation of deoxyguanosine at the C-8 position. 8-OHdG is a highly mutagenic lesion that mispairs with adenine during DNA replication, causing G:C→T: A transversion mutations, and is widely used as a validated biomarker of oxidative DNA damage in both clinical studies and epidemiological research [15, 9]. Additional oxidative DNA lesions include thymine glycols, formamidopyrimidines (FapyG and FapyA), oxidised cytosine derivatives, a basic sites, single-strand breaks (SSBs), and double-strand breaks (DSBs) generated by the clustering of base oxidation lesions and/or strand breaks within a few base pairs [10].

Oxidative damage to mitochondrial DNA (mtDNA) is of particular clinical significance because mtDNA is located in close proximity to the primary ROS-generating sites of the inner mitochondrial membrane, lacks the protective histone coating of nuclear DNA, has fewer and less efficient DNA repair systems, and exists in multiple copies per cell - allowing a mixture of normal and mutated mtDNA (heteroplasmy) to accumulate and progressively shift towards mutant genomes [13]. Accumulation of mtDNA mutations impairs the expression of ETC subunits encoded by mtDNA, reducing respiratory chain efficiency and further elevating mitochondrial ROS generation - a self-reinforcing cycle now termed the 'mitochondrial ROS vicious cycle' [13]. Oxidative damage to RNA, including oxidation of mRNA and tRNA by 8-oxoguanosine incorporation, impairs translational fidelity and protein synthesis, contributing to the proteotoxic stress associated with ageing and neurodegenerative disease [10].

V. PATHOGENESIS OF CHRONIC DISEASES: OXIDATIVE STRESS AS THE UNIFYING MECHANISM

The molecular damage inflicted upon lipids, proteins, and nucleic acids by an uncontrolled oxidative milieu translates directly into cellular dysfunction, tissue injury, organ failure, and ultimately the clinical manifestation of chronic disease. Oxidative stress is now recognised as a unifying pathophysiological thread connecting a remarkably broad spectrum of non-communicable diseases - a mechanistic convergence that reflects the ubiquitous nature of ROS generation in living systems and the fundamental vulnerability of biological macromolecules to oxidative attack [1, 10, 16].

In cardiovascular disease, ROS-mediated endothelial dysfunction - characterised by reduced bioavailability of vasodilatory nitric oxide due to its quenching by superoxide to form peroxynitrite - constitutes the earliest and most pivotal pathological event [25]. Oxidative modification of LDL, NADPH oxidase-dependent vascular inflammation, smooth muscle cell proliferation and migration, and matrix metalloproteinase activation collectively drive atherosclerotic plaque formation, progression, and rupture [26, 27]. In the nervous system, the brain's extraordinary susceptibility to oxidative damage - attributable to its high oxygen consumption, high PUFA content, and comparatively limited antioxidant enzyme levels - underlies the central role of ROS in the pathogenesis of Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis [19, 21, 22]. In diabetes, hyperglycaemia-driven superoxide overproduction from mitochondria activates multiple downstream pathological pathways including the polyol pathway, protein kinase C, advanced glycation end-products, and hexosamine pathway, collectively causing diabetic microvascular and macrovascular complications [28]. Oxidative stress is also fundamental to the pathogenesis of cancer through ROS-mediated mutagenesis, epigenetic dysregulation, and oncogenic signalling activation [15]; liver disease including NASH, NAFLD, and hepatocellular carcinoma [30]; chronic kidney disease [38]; inflammatory bowel disease [37]; respiratory viral infections including RSV [39]; reproductive disorders [33, 34]; ocular pathologies [40]; and accelerated biological ageing [41].

Table 1: Oxidative Stress and Disease — Summary

Disease / Condition	Key ROS Sources & Mechanism	Primary References
Cardiovascular Disease	Nox2, eNOS uncoupling → endothelial dysfunction, oxLDL, plaque	[24, 25, 26, 27]
Neurodegenerative (AD, PD)	Mitochondrial ROS, iron dysregulation, Aβ-induced oxidative damage	[18, 19, 21, 22, 23]
Diabetes Mellitus	Mitochondrial glucose oxidation → polyol pathway, PKC, AGEs	[28, 31]
Cancer	Oxidative mutagenesis, 8-OHdG, Nrf2 hijacking, oncogenic ROS	[15, 29]
Chronic Kidney Disease	Oxidative tubular injury, glomerulosclerosis	[38]
Inflammatory Bowel Disease	Mucosal ROS, NF-κB activation, epithelial barrier disruption	[37]
Reproductive Disorders	Sperm lipid peroxidation, mtDNA damage, pregnancy complications	[32, 33, 34, 35]
Liver Disease (NAFLD/NASH)	Lipid peroxidation, CYP2E1 ROS, stellate cell activation	[30]
Ocular Diseases (AMD, cataract)	UV-induced ROS, lens protein aggregation, RPE damage	[40]
Ageing & Skin	Cumulative mtDNA damage, collagen oxidation, UV photooxidation	[41, 42]

VI. ENDOGENOUS ANTIOXIDANT DEFENCE SYSTEM

6.1 Enzymatic Antioxidants

In response to the perpetual oxidative challenge of aerobic metabolism, living organisms have evolved a sophisticated multi-tiered endogenous antioxidant defence network. This system is broadly divided into enzymatic antioxidants, non-enzymatic low-molecular-weight antioxidants, and repair/regeneration systems, all of which function in a highly coordinated and compartment-specific manner [43, 45].

Superoxide dismutase (SOD) catalyses the dismutation of superoxide anion to H_2O_2 and molecular oxygen at rates approaching the diffusion limit (~2×10^9 $M^{-1}s^{-1}$). Three isoforms exist in mammals: Cu/Zn-SOD (SOD1) in the cytoplasm and intermembrane space of mitochondria; Mn-SOD (SOD2) in the mitochondrial matrix, widely considered the most critical antioxidant enzyme for cellular survival under oxidative stress conditions; and EC-SOD (SOD3), the extracellular glycoprotein form anchored to the vascular endothelium and extracellular matrix [43, 45]. Catalase (CAT), a haem-containing tetrameric enzyme concentrated in peroxisomes, catalyses the dismutation of H_2O_2 to water and molecular oxygen at one of the highest known catalytic rates (kcat ~10^7 s^{-1}), providing a critical mechanism for the elimination of the H_2O_2 produced by SOD and the numerous H_2O_2-generating oxidases in peroxisomes [43].

Glutathione peroxidases (GPx) are a family of selenium-dependent (GPx1–4, 6) and selenium-independent (GPx5, 7, 8) enzymes that reduce H_2O_2, organic hydroperoxides, and phospholipid hydroperoxides using GSH as the electron donor. GPx4, also known as phospholipid hydroperoxide glutathione peroxidase (PHGPx), is uniquely capable of directly reducing phospholipid hydroperoxides within intact membranes and is essential for the prevention of ferroptosis, a regulated form of iron-dependent cell death driven by uncontrolled lipid peroxidation [14, 43]. Thioredoxin reductase (TrxR), a selenocysteine-containing flavoenzyme, reduces oxidised thioredoxin (Trx) using NADPH, regenerating the reduced Trx that participates in the reduction of ribonucleotide reductase, peroxiredoxins, and various transcription factors. Peroxiredoxins (Prx), a family of six thiol-dependent peroxidases, are now recognised as quantitatively the most important H_2O_2-scavenging enzymes in most mammalian cell types at physiological H_2O_2 concentrations [45].

Glutathione S-transferases (GSTs) catalyse the conjugation of GSH to electrophilic substrates including lipid peroxidation products (4-HNE, MDA), xenobiotics, and oxidised DNA bases, facilitating their detoxification and elimination. Heme oxygenase-1 (HO-1), the inducible isoform of haem oxygenase, degrades pro-oxidant free haem to biliverdin (subsequently converted to antioxidant bilirubin), carbon monoxide (with anti-inflammatory and Vaso protective properties), and free iron (sequestered by ferritin). HO-1 is a key Nrf2 target gene and serves as a sensitive indicator of cellular oxidative stress [43, 45].

6.2 Non-Enzymatic Antioxidants and the Nrf2 Master Regulator

Glutathione (GSH), the tripeptide γ-glutamyl-cysteinyl-glycine, is the most abundant intracellular low-molecular-weight antioxidant, present at millimolar concentrations (1–10 mM) in most mammalian cells. The reactive thiol group of its cysteine residue provides the electron-donating capacity for direct radical scavenging, GST-catalysed conjugations, GPx-catalysed peroxide reduction, and regeneration of ascorbate and α-tocopherol from their oxidised forms [43, 44]. The ratio of reduced GSH to oxidised GSSG serves as a sensitive and widely used indicator of the cellular redox state. Ascorbic acid (Vitamin C), the most abundant water-soluble antioxidant in plasma and tissues, scavenges $O_2^{\bullet-}$, $^{\bullet}OH$, HOCl, and $^1O_2$ and regenerates α-tocopherol from the tocopheroxyl radical; it is also essential for collagen hydroxylation and iron absorption [43]. α-Tocopherol (Vitamin E), the major lipid-soluble antioxidant in cell membranes and lipoproteins, interrupts lipid peroxidation chain reactions by donating a hydrogen atom to lipid peroxyl radicals ($LOO^{\bullet}$), generating the relatively stable tocopheroxyl radical that can be regenerated by vitamin C [14, 44]. Coenzyme Q10 (ubiquinol), carotenoids, bilirubin, uric acid, lipoic acid, and melatonin constitute additional important endogenous non-enzymatic antioxidants each with distinct compartmentalisation and mechanisms [43].

The transcription factor Nrf2 (Nuclear factor erythroid 2-related factor 2) is universally recognised as the master regulator of the cellular antioxidant and cytoprotective response. Under basal conditions, Nrf2 is constitutively degraded through Keap1 (Kelch-like ECH-associated protein 1)-mediated ubiquitination and proteasomal degradation. Keap1 functions as a molecular sensor of electrophilic and oxidative stress through its 27 reactive cysteine residues; oxidation or electrophilic modification of key sensor cysteines (Cys151, Cys273, Cys288) induces conformational changes in Keap1 that release Nrf2, allowing its nuclear translocation and binding to antioxidant response elements (AREs) in the promoters of over 200 target genes. These Nrf2 target genes encode antioxidant enzymes (SOD, CAT, GPx, HO-1, NQO1), GSH biosynthetic enzymes (GCLc, GCLm, GSS), thioredoxin and peroxiredoxin systems, and multiple Phase II detoxification enzymes [43, 46]. Many natural phytochemical antioxidants exert their cytoprotective effects at least in part through Nrf2 activation, making the Nrf2 pathway a key target for nutraceutical antioxidant development

VII. EXOGENOUS ANTIOXIDANTS: AN OVERVIEW

When endogenous antioxidant defences are overwhelmed by elevated ROS generation - whether due to chronic lifestyle exposures, disease states, ageing, or nutritional deficiencies - supplementation with exogenous antioxidants provides a critical complementary defence strategy. Exogenous

antioxidants are broadly classified into two major categories based on their origin and chemical nature: synthetic antioxidants, which are industrially manufactured chemical compounds; and natural antioxidants, derived from plant, animal, or microbial sources [43, 44]. Each category encompasses structurally diverse compounds operating through multiple antioxidant mechanisms and exhibiting distinct pharmacokinetic properties, safety profiles, and practical applications in food preservation, pharmaceutical formulation, and clinical/nutraceutical contexts [44, 46].

VIII. PLANT-DERIVED ANTIOXIDANTS: POLYPHENOLS, FLAVONOIDS, TANNINS, PHENOLIC ACIDS, AND TERPENOIDS

8.1 Polyphenols and Phenolic Acids

Polyphenols constitute the most structurally diverse and quantitatively abundant class of plant-derived secondary metabolites with antioxidant properties, encompassing over 8,000 identified structures. They are characterised by the presence of at least one aromatic ring bearing one or more hydroxyl substituents and are biosynthesised primarily through the shikimate/phenylpropanoid pathway from phenylalanine or tyrosine precursors [50, 53]. Phenolic acids are the simplest class of polyphenols and are subdivided into hydroxybenzoic acids (e.g. gallic acid, protocatechuic acid, syringic acid, vanillic acid) and hydroxycinnamic acids (e.g. ferulic acid, caffeic acid, p-coumaric acid, synaptic acid). Gallic acid, found abundantly in pomegranate, grapes, and tea, is one of the most potent free radical scavengers known, with multiple ortho-hydroxyl groups that facilitate hydrogen atom transfer and electron transfer to ROS. Ferulic acid, a major component of whole grains and the cell walls of cereals, demonstrates exceptional antioxidant activity in both aqueous and lipid environments, as well as significant anti-inflammatory and photoprotective activities [2, 43].

The antioxidant activity of polyphenols operates through multiple complementary mechanisms including:

direct radical scavenging via hydrogen atom transfer (HAT) or single electron transfer (SET) from phenolic OH groups to ROS;

metal chelation, particularly of Fe^{2+} and Cu^{+} involved in Fenton/Haber-Weiss reactions, through the formation of stable metal-polyphenol complexes that prevent hydroxyl radical generation;

inhibition of pro-oxidant enzymes including xanthine oxidase, NADPH oxidase, lipoxygenase, and cyclooxygenase;

upregulation of endogenous antioxidant defences through Nrf2/ARE pathway activation; and

anti-inflammatory activities including NF-κB inhibition that reduce the inflammatory ROS generation cascade [43, 46, 48]. The chemical structure-activity relationships that govern polyphenol antioxidant potency - particularly the presence of catechol (o-dihydroxyphenyl) groups, conjugated double bonds, and free hydroxyl groups - have been extensively characterised and provide the basis for rational structure-optimisation in synthetic antioxidant drug design [43].

8.2 Flavonoids

Flavonoids, the most studied subclass of polyphenols, are characterised by a C6-C3-C6 benzo-γ-pyrone skeleton comprising two aromatic rings (A and B) linked through a three-carbon heterocyclic C ring. The six major flavonoid subclasses include flavanols (quercetin, kaempferol, myricetin, fisetin), flavones (apigenin, luteolin, chrysin), flavanones (hesperidin, naringenin, eriodictyol), flavanols/flavan-3-ols (catechin, epicatechin, EGCG, gallocatechin), anthocyanins (cyanidin, delphinidin, pelargonidin), and isoflavones (genistein, daidzein, formononetin) [49, 51, 17]. The structural determinants of flavonoid antioxidant potency include: the catechol moiety (3',4'-OH group) on the B ring, which is the primary radical scavenging site; the 2,3-double bond conjugated with the 4-oxo group in ring C, enabling electron delocalisation; and the 3-OH group on ring C, which together with the 2,3-double bond and 4-oxo group confers metal chelation capability particularly through the 3-hydroxy-4-keto arrangement [17, 51].

Quercetin, the most abundant dietary flavanol found in onions, apples, capers, and green tea, is considered one of the most biologically potent flavonoids. Its four OH groups and catechol B ring confer exceptional ROS scavenging capacity, while its 3-OH and 4-oxo arrangement provides strong iron-chelating activity

that prevents Fenton chemistry-mediated •OH generation [52]. Quercetin also inhibits xanthine oxidase, suppresses NF-κB-mediated inflammation, activates the Nrf2 pathway, and exhibits anti-platelet, anti-carcinogenic, and neuroprotective activities in experimental models [17]. Epigallocatechin-3-gallate (EGCG), the major catechin of green tea (Camellia sinensis), is among the most potent naturally occurring antioxidants identified, with a galloyl ester group providing additional radical scavenging capacity beyond the catechol moieties [43]. Hesperidin and naringenin from citrus fruits, apigenin from parsley and chamomile, and luteolin from celery and thyme each exhibit distinct pharmacological profiles spanning antioxidant, anti-inflammatory, anti-diabetic, neuroprotective, and cardioprotective activities [51, 17].

8.3 Tannins

Tannins are high-molecular-weight polyphenolic compounds characterised by their ability to precipitate proteins from solution - a property underlying their traditional use in leather tanning and their astringent taste in foods and beverages. Tannins are classified into two major groups: hydrolysable tannins, which consist of a polyol (typically glucose) core esterified with gallic acid (gallotannins, e.g. tannic acid, pentagalloylglucose) or ellagic acid (ellagitannins, e.g. punicalagin from pomegranate, which is one of the most potent antioxidant compounds identified in any food source); and condensed tannins (proanthocyanidins), which are oligomers and polymers of flavan-3-ol units (catechin and epicatechin) linked through C4→C8 or C4→C6 bonds, found abundantly in grape seeds, bark, and cocoa [43, 50]. The antioxidant activity of tannins is exceptional due to their numerous hydroxyl groups; gallic acid-containing hydrolysable tannins exhibit particularly potent radical scavenging and metal chelation activities, with galloyl groups contributing substantially to antioxidant capacity through the formation of stable, delocalised radical cation intermediates [43].

8.4 Terpenoids and Carotenoids

Terpenoids (also called isoprenoids) constitute the largest and most structurally diverse class of plant secondary metabolites, encompassing over 55,000 identified structures derived biosynthetically from the five-carbon isoprene unit (C5H8). Many terpenoids possess significant antioxidant properties through diverse mechanisms. Monoterpenoids (C10), including thymol and carvacrol from thyme and oregano, and limonene from citrus peel, exhibit antioxidant activity through direct radical scavenging and stimulation of endogenous antioxidant enzyme activity. Sesquiterpenoids (C15) include farnesol and bisabolol from chamomile. Diterpenoids (C20) include carnosic acid and carnosol from rosemary, which are potent chain-breaking antioxidants protecting against lipid oxidation. Triterpenoids (C30) include oleanolic acid, ursolic acid, and betulinic acid from various medicinal plants, with demonstrated antioxidant and anti-inflammatory activities through NF-κB inhibition and Nrf2 activation [3, 43].

Carotenoids, the most important class of tetraterpenoids (C40) in the antioxidant context, are fat-soluble pigments found in red, orange, and yellow plant foods. Their extended conjugated polyene chain (typically 9–11 double bonds) enables efficient physical quenching of singlet oxygen ($^1O_2$) - the most important mechanism of carotenoid antioxidant activity in tissues with high photooxidative stress - as well as chemical quenching of peroxyl radicals through electron transfer and radical addition reactions. Lycopene (from tomatoes) is the most potent singlet oxygen quencher among carotenoids; β-carotene is a provitamin A carotenoid with broad antioxidant activity; lutein and zeaxanthin are specifically concentrated in the macula of the retina where they serve as 'biological sunglasses' filtering blue light and quenching photo-generated singlet oxygen [2, 43]. Astaxanthin, a xanthophyll carotenoid from marine organisms including Haematococcus pluvialis microalgae, demonstrates antioxidant potency estimated at 10–100 times greater than β-carotene and 500 times greater than vitamin E in some assay systems [20].

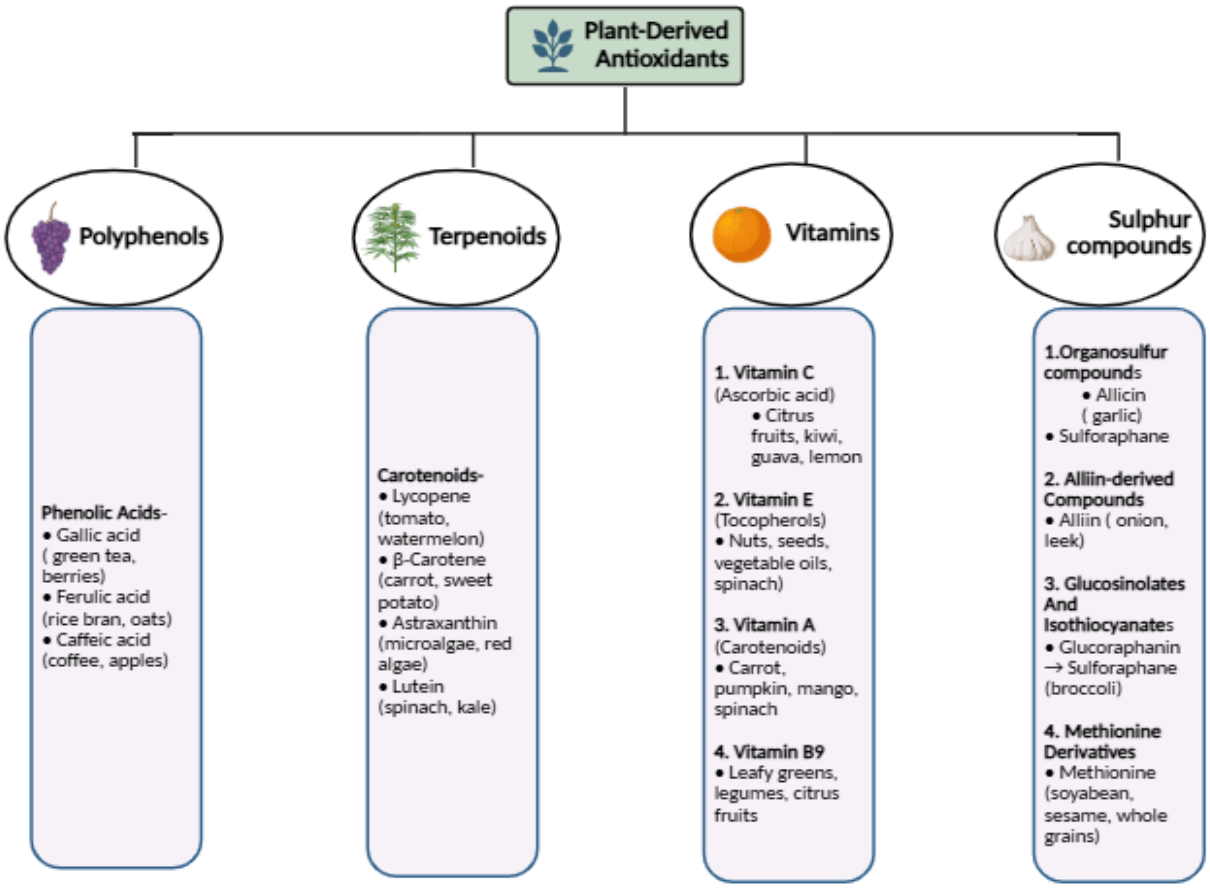

Fig.2. Classification of Plant-Derived Natural Antioxidants

IX. MEDICINAL PLANTS AS SOURCES OF NATURAL ANTIOXIDANTS

Medicinal plants have served as humanity's primary therapeutic resource for millennia, and their enduring use across diverse cultural and geographical contexts is increasingly validated by modern phytochemical and pharmacological research. Plants biosynthesize an extraordinary diversity of secondary metabolites - estimated at over 200,000 distinct structures - many of which evolved as part of the plant's own defence against oxidative stress induced by UV radiation, ozone, pathogen attack, herbivory, drought, and heavy metal toxicity [3, 48]. It is therefore not coincidental that the most potent plant-derived antioxidants are found in species that experience the most intense oxidative/environmental stresses during their growth and development. This co-evolutionary relationship between plant oxidative stress and antioxidant phytochemical synthesis provides both the scientific rationale and the ethnopharmacological foundation for the therapeutic use of medicinal plants as natural antioxidant sources [3, 50].

Indian traditional medicine systems, particularly Ayurveda, Siddha, and Unani, have documented hundreds of medicinal plants with antioxidant, adaptogenic, anti-inflammatory, and rasayana (rejuvenating) properties over three millennia of empirical observation and clinical practice. Among the most pharmacologically validated Indian medicinal plants with exceptional antioxidant properties are: Phyllanthus emblica (Amla/Indian gooseberry), arguably the richest known natural source of vitamin C and emblicanin tannins; Curcuma longa (Turmeric), whose active constituent curcumin is among the most extensively studied natural antioxidants and Nrf2 activators; Withania somnifera (Ashwagandha), whose withanolide steroidal lactones exhibit adaptogenic and antioxidant effects through Nrf2 activation and inflammatory cascade inhibition;

Tinospora cordifolia (Guduchi), with abundant berberine, tinosporin, and various phenolic antioxidants; Bacopa monnieri (Brahmi), containing saponins and polyphenols with demonstrated neuroprotective antioxidant activity; Ocimum tenuiflorum (Tulsi/Holy Basil), rich in eugenol, rosmarinic acid, and flavonoids; and Azadirachta indica (Neem), containing limonoids, flavonoids, and quercetin with potent antioxidant and immunomodulatory activities [3, 4, 23].

Beyond Indian traditional medicine, numerous globally distributed medicinal plants have contributed validated antioxidant phytochemicals to modern pharmacology. Green tea (Camellia sinensis) provides EGCG, one of the most potent naturally occurring antioxidants; grape (Vitis vinifera) seeds and skin supply oligomeric proanthocyanidins and resveratrol; pomegranate (Punica granatum) fruit provides punicalagin and ellagic acid; rosemary (Rosmarinus officinalis) contributes carnosic acid and rosmarinic acid; milk thistle (Silybum marianum) provides the flavonolignan complex silymarin (silybin, silydianin, silychristin) with documented hepatoprotective antioxidant activity; and Ginkgo biloba provides ginkgoflavonoids and bilobalide with neuroprotective antioxidant properties [2, 4, 43]. The characterisation of medicinal plants' antioxidant phytochemical profiles through advanced analytical techniques including HPLC, LC-MS/MS, NMR spectroscopy, and total phenolic/flavonoid content determination is a prerequisite for their scientific standardisation, quality control, and evidence-based clinical application [53].

X. SYNTHETIC ANTIOXIDANTS: EXAMPLES, APPLICATIONS, AND SIGNIFICANT LIMITATIONS

10.1 Overview and Examples of Synthetic Antioxidants

Synthetic antioxidants are chemically manufactured compounds intentionally added to foods, cosmetics, pharmaceuticals, and industrial materials to retard oxidative deterioration. They were developed from the mid-twentieth century onwards to address the commercial need for effective, low-cost, chemically stable, and easily manufactured antioxidant additives that could extend the shelf life of lipid-rich food products and protect pharmaceutical formulations from oxidative degradation [43, 57]. The most widely used synthetic food antioxidants include butylated hydroxyanisole (BHA, E320), butylated hydroxytoluene (BHT, E321), tertiary butylhydroquinone (TBHQ, E319), propyl gallate (PG, E310), ethoxyquin, and nordihydroguaiaretic acid (NDGA). Synthetic antioxidants used in pharmaceutical formulations include ascorbyl palmitate, sodium metabisulphite, sodium sulphite, tocopherol acetate (synthetic α-tocopherol), and various chelating agents such as EDTA (ethylenediaminetetraacetic acid) that prevent metal-catalysed oxidation [57, 58].

BHA (a mixture of 2-tBHA and 3-tBHA isomers) and BHT are phenolic compounds structurally related to vitamin E that function as chain-breaking antioxidants by donating a hydrogen atom to lipid peroxyl radicals, thereby interrupting the lipid peroxidation propagation cycle. They are highly effective at preventing rancidity in fats and oils at low concentrations (typically 0.01–0.02% w/w) and are approved food additives in most countries. TBHQ, a hydroquinone derivative, is particularly effective as a frying oil antioxidant due to its high heat stability and excellent antioxidant efficacy against polyunsaturated fats. Propyl gallate is an ester of gallic acid that exhibits strong antioxidant activity through multiple mechanisms including radical scavenging and metal chelation, but it has relatively low heat stability compared to BHA and BHT [57, 58].

In pharmaceutical and biomedical research, synthetic antioxidants including N-acetylcysteine (NAC, a GSH precursor and direct thiol antioxidant), MnTBAP (a synthetic SOD mimetic porphyrin), EUK-8 and EUK-134 (synthetic SOD/catalase mimetics), MitoQ and SkQ1 (mitochondria-targeted synthetic antioxidants conjugated to the lipophilic triphenylphosphonium cation for mitochondrial membrane accumulation), and Tempol (a nitroxide radical scavenger) have been extensively investigated in preclinical disease models and some clinical trials [47, 58]. These synthetic compounds were developed specifically to overcome the limitations of natural antioxidants in terms of bioavailability, metabolic stability, and targeted delivery to specific subcellular compartments - particularly the mitochondria, which are both the primary ROS source and a critical therapeutic target [47].

10.2 Significant Limitations and Safety Concerns of Synthetic Antioxidants

Despite their widespread industrial use and initial promise in preclinical studies, synthetic antioxidants are burdened by a number of significant and increasingly well-documented limitations that have substantially undermined their therapeutic viability and safety acceptability - particularly in the context of human health applications [57, 58, 59].

Toxicological concerns represent the most critical limitation of synthetic antioxidants. Long-term feeding studies in rodents have revealed dose-dependent carcinogenic potential for several widely used synthetic antioxidants. BHA has been classified as a possible human carcinogen (Group 2B) by the International Agency for Research on Cancer (IARC) based on evidence of forestomach carcinogenicity in rats and mice at high doses; this tumorigenic effect is mediated through BHA's conversion to a quinone metabolite capable of alkylating DNA [57, 59]. TBHQ has been associated with increased incidence of stomach tumours in high-dose rodent studies and demonstrated genotoxic activity in some in vitro assays. Propyl gallate raises concerns regarding reproductive and developmental toxicity in animal models, with observed effects on male fertility including testicular damage and reduced sperm motility [57]. Ethoxyquin, approved as an antioxidant preservative in pet foods and certain seafood products, has been associated with hepatotoxicity, nephrotoxicity, and genotoxicity in animal studies, and its safety for human exposure through the food chain has been questioned by the European Food Safety Authority (EFSA) [58, 59].

The prooxidant paradox represents a fundamental and under-appreciated limitation of synthetic antioxidants. Under certain conditions of concentration, pH, oxygen tension, transition metal availability, and cellular redox environment, synthetic antioxidants can paradoxically function as pro-oxidants, generating reactive radical intermediates rather than quenching them. BHT, for example, can generate a BHT phenoxyl radical that initiates rather than terminates lipid peroxidation chains under conditions of insufficient co-antioxidant regeneration. This prooxidant behaviour has been documented in vivo and may contribute to the adverse outcomes observed in clinical trials of synthetic antioxidant supplementation at high doses [57, 59]. The concentration-dependence of antioxidant vs prooxidant activity is a critical consideration that natural antioxidant systems manage through complex regulatory networks including Nrf2-mediated transcriptional control, which are entirely absent in the context of synthetic antioxidant supplementation [43].

Allergic and hypersensitivity reactions represent another clinically significant concern. BHA, BHT, and TBHQ have been documented to cause contact dermatitis, urticaria, rhinitis, asthma, and anaphylaxis in sensitive individuals, including cross-reactivity with structurally related compounds [59]. The gallic acid moiety in propyl gallate is a recognised allergen capable of causing contact dermatitis. These adverse immunological reactions have led to regulatory restrictions on synthetic antioxidant use in products intended for sensitive populations including infants, pregnant women, and individuals with known atopic disease [58].

Bioavailability and pharmacokinetic limitations further constrain the therapeutic utility of synthetic antioxidants. Many synthetic antioxidants exhibit poor aqueous solubility, rapid first-pass hepatic metabolism, short plasma half-lives, and inability to reach critical target compartments - particularly the mitochondrial matrix, the primary site of pathological ROS generation in most chronic diseases [47]. While mitochondria-targeted synthetic antioxidants (MitoQ, SkQ1) have been engineered to address this specific limitation, they raise concerns about mitochondrial membrane potential disruption at higher concentrations and have thus far demonstrated limited clinical efficacy in human trials [47]. N-acetylcysteine (NAC), one of the most clinically used synthetic antioxidants and thiol replenishment agents, undergoes rapid systemic deacetylation, and its bioavailability after oral administration is limited by first-pass metabolism and erratic absorption [57].

The failure of large-scale clinical trials with synthetic antioxidants has been perhaps the most discouraging aspect of synthetic antioxidant medicine. The SELECT trial (Selenium and Vitamin E Cancer Prevention Trial), the HOPE trial (Heart Outcomes Prevention Evaluation), the CARET trial (Beta-Carotene and Retinol Efficacy Trial), and the ATBC trial (Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study) all failed to demonstrate the protective effects anticipated from preclinical data and epidemiological observations, with some trials

reporting paradoxical increases in cancer risk (particularly lung cancer in smokers supplemented with β-carotene) and cardiovascular events [43, 58, 59]. These sobering results have catalysed a fundamental reassessment of the antioxidant supplementation paradigm, with growing recognition that the complex, multi-component, and biologically regulated antioxidant systems present in whole plant foods cannot be replicated by isolated synthetic antioxidants [4, 46].

Table 2: Synthetic vs Natural Antioxidants - Comparative Profile

Parameter	Synthetic Antioxidants	Natural Antioxidants
Examples	BHA, BHT, TBHQ, PG, NAC, MitoQ	Quercetin, EGCG, curcumin, resveratrol, ascorbic acid, carotenoids
Source	Chemical synthesis / industrial manufacture	Plants, fruits, vegetables, herbs, microorganisms
Mechanism	Chain-breaking (phenolic), thiol replenishment, metal chelation	Multi-mechanistic: HAT, SET, metal chelation, Nrf2 activation, enzyme inhibition
Carcinogenicity	BHA (IARC Group 2B), TBHQ concerns	Generally anticarcinogenic; no carcinogenicity reported
Toxicity	Hepatotoxicity, nephrotoxicity, reproductive toxicity at high doses	GenerallyGRAS; high safety at normal dietary doses
Prooxidant Risk	Documented under certain conditions (BHT, BHA)	Lower risk; modulated by cellular antioxidant networks
Allergenicity	BHA, BHT, PG cause contact dermatitis, urticaria	Generally non-allergenic; rare sensitisation reported
Clinical Trial Outcomes	Multiple failures (SELECT, HOPE, CARET, ATBC)	Epidemiological support; promising clinical data for specific compounds
Bioavailability	Variable; often poor without formulation enhancement	Variable; enhanced by food matrix, metabolite bioactivation
Regulatory Status	Permitted at limited levels; EFSA restrictions ongoing	Generally unrestricted as food/nutraceutical ingredients

XI. MECHANISMS OF ANTIOXIDANT ACTION: A COMPREHENSIVE FRAMEWORK (GULCIN, 2025)

The antioxidant activity of both synthetic and natural antioxidants can be categorised into a comprehensive mechanistic framework as delineated by Gulcin (2025) in his landmark comprehensive review of antioxidants - the most extensive and authoritative treatment of this subject to date [43]. This framework identifies multiple distinct mechanisms through which antioxidants protect biological systems from oxidative damage, recognising that most effective antioxidants operate through several of these mechanisms simultaneously, contributing to their superior efficacy over single-mechanism synthetic compounds.

The primary mechanisms are: (i) Hydrogen Atom Transfer (HAT): the antioxidant (ArOH) donates a hydrogen atom ($H\bullet = H^+ + e^-$) directly to the radical species, converting it to a stable non-radical product ($ArOH + R\bullet \rightarrow ArO\bullet + RH$). This mechanism is predominant for phenolic antioxidants at lipid

interfaces and in non-polar media, and the rate constant for HAT is strongly influenced by the O–H bond dissociation enthalpy (BDE), with lower BDE indicating more facile hydrogen donation and greater antioxidant potency. The catechol group in many polyphenols has particularly low BDE, explaining their superior HAT-based antioxidant activity [43, 46]. (ii) Single Electron Transfer (SET): the antioxidant donates one electron to the radical (AntiOx + R• → AntiOx•$^{+}$ + R^{-}), generating a stable radical cation. The ionisation potential (IP) of the antioxidant governs the thermodynamics and kinetics of SET reactions, with lower IP favoring electron donation; (iii) Sequential Proton Loss Electron Transfer (SPLET): a two-step mechanism in which the antioxidant first undergoes deprotonation (ArOH → ArO^{-} + H^{+}) followed by electron transfer from the phenoxide anion (ArO^{-} + R• → ArO• + R^{-}). SPLET is thermodynamically more favourable than HAT in polar protic solvents at physiological pH, and many polyphenols operate primarily through SPLET in aqueous biological environments [43, 54]; (iv) Metal chelation: the antioxidant forms stable coordination complexes with redox-active transition metals (Fe^{2+}, Cu^{+}) through hydroxyl and carbonyl groups, preventing their participation in Fenton/Haber-Weiss reactions that generate the highly damaging hydroxyl radical. Flavonoids with the 3-hydroxy-4-keto and catechol arrangements are particularly effective metal chelators [52, 43]; (v) Singlet oxygen quenching: physical (energy transfer) or chemical quenching of $^{1}O_2$, predominantly by carotenoids and tocopherols, preventing photosensitisation-induced oxidative damage [14, 43].

(vi) Enzymatic mechanisms - upregulation of endogenous antioxidant enzymes (SOD, CAT, GPx, HO-1, NQO1) through Nrf2/ARE pathway activation by electrophilic and antioxidant phytochemicals, providing an amplified and sustained antioxidant response far exceeding the stoichiometric capacity of direct radical scavenging [43, 45]; (vii) Enzyme inhibition - inhibition of pro-oxidant enzymes including NADPH oxidase, xanthine oxidase, lipoxygenase, and cyclooxygenase, reducing upstream ROS generation at source; (viii) Anti-inflammatory activity - inhibition of NF-κB signalling, reduction of inflammatory cytokine production (TNF-α, IL-1β, IL-6), and suppression of iNOS expression, thereby reducing ROS and RNS generated during the inflammatory response [36, 43]; (ix) Repair and regeneration - regeneration of oxidised antioxidants (e.g., vitamin C regenerates vitamin E; glutathione reductase regenerates GSH from GSSG) and enzymatic repair of oxidatively damaged biomolecules (methionine sulphoxide reductase, thioredoxin system, base excision repair enzymes) [43, 45].

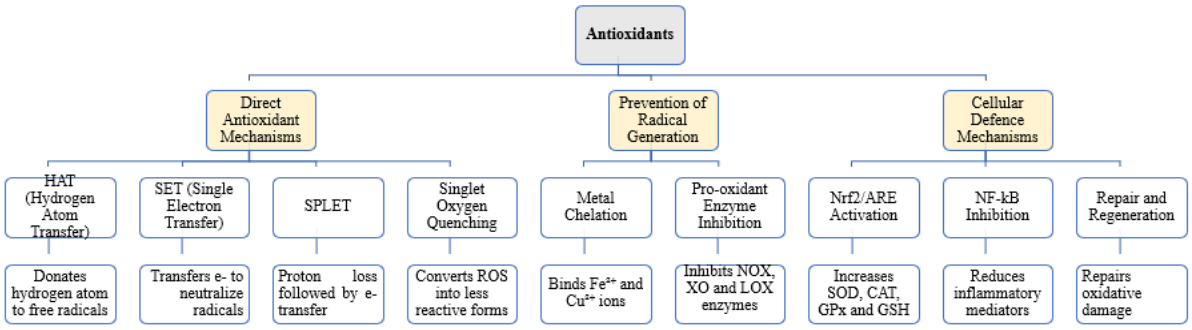

Fig.3. Mechanisms of Antioxidant Action.

XII. IMPORTANCE OF NATURAL ANTIOXIDANTS OVER SYNTHETIC ANTIOXIDANTS: A CRITICAL EVALUATION

The accumulated evidence from toxicological research, clinical trials, epidemiological studies, and mechanistic pharmacology now strongly supports the superiority of natural plant-derived antioxidants over synthetic analogues for long-term health applications. This superiority is not merely a matter of cultural preference or naturalistic fallacy, but rests on a robust scientific foundation encompassing mechanistic breadth, safety profile, pleiotropic biological activities, ecological sustainability, and alignment

with the complexity of oxidative stress in biological systems [4, 43, 46, 57].

Mechanistic superiority constitutes the most compelling scientific argument for natural antioxidants. Unlike synthetic antioxidants, which typically operate through a single primary mechanism (usually chain-breaking radical scavenging), natural phytochemical antioxidants - particularly polyphenols and flavonoids - simultaneously deploy multiple complementary antioxidant mechanisms including direct radical scavenging (HAT, SET, SPLET), metal chelation, Nrf2-mediated upregulation of the entire antioxidant enzyme battery (SOD, CAT, GPx, HO-1, NQO1, GCL), inhibition of pro-oxidant enzymes (Nox, XO, LOX, COX), anti-inflammatory NF-κB suppression, and modulation of cellular signalling pathways governing apoptosis, proliferation, and survival [43, 46]. This multi-mechanistic approach provides broader, more sustained, and more contextually appropriate antioxidant protection compared to the point-action of synthetic antioxidants, and more closely replicates the evolved biological logic of integrated antioxidant defence [46].

Pleiotropic bioactivities represent a uniquely valuable property of natural antioxidants that is entirely absent in synthetic compounds. Curcumin, for example, simultaneously acts as an antioxidant, anti-inflammatory (NF-κB inhibition), anticancer (apoptosis induction, anti-angiogenic), neuroprotective (Aβ disaggregation, tau phosphorylation inhibition), hepatoprotective, anti-diabetic, and antimicrobial compound through distinct molecular targets [43]. Quercetin combines antioxidant activity with anti-atherogenic, anti-thrombotic, anti-hypertensive, anti-diabetic, and anti-neurodegenerative properties [17]. Resveratrol activates SIRT1 and AMPK pathways in addition to its antioxidant effects, producing metabolic and longevity-promoting benefits beyond oxidative stress reduction [4]. These pleiotropic activities mean that natural antioxidant formulations address multiple pathological processes simultaneously, providing synergistic therapeutic benefits unachievable through synthetic single-agent antioxidant approaches [4, 43].

The 'food matrix effect' and synergistic interactions within natural plant extracts constitute another critical advantage of natural over synthetic antioxidants. Epidemiological evidence consistently demonstrates that the health benefits of antioxidant-rich diets cannot be replicated by isolated antioxidant supplementation, because the complex mixture of phytochemicals in whole plant foods exerts antioxidant effects that are substantially greater than the sum of individual compound activities - a consequence of complementary mechanisms, mutual regeneration, and bioavailability enhancement from the natural food matrix [2, 4]. The bioactive metabolites generated by gut microbial biotransformation of polyphenols (e.g., urolithins from ellagic acid, enterolactone from lignans, phenolic acids from flavonoids) contribute substantially to the antioxidant effects observed after whole-food consumption and may be more potent and bioavailable than the parent compounds - a complexity that cannot be replicated in synthetic antioxidant formulations [43, 46].

Safety and regulatory acceptability strongly favour natural antioxidants. In striking contrast to the carcinogenicity, hepatotoxicity, reproductive toxicity, and allergenicity concerns surrounding several synthetic antioxidants, plant-derived antioxidants have long histories of safe human consumption at dietary levels and generally excellent safety profiles in clinical settings [57, 59]. The GRAS (Generally Recognised As Safe) status of many natural antioxidant sources, the vast ethnobotanical safety data from traditional medicine systems, and the general principle of evolutionary co-adaptation between humans and dietary plant constituents provide a substantially more robust safety foundation than is available for synthetic antioxidants, which lack this historical human exposure evidence [43, 4].

Environmental sustainability considerations further support the preference for natural over synthetic antioxidants. Plant-derived antioxidants are renewable, biodegradable, and can be obtained as value-added by-products of food processing industries (e.g., grape seed extract from winemaking, pomegranate peel extract from juice production, green tea extract from tea manufacturing), contributing to a circular bio-economy model and reducing the environmental footprint of chemical synthesis [4]. The growing consumer preference for 'clean label' food products without synthetic additives has further accelerated market and regulatory incentives for the replacement of synthetic food antioxidants (BHA, BHT, TBHQ) with natural plant-derived alternatives [58, 59].

XIII. NEED FOR THE CURRENT REVIEW

Oxidative stress is now well established as one of the root causes of most serious chronic diseases that affect millions of people worldwide. When the human body produces more free radicals and reactive oxygen species (ROS) than it can neutralise with its own antioxidant defences, the resulting imbalance causes progressive damage to lipids, proteins, and DNA - which over time contributes to conditions such as heart disease, diabetes, cancer, Alzheimer's disease, and premature ageing [1, 9, 10, 16]. Given the scale of this problem, particularly in a rapidly ageing global population and in countries like India where lifestyle-related chronic diseases are rising sharply, there is an urgent need for safe, effective, and affordable antioxidant solutions.

For many decades, the food and pharmaceutical industries relied heavily on synthetic antioxidants - compounds like BHA (butylated hydroxyanisole), BHT (butylated hydroxytoluene), TBHQ, and ethoxyquin - because they are cheap, stable, and easy to manufacture. However, growing experimental and clinical evidence has shown that these synthetic compounds carry serious safety risks. They have been found to act as prooxidants under certain conditions (meaning they actually increase oxidative damage instead of preventing it), and some have been linked to carcinogenic effects, allergic reactions, and endocrine disruption [57, 58, 59]. Major clinical trials - including the CARET trial, the HOPE trial, and the SELECT trial - found that high-dose synthetic antioxidant supplementation either provided no benefit or actually increased disease risk in human participants. This repeated failure at the clinical level has pushed researchers and healthcare professionals to look for better, naturally derived antioxidant alternatives [4, 43, 46].

Medicinal plants and plant-derived foods offer a compelling and scientifically validated answer to this problem. Unlike synthetic antioxidants that work through a single mechanism, the phytochemicals found in plants - including polyphenols, flavonoids, tannins, terpenoids, and alkaloids - work through multiple pathways at the same time. They can directly scavenge free radicals through hydrogen atom transfer (HAT) and single electron transfer (SET), chelate metal ions to prevent the Fenton reaction, inhibit lipid peroxidation chain reactions, and even activate the body's own antioxidant enzyme system through the Nrf2 signalling pathway [43, 46]. This multi-target approach makes plant antioxidants far more effective in a biological setting than any single synthetic molecule. Additionally, many plant phytochemicals are further converted by gut bacteria into even more potent antioxidant metabolites such as urolithins and equol - an advantage that no synthetic compound can replicate [46]. Equally important is the safety advantage: plants used in traditional medicine systems like Ayurveda have been safely consumed for thousands of years, and epidemiological evidence consistently shows that populations eating diets rich in plant antioxidants have significantly lower rates of chronic disease [4, 43].

Despite this strong evidence in favour of plant-derived antioxidants, several important gaps in knowledge still exist. First, there is a lack of rigorous, standardised comparative studies that evaluate antioxidant activity across many plant species using multiple validated assay methods simultaneously [55, 56]. This matters because different assays measure different mechanisms - for example, DPPH and ABTS measure radical scavenging ability, while FRAP and CUPRAC measure electron-donating/reducing capacity, and metal chelation assays measure the ability to bind pro-oxidant metal ions - and no single assay can fully capture the total antioxidant potential of a plant [54, 55, 56]. Second, the relationship between a plant's phytochemical composition and its antioxidant potency is not yet fully understood, especially when the whole plant extract is used rather than isolated pure compounds [53]. Third, and very importantly for Indian researchers and pharmacists, a single comprehensive review that brings together recent evidence on traditional Indian medicinal plants alongside globally important food and medicinal plants - all evaluated with modern, validated methods - is currently not available in the literature.

The present review was therefore conducted with the specific aim of filling these gaps. It systematically brings together published evidence from the period 2020 to 2026, covering: (i) the molecular biology of free radical generation and oxidative stress; (ii) the mechanisms by which ROS damage biological macromolecules and drive chronic disease; (iii) the endogenous antioxidant defence system of the human body; (iv) the major classes of plant-derived antioxidants and their chemical structures and

mechanisms; (v) the known limitations and clinical failures of synthetic antioxidants; and (vi) the validated antioxidant activity of sixty (60) botanically diverse plant species, documented using rigorous in vitro methodology. By presenting all of this in a coherent, integrated framework, this review aims to serve as a reliable scientific reference for students, researchers, pharmacists, and pharmaceutical scientists working in the fields of natural product pharmacology, nutraceutical development, and antioxidant drug discovery.

The superiority of medicinal plants over synthetic antioxidants is most convincingly demonstrated when we look at the accumulated experimental evidence from individual plant studies. The sixty plant species reviewed in this paper - spanning traditional Indian medicinal plants (Curcuma longa [60], Ocimum sanctum [61], Azadirachta indica [62], Phyllanthus emblica [73], Aegle marmelos [115], Moringa oleifera [109]), major fruits and berries (Punica granatum [64, 82], Litchi chinensis [90], Vaccinium myrtillus [103], Rubus occidentalis [104], Fragaria ananassa [102], Vitis labrusca [105]), aromatic spices (Zingiber officinale [70], Piper nigrum [71], Syzygium aromaticum [114], Lavandula viridis [110]), and diverse medicinal plants from Africa, Europe, and Asia (Urtica dioica [76], Scutellaria baicalensis [70], Moringa oleifera [109], Hippophae rhamnoides [97], Rosa rubiginosa [96], Pistacia lentiscus [111]) - all consistently showed strong to very strong antioxidant activity when tested with validated in vitro assays including DPPH, ABTS, FRAP, CUPRAC, ORAC, NO scavenging, metal chelation, and lipid peroxidation inhibition methods. Several plants, particularly Punica granatum peel [82], Syzygium aromaticum [114], Areca catechu [107], Cocos nucifera [106], Rubus occidentalis [104], Halimium antiatlanticum [111], and Pistacia lentiscus [111] showed antioxidant potency comparable to or exceeding synthetic antioxidant standards. Table 3 below provides a detailed summary of all sixty plants, including the assay methods used, the proposed mechanisms, and the study conclusions.

Table 3: Summary of Antioxidant Activity of Sixty Medicinal and Food Plants Reviewed in the Present Study (Literature: 2020–2026)

Sr.	Plant Name	Method Used	Mechanism Proposed	Conclusion	Reference
1	*Curcuma longa*	DPPH, FRAP	Curcumin scavenges ROS through HAT and SET pathways	Very strong antioxidant	[60]
2	*Ocimum sanctum*	DPPH, ABTS	Eugenol neutralises free radicals via hydrogen donation	Strong antioxidant	[61]
3	*Azadirachta indica*	DPPH	Polyphenols donate hydrogen/electrons to stabilise radicals	Strong antioxidant	[62]
4	*Syzygium cumini*	DPPH	Anthocyanins reduce and scavenge free radicals	Strong antioxidant	[63]
5	*Punica granatum (Fruit)*	DPPH, H2O2, ABTS, FRAP, CUPRAC, Reducing power	Ellagic acid, punicalagin, phenolics, flavonoids, tannins act via multi-mechanism scavenging	Strong antioxidant	[64]
6	*Macaranga hypoleuca*	DPPH, ABTS, FRAP, TPC, TFC	Ethyl acetate fraction rich in phenolics showed highest radical scavenging	Strong antioxidant	[65]

7	*Litsea cubeba*	DPPH, ABTS, FRAP	Leaf phenolics showed stronger activity than branch extracts	Strong antioxidant	[66]
8	*Emblica officinalis (formulation)*	DPPH, ABTS, FRAP, TPC	Synergistic action of phenolics, flavonoids, carotenoids, and curcumin	Strong antioxidant (functional beverage)	[67]
9	*Averrhoa carambola*	DPPH, ABTS, FRAP, NO, TAC, Metal chelation	Phenolic compounds correlated strongly with multi-mechanism antioxidant capacity	Strong antioxidant	[68]
10	*Clitoria ternatea*	DPPH, ABTS, FRAP	Flavonoids and anthocyanins; ethanol extract most active fraction	Strong antioxidant	[69]
11	*Scutellaria baicalensis*	DPPH, ABTS	Baicalin, baicalein, wogonin scavenge radicals via HAT/SET	Strong antioxidant	[70]
12	*Zingiber officinale*	DPPH, ABTS, FRAP	Gingerols donate hydrogen and electrons to neutralise free radicals	Strong antioxidant	[70]
13	*Piper nigrum (isolated piperine)*	DPPH, ABTS, FRAP	Piperine alkaloid scavenges radicals through electron donation	Strong antioxidant	[71]
14	*Ficus religiosa*	DPPH, NO scavenging	Phenolics and flavonoids scavenge DPPH and nitric oxide radicals	Strong antioxidant	[72]
15	*Phyllanthus emblica (Amla)*	DPPH radical scavenging	H/e- donation neutralises DPPH; ethyl acetate fraction highest (IC50 ~3.20 ug/mL)	Strong antioxidant	[73]
16	*Indigofera heterantha*	DPPH, ABTS, Metal chelating, beta-carotene bleaching	Scavenges radicals, chelates metal ions, inhibits lipid peroxidation	Moderate to strong antioxidant	[74]
17	*Achillea ligustica*	DPPH, ABTS, Phenanthroline, Reducing power	H donation (DPPH), electron transfer (ABTS), Fe2+ chelation, reducing activity	Moderate to strong antioxidant	[75]
18	*Urtica dioica (leaf fraction)*	DPPH, ABTS, FRAP, CUPRAC, TPC, ROS assay (H2DCFDA), SOD, CAT, MDA	Multi-mechanism: radical scavenging, electron transfer, intracellular ROS reduction, enzyme (SOD/CAT) activation	Strong antioxidant; leaf fraction most potent	[76]
19	*Achillea millefolium*	DPPH, TPC, TFC	Phenolic hydrogen donation and radical scavenging	Strong antioxidant	[77]

20	*Adenium obesum*	DPPH, ABTS, FRAP	H/e- donation for free radical scavenging across multiple assays	Strong antioxidant	[78]
21	*Tamarindus indica*	DPPH, ABTS	Phenolic compounds neutralise DPPH and ABTS+ radicals	High antioxidant	[79]
22	*Crotalaria burhia*	DPPH, ABTS, FRAP, CUPRAC, Phosphomolybdenum, Metal chelation	Electron transfer and metal chelation across six assay systems	Strong antioxidant	[80]
23	*Pistacia terebinthus*	DPPH, ABTS, Reducing power, Metal chelation	Radical scavenging plus metal chelation contribute to high antioxidant capacity	High antioxidant potential	[81]
24	*Punica granatum (Peel)*	DPPH, ABTS, Lipid peroxidation, OH scavenging, NO scavenging, Metal chelation, Reducing power, TAC, Protein protection (BSA-AAPH)	Phenolics donate H/e-, neutralise reactive species, chelate Fe2+, inhibit lipid peroxidation, protect biomolecules	Very strong; IC50 DPPH/ABTS ~0.1 ug/mL; NO = 0.02 ug/mL	[82]
25	*Hibiscus sabdariffa*	DPPH, FRAP, TPC, TAC	Phenolics and anthocyanins via H donation (DPPH) and electron transfer (FRAP)	High antioxidant	[83]
26	*Persea americana (Avocado)*	DPPH, FRAP	Phenolics and flavonoids donate H/electrons for radical scavenging and reducing power	Potent antioxidant	[84]
27	*Musa paradisiaca (Banana)*	DPPH, FRAP	Phenolic H donation (DPPH) and electron transfer (FRAP)	Moderate antioxidant	[85]
28	*Citrus sinensis (Orange)*	DPPH, ABTS, FRAP, Lipid peroxidation, Protein carbonyl assay	Hesperidin and phenolics scavenge radicals, transfer electrons, inhibit lipid/protein oxidation	Strong antioxidant	[86]
29	*Citrus reticulata (Mandarin)*	DPPH, FRAP	Polyphenols and ascorbic acid donate H (DPPH) and transfer electrons (FRAP)	Strong antioxidant	[87]
30	*Citrus paradisi (Grapefruit)*	DPPH, ABTS, FRAP	Naringin, naringenin, and phenolics scavenge radicals via H donation, electron transfer (FRAP), and ABTS+ scavenging	Strong antioxidant	[88]

31	*Ananas comosus (Pineapple)*	DPPH, ABTS, FRAP	Phenolics and volatile compounds donate H/electrons and scavenge radicals	Good antioxidant	[89]
32	*Litchi chinensis*	FRAP, DPPH, ABTS, NO scavenging, Anti-lipid peroxidation	Epicatechin and phenolics donate electrons (FRAP), scavenge radicals, inhibit lipid peroxidation, suppress ROS	Highest antioxidant; also inhibits alpha-glucosidase	[90]
33	*Solanum betaceum (Tamarillo)*	FRAP, CUPRAC	Phenolics and anthocyanins donate electrons (FRAP, CUPRAC); shikimic acid pathway biosynthesis	Highest antioxidant	[91]
34	*Ficus carica (Fig)*	DPPH, ABTS, FRAP	Phenolics donate H (DPPH, ABTS) and electrons (FRAP)	Moderate antioxidant	[92]
35	*Ziziphus jujuba (Jujube)*	TEAC, FRAP	Phenolics and flavonoids via electron transfer and reducing mechanisms	Strong antioxidant	[93]
36	*Elaeagnus angustifolia*	DPPH, ABTS, FRAP	Phenolics and flavonoids donate H (DPPH, ABTS) and transfer electrons (FRAP)	Strong antioxidant	[94]
37	*Berberis vulgaris*	DPPH, ABTS, FRAP	Phenolics and berberine alkaloid donate H and transfer electrons	Good antioxidant	[95]
38	*Rosa rubiginosa (Rosehip)*	DPPH, TEAC, CUPRAC, ORAC	Phenolics and vitamins via H donation, electron transfer, and peroxyl radical scavenging (ORAC)	Strong antioxidant	[96]
39	*Hippophae rhamnoides (Sea buckthorn)*	CUPRAC, FRAP	Phenolic constituents reduce Cu2+ to Cu+ (CUPRAC) and Fe3+ to Fe2+ (FRAP)	Significant antioxidant	[97]
40	*Prunus domestica (Plum)*	FRAP, DPPH	Phenolics and anthocyanins donate electrons (FRAP) and scavenge radicals (DPPH)	Moderate to strong antioxidant	[98]
41	*Prunus persica (Peach)*	DPPH, FRAP, CUPRAC, ABTS	Anthocyanins and phenolics donate H and transfer electrons; peel most active	Highest antioxidant (peel fraction)	[99]
42	*Malus domestica (Apple)*	DPPH, Xanthine/Xanthine Oxidase	Quercetin-rich phenolics scavenge radicals and inhibit oxidative enzymes	High antioxidant	[100]

43	*Pyrus communis (Pear)*	DPPH, FRAP	Phenolics and ascorbic acid donate H (DPPH) and transfer electrons (FRAP)	Significant antioxidant	[101]
44	*Fragaria x ananassa (Strawberry)*	DPPH, ABTS, FRAP	Phenolics and anthocyanins donate electrons and scavenge radicals	Strong antioxidant	[102]
45	*Vaccinium myrtillus (Bilberry)*	ABTS, FRAP	Phenolics and anthocyanins scavenge radicals (ABTS) and transfer electrons (FRAP)	High antioxidant	[103]
46	*Rubus occidentalis (Black raspberry)*	DPPH, ABTS, FRAP	Anthocyanins donate H+/e-, reduce Fe3+ to Fe2+, and inhibit oxidative chain reactions	Highest antioxidant	[104]
47	*Vitis labrusca (Grape seed)*	DPPH, FRAP	Phenolics donate H/e- (DPPH) and reduce Fe3+ to Fe2+ (FRAP) indicating strong reducing power	Very high antioxidant	[105]
48	*Rubus fruticosus (Blackberry seed)*	Fe2+ chelation, FRAP	Phenolics chelate Fe2+ ions preventing Fenton reaction; electron transfer via FRAP	Good antioxidant; metal chelating	[105]
49	*Cocos nucifera (Coconut)*	DPPH, ABTS, Hydroxyl radical scavenging	Polysaccharides/phenolics donate H/e- and neutralise hydroxyl radicals	Highest antioxidant	[106]
50	*Areca catechu (Betel nut)*	DPPH, ABTS, FRAP	High phenolic content enables strong H donation and electron transfer across assays	Highest antioxidant	[107]
51	*Piper nigrum (whole extract)*	DPPH, ABTS, FRAP	Synergism between phytochemicals improves radical scavenging beyond isolated piperine	Whole extract > isolated compound	[71]
52	*Colebrookea oppositifolia*	ABTS, FRAP	Phenolics scavenge ABTS+ (ABTS) and reduce Fe3+ to Fe2+ (FRAP)	Root extract > aerial extract	[108]
53	*Moringa oleifera*	DPPH, ABTS, FRAP	Free radical scavenging (DPPH, ABTS) and electron donation/reducing power (FRAP)	Very strong antioxidant	[109]
54	*Lavandula viridis*	DPPH, H2O2, Lipid peroxidation	Phenolics scavenge radicals, reduce H2O2, protect	Strong antioxidant	[110]

			membranes via lipid peroxidation inhibition		
55	*Halimium antiatlanticum*	DPPH, ABTS, FRAP	H/e- donation stabilises DPPH radical; ABTS+ scavenging; Fe3+-TPTZ to Fe2+ reduction (FRAP)	Strongest among tested plants	[111]
56	*Pistacia lentiscus*	DPPH, ABTS, FRAP	H/e- donation (DPPH), electron/H transfer to ABTS+, Fe3+-TPTZ to Fe2+ (FRAP)	Strongest among tested plants	[111]
57	*Humulus lupulus (Hops)*	DPPH, ABTS, FRAP, Folin-Ciocalteu (TPC)	Radical scavenging via H/e-donation (DPPH), ABTS+ neutralisation, Fe3+ reduction; TPC via phenolic redox	Strong antioxidant	[112]
58	*Phyllostachys pubescens (Bamboo shoot)*	DPPH, ABTS, FRAP	H/e- donation (DPPH), ABTS+ neutralisation, Fe3+-TPTZ to Fe2+ (FRAP)	Strong antioxidant	[113]
59	*Syzygium aromaticum (Clove)*	DPPH, ABTS	Phenolic H/e- donation stabilises DPPH; electron transfer neutralises ABTS+	Strongest antioxidant among tested	[114]
60	*Aegle marmelos (Bael)*	DPPH, FRAP	Phenolics/flavonoids donate H/e- (DPPH); Fe3+-TPTZ to Fe2+ (FRAP)	Strong antioxidant	[115]

XIV. CONCLUSION

This review has provided a comprehensive and integrated analysis of oxidative stress, free radical chemistry, antioxidant defence mechanisms, and the pharmacology of plant-derived antioxidants, clearly establishing the scientific superiority of medicinal plants over synthetic antioxidant compounds.

Oxidative stress - the imbalance between ROS generation and the body's antioxidant capacity - is a central pathological mechanism in cardiovascular disease, type 2 diabetes, Alzheimer's and Parkinson's diseases, cancer, chronic kidney disease, inflammatory bowel disease, liver disease, and accelerated ageing. The body's own defence network, comprising enzymatic antioxidants (SOD, catalase, GPx) and the Nrf2 master transcription factor, is frequently overwhelmed under chronic disease and persistent lifestyle stress, making external antioxidant support a scientifically justified therapeutic strategy.

Synthetic antioxidants - BHA, BHT, TBHQ, and ethoxyquin - were developed as cost-effective industrial additives, but their application in human health is seriously compromised. BHA is classified as a possible human carcinogen (IARC Group 2B); BHT and TBHQ exhibit prooxidant behaviour at higher concentrations; propyl gallate causes allergic reactions; and several show reproductive toxicity in animal studies. Most significantly, the largest randomised clinical trials conducted - SELECT, HOPE, CARET, and ATBC - all failed to demonstrate meaningful health benefits from synthetic antioxidant supplementation. This consistent clinical failure confirms that isolated, single-mechanism synthetic molecules are fundamentally inadequate as antioxidant therapies in the biological context of chronic disease.

Plant-derived antioxidants operate through multiple simultaneous mechanisms: direct radical scavenging via HAT and SET; metal ion chelation preventing

Fenton chemistry; Nrf2 pathway activation that upregulates the entire antioxidant enzyme battery (SOD, catalase, GPx, HO-1); inhibition of pro-oxidant enzymes (NADPH oxidase, xanthine oxidase); and NF-κB anti-inflammatory suppression. Gut microbial biotransformation of plant polyphenols into bioactive metabolites like urolithins and equol adds a further protective dimension unique to plant-based systems. These properties collectively make plant antioxidants far more biologically relevant and therapeutically effective than synthetic compounds.

The sixty plant species reviewed - spanning Indian medicinal plants (Curcuma longa, Phyllanthus emblica, Ocimum sanctum, Moringa oleifera, Aegle marmelos), fruits and berries (Punica granatum, Rubus occidentalis, Litchi chinensis, Vaccinium myrtillus), and spices (Syzygium aromaticum, Zingiber officinale, Piper nigrum) - all showed strong antioxidant activity across DPPH, ABTS, FRAP, CUPRAC, and related assays. Punica granatum peel, Syzygium aromaticum, and Rubus occidentalis showed potency exceeding synthetic standards, while Indian traditional plants confirmed their Ayurvedic pharmacological basis with modern experimental data.

In conclusion, plant-derived antioxidants are scientifically superior, clinically safer, and pharmacologically more versatile than synthetic alternatives. Future research should prioritise in vivo validation, standardised phytochemical profiling, bioavailability enhancement through modern formulation strategies, and well-designed clinical trials. India's rich Ayurvedic botanical heritage, validated here through modern experimental evidence, represents a highly promising foundation for future antioxidant-based drug discovery and nutraceutical development.

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