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Phytotherapeutics Attenuation of Oxidative Stress, Inflammation and Lipid Peroxidation in Severe and Chronic Diseases

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Abstract

Lipid peroxidation is an end process of cellular injury driven by oxidative stress (OS) and inflammation through several molecular changes. Metabolism-generated reactive oxygen species avidly attack the polyunsaturated fatty acids in lipid cell membranes, initiating a self-propagating chain-reaction. Cell membrane destruction, lipids and the end-products of lipid peroxidation reactions are hostile to the viability of cells, even tissues causing and exacerbating Diabetes Mellitus (DM), neurodegenerative disorders (NDDs), cardiovascular diseases (CVDs) and Rheumatoid Arthritis (RA). Current treatment regimens have untoward side effects in the long-term necessitating phytochemical use as these are part of natural food sources. Enzymatic and non-enzymatic antioxidant defense mechanisms may be over run causing lipid peroxidation to take place. In disease states, oxidative stress may increase with subsequent production of increased free radicals which may over run the antioxidant capacity of the body with resultant oxidative damage on polyunsaturated fatty acids in the cell fluid membranes with cellular and tissue damage. Phytochemicals, have been shown to ameliorate diseases through attenuation of oxidative stress, inflammation, lipid peroxidation, causing tissue regeneration by regulating signaling systems and neuroprotective processes. Involvement of polyphenolic and non-phenolic phytochemical in the attenuation of OS, inflammation and lipid peroxidation remain areas of critical importance in combating DM, CVDA, NDD and RA.

Keywords: phytotherapeutics, oxidative stress, inflammation, lipid peroxidation, severe and chronic diseases, phytochemicals

1. Introduction

There is a significant contributory role the Fenton and Haber Weiss reaction makes in oxidative stress (OS) building up to several progressive diseases such as Alzheimer's disease (AD). Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are manufactured by these reactions causing OS in AD. Iron, copper

and aluminum influences creation of free radicals such as hydroxyl radicals with impairment to DNA, proteins, lipids and carbohydrates.

Beta amyloid (A β 42) toxicity is created by hydroxyl (OH $^{\cdot}$) radicals from the Fenton reaction [1, 2] in AD. Soluble human fibrinogen is converted into an insoluble fibrin-like aggregate seen in neurodegenerative diseases such as AD when it reacts with hydroxyl radical [3]. The Fenton gated OS attenuates DNA base substitutions of guanine to cytosine when catalyzed by iron and guanine to thymine and cytosine to thymine when catalyzed by copper and Nickel [4].

Phosphoinositide 3- kinase (PI3K), c-Jun N-terminal kinase (JNK), extracellular signal-regulated kinase 1 and 2 (ERK1/2), p38 and transcription factors such as activator protein-1(AP-1), and p53 are signal transduction molecules that are stimulated by ROS [5]. Hastening of AD development are OH $^{\cdot}$ radicals that impair DNA through p53 pathway. When tumor suppressor gene (TP53) has a mutation, there is increased potential for AD pathogenesis development [6].

The Fenton reaction triggers OS through subtraction of one electron from the molecular oxygen (O $_2$) resulting in the formation of superoxide (O $_2^{\cdot-}$) which often produces other ROS species such as H $_2$ O $_2$ and peroxynitrite (ONOO $^{\cdot-}$) and hydroxyl radicals (OH $^{\cdot}$) [7]. This may imply that phytotherapeutics which are able to quench the electron abstraction may alleviate oxidative stress. Moreover, under normal conditions, O $_2^{\cdot-}$ has emerged as an important signaling molecule, which regulates precise biochemical reactions and metabolic progressions [8].

The linkage between O $_2^{\cdot-}$ production and H $_2$ O $_2$ may involve a reduced flavin enzyme by transferring an electron to activate molecular oxygen into superoxide which is either released or enzymatically converted into H $_2$ O $_2$ [9, 10] or drugs like statins may modify the process [11, 12].

Extreme challenges in the field of ROS-gated diseases is to bridge the knowledge gap between atomic, cellular level and how natural phytochemicals may be used to attenuate OS in certain diseases [13, 14].

The understanding of the Fenton and Haber Weiss reaction and how it may be modified or detoxified or neutralized by phytotherapeutics or nutraceuticals may assist to bridging the knowledge and practice of treating chronic diseases of old age. When phytochemicals stop the subtraction of one electron in Fenton reaction, creation of OS may be averted.

2. Lipid peroxidation products

Characteristics of various lipid peroxidation products as biomarkers have been reviewed on the basis of mechanisms and dynamics of their formation and metabolism and also on the methods of measurement, with an emphasis on the advantages and limitations [15].

Lipid peroxidation or unsaturated lipid reaction with molecular or ROS produces a wide variety of oxidation products with the main primary products being lipid hydroperoxides (LOOH). Many different aldehydes which can be formed as subsequent products during lipid peroxidation include malondialdehyde (MDA), propanal, hexanal, and 4-hydroxynonenal (4-HNE) (**Figure 1**) [16–20].

MDA gives the impression to be the most mutagenic product of lipid peroxidation, whereas 4-HNE is the most toxic [21]. MDA has been extensively used for many years as an expedient biomarker for lipid peroxidation of omega-3 and omega-6 fatty acids because of its simplistic reaction with thiobarbituric acid (TBA) [22]. The TBA test is predicated on the reactivity of TBA toward MDA to yield an intensely colored chromogen fluorescent red adducts. Food chemists used this test initially to evaluate autoxidative degradation of fats and oils [23].

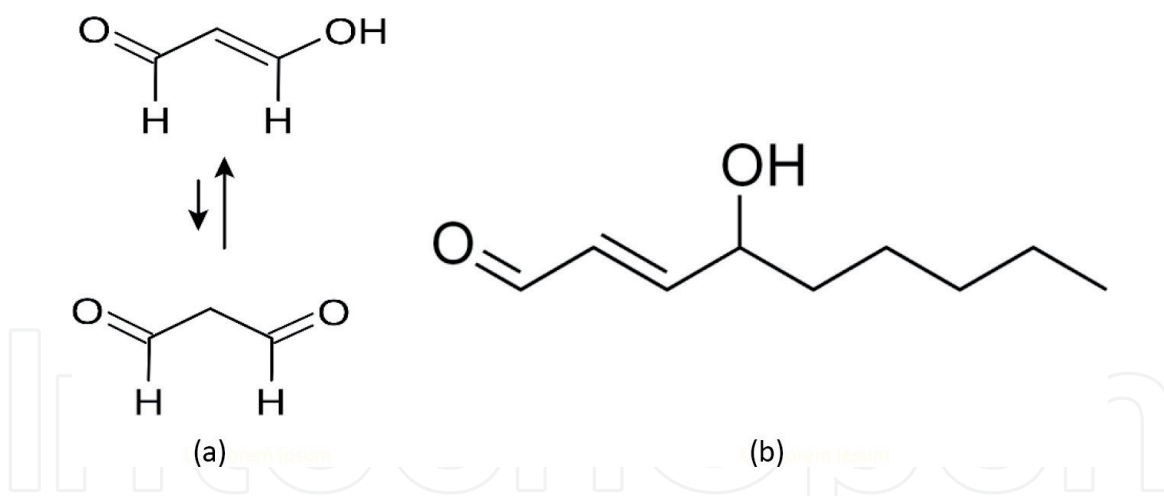


Figure 1.
(a): Structure of 4-hydroxymalondialdehyde and malondialdehyde at equilibrium and (b) 4-hydroxynonenal.

MDA is one of the most popular and reliable biomarkers that determine OS in clinical situations and due to MDA's high reactivity and the toxicity underlying the molecular effect, this molecule is very relevant to biomedical research community [24].

First to be discovered in the 1960s was 4-HNE [25]. Later, in 1980s 4-HNE was described as a cytotoxic product originating from the peroxidation of liver microsomal lipids [26]. The genotoxic effects exerted on human beings results from the subsequently produced 4-HNE from progression of bio membranes lipids peroxidation elicited by free radicals or chemicals [27]. Comparatively large amounts of 4-HNE are produced and they are very reactive aldehydes that act as second messengers of free radicals making them of high significance in disease of old age [28]. Therefore, 4-HNE the most likely easier target for phytotherapeutics as antioxidant in lipid peroxidation.

Also, 4-HNE is a major bioactive marker of lipid peroxidation and a signaling molecule elaborate in regulation of several transcription mediators that are sensitive to stress such as nuclear factor erythroid 2-related factor 2 (Nrf2), activating protein-1 (AP-1), NF- κ B, and peroxisome-proliferator-activated receptors (PPAR). These play a critical role in cell proliferation and/or differentiation, cell survival, autophagy, senescence, apoptosis, and necrosis [29]. 4-HNE may stimulate intrinsic and extrinsic apoptotic pathways and interact with typical actors such as tumor protein 53, JNK, Fas or mitochondrial regulators, due to its oxidant status. Simultaneous 4-HNE induces cellular defense mechanisms against OS, thus being involved in its own detoxification and in turn limiting its apoptotic potential [30]. These dualities can imbalance cell fate, either toward cell death or toward survival, depending on the cell type, the metabolic state and the ability to detoxify [31]. The pleiotropism displayed by phytotherapeutics like Asiatic acid [13, 32–36], maslinic acid [37, 38] and oleanolic acid [36] and their involvement in redox reactions may influence 4-HNE activity thus modulating the its function in stress induces pathology of old age.

3. Phytotherapeutics and lipid peroxidation products

Phytotherapeutics which may restore or facilitate the restoration of 4-HNE's apoptotic inhibition potential as well as catalyze its oxidant signaling pathways through direct redox reactions or attenuation of enzymatic antioxidant systems, have a great capacity in modulating lipid peroxidation related diseases [13, 14, 35]. Triterpenes with pleiotropic activities have been shown to possess antioxidant properties as well oxidative functions in certain parasitic infections ameliorating disease outcomes and outputs [33, 39].

Other phytochemicals also follow in this narrative in their use as antioxidants in lipid peroxidation agents and their use to fight against associated diseases using various mechanism. By inhibiting formation of both primary and secondary products of the lipid peroxidation process, plant phytochemicals may exert their effect on hydroperoxide groups from attaching to free fatty acids, triacylglycerols, phospholipids, and sterols [40].

While, hydroperoxides may decompose *in vivo* through two-electron reduction, which may inhibit the peroxidative damage, phytochemicals may also facilitate this process of antioxidant lipid peroxidation through enhancing activity of enzymes for two-electron reduction of hydroperoxides such as selenium-dependent glutathione peroxidases (GPx) and selenoprotein P (SeP) [41, 42].

4. Phytochemical and Antioxidative activity in lipid peroxidation

4.1 *Salix aegyptiaca* and lipid peroxidation

Salix aegyptiaca is a deciduous plant belonging to *Salicaceae* family and is popularly known as Musk Willow from the Middle-East [43]. As part of a traditional medicine from ancient times, *S. aegyptiaca* is used as a confectionary, flavourful syrup and fragrance additive. The extract from bark and leaves have shown to exert beneficial effects, as laxative, cardioprotective, nervonic, sedative, hypnotic, somnolent, aphrodisiac, orexoigenic, carnative, gastroprotector, anthelmintic and vermifuge [44]. Important findings associated with *salicaceae* family is that they contain salicylate composites such as salicylic acid which subsequently led to the finding of acetylsalicylic acid identified as aspirin, a worldwide analgesic, anti-pyretic, anti-inflammatory drug [45].

Later, the presence of other polyphenols such as gallic acid, caffeic acid, vanillin, p-coumaric acid, myricetin, catechin, epigallocatechin gallate, rutin and quercetin were confirmed to contribute as to the beneficial effects of *S. aegyptiaca* [46].

With the body generating OS through the Fenton and Haber Weiss leading to the initiation and development of several health complications such as diabetes, Alzheimer's disease, atherosclerosis, cardiovascular problems and various kinds of cancers [47–49] and considering the wide range of medicinal applications of *S. aegyptiaca*, the interesting and essential component in delineation of the bioactivity of its flavonoid and phenolic phytochemicals other than salicylates, is astounding.

Invariably, plant natural compounds with antioxidant activity are likely to preserve redox homeostasis disturbed during the natural cellular mechanism or the consequences of exposure to detrimental chemical agents. By rummaging for the free radicals, influencing the antioxidant non-enzymatic and enzymatic defense systems as well as drug metabolizing enzyme systems, *S. aegyptiaca* proves influential in the attenuation of OS and lipid peroxidation. These phytochemicals are expectable to modify the diverse biological activities such as inflammation, necrosis and carcinogenesis leading to cytoprotecting of cellular environment [50].

The interdependency of redox-potential, antioxidant activity and anti-inflammatory activity of gallic acid, quercetin, rutin and vanillin as well as acetylsalicylic acid has been examined [50]. Finding the relevance of the biological systems, the influence of gallic acid and acetylsalicylic acid have been studied on the drug metabolizing phase I and phase II enzymes as well as on endogenous antioxidant enzymes and peroxidative damage in the liver of C57BL/6 mice.

Oxidation–reduction potential of gallic acid, acetylsalicylic acid, rutin, quercetin and vanillin have been tested with the agents exhibiting reduction potential in

a dose dependent manner of 5–50 µg/ml [50]. The reduction potential was in the order of gallic acid > quercetin > rutin > vanillin > acetylsalicylic acid.

In red and yellow onion [51] and in *S. aegyptiaca*, the antioxidant activity of gallic acid, acetylsalicylic acid, rutin, quercetin and vanillin have been examined for their scavenging of 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals and displayed inhibition of DPPH radicals, an indicator of antioxidant activity, in concentration dependent manner. In the *S. aegyptiaca* experiments, DPPH radical scavenging activity was shown by gallic acid to be greater than that of quercetin which was greater than of rutin which was greater than that of vanillin which was greater than that of acetylsalicylic acid [50].

4.1.1 *Salix aegyptiaca* anti-inflammatory and antioxidant activity

To determine the anti-inflammatory activity of the *S. aegyptiaca* phytochemicals (62.5–1000 µg/ml) inhibition of protein denaturation was used. The phytochemicals' concentration-dependent inhibitory effect displayed a relative repressive effect in the ensuing order of acetylsalicylic acid > gallic acid > rutin > quercetin > vanillin [50]. Also, cumulative therapeutic effects of phytochemicals in *Arnica montana* flower extract has been reported to alleviate collagen-induced arthritis while inhibition of both pro-inflammatory mediators and OS [52].

4.1.2 *Salix aegyptiaca* and protein carbonyl estimation and oxidative stress

Protein carbonyl measurements provide a sensitive index of OS damage occurring early in severe sepsis and major trauma patients. Elevated protein carbonyl concentrations in plasma and in bronchial aspirates indicates wide spread of oxidation though out the body beyond the lungs. The correlation between oxidative biomarkers and myeloperoxidase concentrations correlations in the lung may indicate that neutrophil oxidants could be responsible for the lung injury [53, 54] and also, protein carbonyl as a marker of OS is associated with overhydration, sarcopenia and mortality in hemodialysis patients [55]. Moreover, plasma protein carbonyls have been shown to be a predictive biomarker of oxidative stress in chronic kidney disease, dialysis, and transplantation [56]. However, Mkhwanazi *et al.* have reported that a maslinic acid triterpene derivative improved the renal function of streptozotocin-induced diabetic rats [37]. Furthermore, Mavondo *et al.* chronologies how malarial inflammation-driven pathophysiology and were reduced by triterpene application in various *in vivo* and *ex vivo* experiments of Asiatic acid [34].

Phytotherapeutics *S. aegyptiaca* obtained gallic acid, acetylsalicylic acid, rutin and quercetin (62.5–1000 µg/ml) showed a dose-dependent protection against protein carbonyl damage caused by the Fenton reagent with higher protection percentage as compared to the control, being maximum for gallic acid > quercetin > rutin > acetylsalicylic acid [50].

4.1.3 *Salix aegyptiaca* and peroxidative damage and its inhibition

Some water extractable phytochemicals inhibited Fe²⁺-induced *in vitro* lipid peroxidation in a rat's brain [57] while *Solanum xanthocarpum* root extract protective efficacy was demonstrated against free radical damage and its phytochemical analysis was carried out and antioxidant effect determined [58]. Over more, microsomes were used *in vitro* to study the peroxidative damage and its inhibition by phytochemicals (62.5–1000 µg/ml) [50]. In these experiments, the Fenton reagent

initiated by peroxidation and determined in terms of TBARS formation. Ultimately, all the phytochemicals showed inhibitory effect against peroxidative damage, in a dose dependent manner showing inhibition order: gallic acid > quercetin > rutin > acetylsalicylic acid.

Treatment with 50 µg/kg of acetylsalicylic acid and with 100 µg/kg of gallic acid increased cytochrome P450 reductase activity (1.26-fold, $p < 0.01$) and cytochrome b5 reductase (1.45-fold, $p < 0.01$) as equated to control [50]. Treatment using a reversed concentration combination of the two phytochemicals further enhanced the enzymatic activity (cytochrome P450 reductase vs. cytochrome b5 reductase) by a 1.58-fold and 1.66-fold when a larger dose (50 µg/kg body weight) and a lower dose (25 µg/kg body weight) of acetylsalicylic acid was used, respectively, showing their antioxidant capacity [50].

4.1.4 Glutathione S-transferase and DT-diaphorase

Precise activity of glutathione S-transferase (GST) tend to be amplified by 1.92-fold ($p < 0.01$) and 2.11-fold ($p < 0.001$) when animals were treated with 50 µg/kg of acetylsalicylic acid (group III) and 100 µg/kg weight of gallic acid as compared to controls, an observation seen with. The activity of DT-diaphorase (DTD) was also observed to be significantly elevated by 1.79-fold ($p < 0.001$) and 2.36-fold ($p < 0.001$) when animals were treated with 50 µg/kg 100 µg/kg gallic acid, respectively, as compared to control group.

For both phytochemicals, a reversed concentration combination of acetylsalicylic acid and gallic acid treatment increased the activity of both enzymes showing improved anti-inflammatory [50]. Similar observation were demonstrated with thymoquinone on antioxidant enzyme activities, lipid peroxidation and DT-diaphorase in different tissues of mice with possible mechanism of action demonstrated [59]. Also, in early cancer studies similar antioxidant and anti-peroxidation effects of dietary curcumin have been shown on glutathione S-Transferase and the attenuation of malondialdehyde-DNA adducts in rat liver and colon mucosa [60].

4.1.5 Superoxide dismutase (SOD), catalase, glutathione reductase and glutathione peroxidase

Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) plays an important and indispensable role in the entire defense strategy of antioxidants as fundamental first line defense antioxidants. This is more so with reference to super oxide anion radical (O_2^\cdot) which is ceaselessly generated in normal body metabolism, particularly through the mitochondrial energy production pathway (MEPP) [61] and is attenuated when phytotherapeutics are administered.

Significantly increases in activities of SOD, CAT, GPX and glutathione reductase have been shown to be triggered by treating animals with gallic acid and acetylsalicylic acid. Animals treated with 100 µg/kg gallic experience enhanced SOD activity (1.47-fold). Variable concentrations of acetylsalicylic acid addition raises of these enzymatic antioxidants activity even higher [50] testimony to the efficacies of these phytochemicals in fighting lipid peroxidation.

4.2 Phytochemicals neuroprotection against oxidative stress

The foremost causes of dementia include neurodegenerative diseases and ischemic stroke and all have OS as an important player in their pathophysiology [62]. By modifying the expressions of antioxidant molecules and enzymes, the

Nrf2-ARE (nuclear factor erythroid 2-related factor 2/antioxidant responsive element antioxidant) system plays an essential role in neuroprotection as the primary cellular defense against OS. However, concurrent events of overproduction of ROS and dysregulation of the Nrf2-ARE system causes harm to indispensable cell components resulting in loss of neuron structural and functional integrity. On the other hand, TrkB (tropomyosin-related kinase B) signaling which is a classical neurotrophin signaling pathway, regulates neuronal endurance and synaptic plasticity important for fundamental functions in memory and cognition. The TrkB signaling, especially the TrkB/PI3K/Akt (TrkB/phosphatidylinositol 3 kinase/protein kinase B) pathway promotes the initiation and nuclear translocation of Nrf2, and brings in neuroprotection against OS. Essentially, the TrkB signaling pathway is also known to be downregulated in brain disorders due to lack of neurotrophin support. Therefore, activations of TrkB and the Nrf2-ARE signaling system suggests a potential approach to the design of novel phytochemical therapeutic agents for brain disorders.

The association between OS and the pathogenesis of neurodegenerative diseases, brain injury and the neuroprotective effects of phytochemicals that can co-activate the neuronal defense systems orchestrates important facets of the cellular antioxidant defense and TrkB signaling-mediated cell survival systems as possible pharmacological targets for the treatment of neurodegenerative diseases.

Factors contributive to OS in the brain include excitotoxicity, cellular antioxidant system exhaustion, lipid-rich membranes, susceptibility to lipid peroxidation, and brain high oxygen demand [63]. Excess ROS causes structural and functional modifications of cellular biomolecules, including proteins, DNA, and lipids, potentially limiting neuronal function and survival. The mechanisms rudimentary to the pathobiology of neurodegenerative diseases (NDDs) remain elusive. However, indications strongly advocates a noteworthy relationship between OS and NDDs, encompassing AD and Parkinson's disease (PD) [64]. Moreover, OS contributes to the pathogenesis of secondary damage after cerebral ischemia and other brain injuries [65, 66].

The deposition of misfolded proteins, seen in major NDDs, induce inflammatory responses, promoting ROS generation and resulting in OS [67]. Furthermore, OS causes and is caused by mitochondrial dysfunction [68]. Agreed, the central role the mitochondria play in energy metabolism and the regulation of redox homeostasis, mitochondrial malfunction contributes to the pathobiology of brain disorders. However, when encountered, cells compensate for the OS detrimental effect by triggering intracellular antioxidant defense system, unfortunately, contextually compromised in NDD. Therefore, activating the endogenous defense system by actuating Nrf2 using phytotherapeutics might provide a means of suppressing OS mediated cellular damage [62]. However, while OS may harm neuronal cytoarchitecture and restraining the detrimental effect of ROS alone may not suffice to prevent/reverse OS-mediated cellular damage. Approaches that support regeneration of damaged neuronal structures are necessary such that phytochemical interventions may be used for this purpose with outstanding results.

Physiologically, neuronal growth and survival are preserved via the neurotrophic signaling pathway, but modification in the regulation of specific neurotrophic factors and their receptors supervenes in the degenerating and aging brains [69]. Particularly, the brain-derived neurotrophic factor (BDNF)-dependent TrkB pathway, which is a critical signaling

pathway for the survival and normal functioning of mature neurons, is compromised due to lack of BDNF [70, 71]. Put together, the TrkB pathway and the Nrf2 signaling system seem to suggest potential targets for encouraging neuronal survival and initiating the regeneration of injured neuronal structures and synaptic

connectivity. Therefore, phytochemicals and other natural products can directly scavenge oxygen free radicals and boost the expressions of cellular antioxidant enzymes and molecules [36, 72]. This way, protection against OS-mediated cellular injury by these molecules may be possible [73, 74]. The neuritogenic potentials of the phytochemical therapeutics agents have been demonstrated [75, 76] to support the reconstruction of synaptic connectivity by renewing damaged neuronal processes [77, 78].

Different varieties of natural pharmacological modulate co-activate antioxidant defense and neurotrophin signaling-mediated cell survival systems [79–81] signifying that these compounds have therapeutic potential for the treatment of OS-mediated brain disorders. Targeting both of these signaling systems with a single compound offers benefits over combinations through possible the bypass of drug–drug interactions that could be either synergistic or antagonistic [62]. Furthermore, a single compound which can activate both the signaling and defense systems, would be more convenient to establish a therapeutic agent regarding pharmacokinetics and drug delivery.

4.2.1 Oxidative stress in case of neurodegenerative disease or brain injury

Disorders of dementia, to include NDDs, ischemic stroke or traumatic brain injury (TBI, complications are foremost public health concerns intimately linked to OS. Significantly higher concentrations of OS biomarkers and lower amounts of antioxidant biomarkers have been observed in the brain, peripheral tissues and body fluids of patients with brain disorders during preclinical and clinical studies [82, 83]. In these cases, high lipid peroxidation biomarkers are displayed as well.

4.2.1.1 Alzheimer's disease and lipid peroxidation effects

The major cause of dementia and most common progressive NDD is Alzheimer's disease [84, 85]. The main pathological hallmarks of AD, include extracellular β amyloid (β A) plaque deposits, intraneuronal aggregation of neurofibrillary tangles (NFTs), and brain atrophy [86]. Furthermore, OS has been shown to provoke β A deposition (plaque formation), tau hyperphosphorylation (NFT formation), and the ensuing degenerations of synaptic connectivity and neurons by damaging the protein degradation system [85].

Wojsiat et al., and Youssef, P., (2018) have reported raised levels of ROS-mediated vagaries in AD brains, supporting the notion that OS is caught up in the pathobiology of AD [87, 88], as shown by elevated concentrations of MDA and 4-HNE (lipid peroxidation biomarkers) being higher than normal in the brain tissues and cerebrospinal fluid samples of AD patients [84, 89]. Activities of antioxidant enzymes, superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT), and peroxiredoxin (Prdx) were altered in the brain affected areas although 4-HNE levels remained unaffected [88].

Male AD patients display elevated plasma concentrations of protein carbonyls and advanced glycation end products (carboxymethyllysine and carboxyethyl-lysine) [90]. Furthermore, 3-nitrotyrosine (3-NT), a protein nitration product, tend to be increased in CD3C (+) T-cells from AD patients [91]. Plasma antioxidants (uric and bilirubin) are significantly decreased concurrently with reduced activities of antioxidant enzymes in AD patients [92].

Oxidative stress contributes to mitochondrial dysfunction and cellular atrophy [93] while pathological aggregations of proteins such as A β and tau have been reported to target mitochondria and augment ROS production [94]. OS also retards synaptic plasticity contributing to progressive memory impairment, a

distinguishing clinical symptom of AD [95]. The connection between OS and AD strongly may suggest that approaches linked to antioxidant or antioxidant defense system such phytotherapeutics use could play imperative roles in the future management of AD.

4.2.1.2 Parkinson's disease (PD) and OS

The prevalence of PD is preceded only by that of AD being characterized by dopaminergic neuron degeneration in the substantia nigra [82]. A major pathological hallmark of PD is the intraneuronal aggregation of α -synuclein and the formation of Lewy bodies [93]. Crucial participation of OS in PD is intoned by convincing evidence although the exact mechanisms underlying the pathophysiology of this disease remains indescribable [96]. Singh et al., (2019) reported elevated concentration of oxidative damage markers and low concentration of glutathione (GSH) in the substantia nigra of PD patients [93]. Furthermore, high MDA plasma concentrations [97] and elevated protein carbonyl and 8-OHdG (markers of oxidative impairment to protein and DNA, respectively) in brain tissues have been reported [98]. Also, elevated concentrations of 8-OHdG and MDA, reduced activity of catalase and concentration of uric acid, and GSH have been reported in the blood of PD patients [99]. The involvement of OS in the pathobiology of PD and suggestion that targeting OS and lipid peroxidation offers a potential phytochemical therapeutic strategy for addressing this devastating brain disorder is supported.

4.2.1.3 Ischemic stroke and oxidative stress leads to lipid peroxidative damage

A sudden interruption in brain blood supply due to vascular occlusion results in a stroke which is the second leading cause of death [100] and an important source of permanent disability in adults worldwide [101]. Resultantly, a portion of the brain experiences oxygen and nutrient insufficiencies, which causes depolarization of neuronal membranes and glutamate surge into synapses, resulting in a cascade of events, including calcium overload, dissipation of mitochondrial membrane potentials, OS, and inflammation [63, 102].

Inappropriate concentrations of antiapoptotic proteins [e.g., Bcl-2 (B-cell lymphoma 2)] and proapoptotic proteins [e.g., Bax (Bcl-2-associated X protein)] contribute to mitochondrial dysfunction and OS induced apoptosis [103]. Moreover, the reestablishment of blood supply immediately after ischemia exposes brain tissue to excess oxygen, which exacerbates ROS production and in turn, induces further OS-associated injury, lipid peroxidation, protein oxidation, and intracellular DNA damage [63, 104]. After ischemic stroke, oxidative damage follows with elevated OS biomarkers (NO and MDA) concentrations reported [105]. These findings indicate targeting OS and inhibiting lipid peroxidation offers a promising therapeutic strategy to reduce secondary brain injury after ischemic stroke with possible outcomes improvement [63].

4.2.1.4 Traumatic brain injury builds oxidative stress and lipid peroxidation

Traumatic brain injury (TBI) is a major cause of death and disability world over. Non-fatal TBI may lead to neurological deficits due to direct tissue damage (primary injury) or subsequent biochemical changes (secondary injury) [106]. Biochemical factors such as excitotoxicity, inflammation, mitochondrial dysfunction, and OS drive progressive neuronal degeneration in secondary damage [107]. Importantly, further damage need be reduced by targeting the secondary changes. Indications that TBI results in OS are observed by OS biomarkers (oxidized

protein moieties, lipid peroxidation products, DNA damage products) accumulating in the brain with antioxidant molecules concentrations and enzymes activities (GSH, GPx, glutathione reductase (GR), glutathione S-transferase (GST), SOD, and CAT) decline [66]. Phytochemical neuroprotective strategies, directed at salvaging injured brain tissue soon after injury and that promote regeneration during the recovery stage, are beneficial [108]. Therapeutic potentials of BDNF and its analogues have been reported in TBI and other neurological conditions [108, 109]. Therefore, phytotherapeutics targeting cellular antioxidant defense and the BDNF/TrkB signaling pathway might improve cognitive deficits secondary to TBI.

5. Phytochemicals that activate neuronal antioxidant defense and survival mediating against lipid peroxidation

Many plant-derived bioactive molecules deactivate ROS and reportedly, potentiating the cellular antioxidant system. The principle of action of inducing an antioxidant effect by promoting adaptive cellular stress response using phytochemicals is substantially supported [110]. Furthermore, phytochemicals have been shown to protect neurons from OS by activating TrkB signaling pathways and the Nrf2-ARE system promoting cellular survival [77, 78].

5.1 Phenolic compounds and OS in brain neurological damages

5.1.1 Sulfuretin quenches oxidative stress effects

Numerous phenolics exhibit neuroprotective effects against OS in models of AD and other neurodegenerative disorders. Sulfuretin (**Figure 2**), a flavonoid glycoside isolated from the stem bark of *Albizia julibrissin* and heartwood of *Rhus verniciflua*, protected SH-SY5Y cells and primary hippocampal neurons from A β -induced neurotoxicity [111]. The PI3K/Akt and Nrf2/HO-1 signaling pathways may contribute to sulfuretin-mediated neuroprotection through inhibiting cell death by suppressing ROS production, enhancing PI3K/Akt pathway and the nuclear translocation of Nrf2 (**Figure 3**) [62]. Also, the phytochemical sulfuretin was shown to suppress adipocyte differentiation of preadipocytes and prevented obesity and increased insulin sensitivity by suppressing expression of inflammatory markers, inducing expression of adiponectin, and increasing concentrations of phosphorylated ERK and AKT [112]. Using a microarray analysis and identification of activating

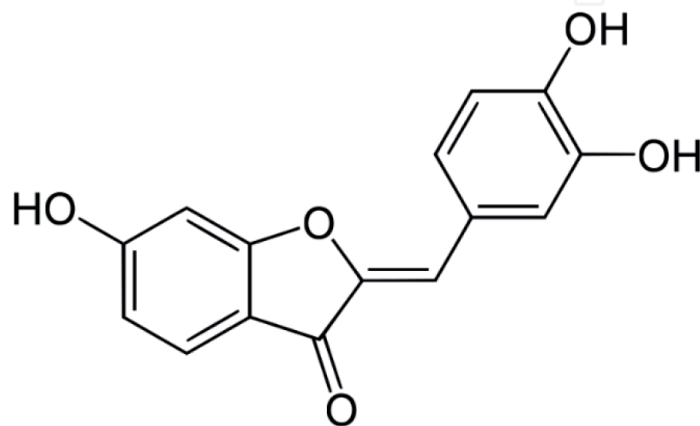


Figure 2.
Sulfuretin.

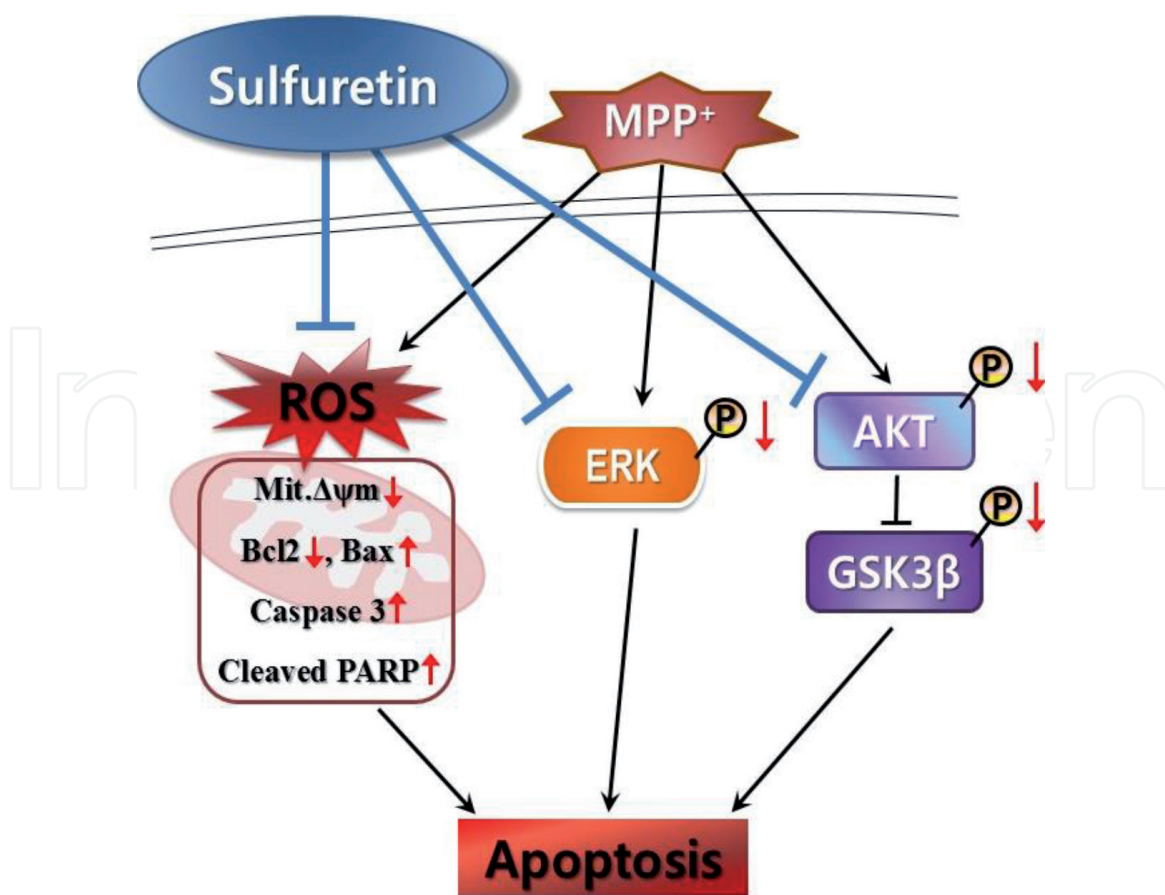


Figure 3.
 Other inhibitory effects of sulfuretin. ERK- extracellular signal-regulated kinase; AKT- protein kinase B (PKB); GSK3β- glycogen synthase kinase 3 beta; PARP = poly (adenosine diphosphate-ribose) polymerase; MPP⁺- 1-methyl-4-phenylpyridinium. — inhibition; ↑ increases; ↓ decreases. MPP⁺ arises as the toxic metabolite of the compound MPTP. MPTP is converted in the brain into MPP⁺ causing parkinsonism killing dopamine-producing neurons in the substantia nigra through oxidative stress generation which is inhibited by sulfuretin.

transcription factor 3 (Atf3) as a sulfuretin-responsive gene, the molecular mechanism of sulfuretin in adipocytes was illuminated. Administration of sulfuretin raised the Atf3 mRNA and protein concentrations in white adipose tissue and adipocytes. Reliably, Atf3 deficiency promoted lipid accretion, the adipocyte expression and lipid peroxidation markers. Sulfuretin's but not resveratrol's anti-adipogenic effects were diminished in cell with Atf3 deficiency, indicating that Atf3 is an essential factor in the function of sulfuretin [112] and that phytochemicals are essential for as antioxidant agents.

5.1.2 Resveratrol has antioxidant effects in brain disease

By activating the PI3K/Akt/Nrf2 pathway, the grape polyphenol and anthocyanin, Resveratrol (**Figure 4**), and a derivative of Korean black beans, protected PC12 cells [81] and HT22 cells [113], respectively, against Aβ-induced toxicity. In Aβ-induced toxicity, resveratrol inhibited cell death and suppressed OS markers such as MDA and ROS by elevation of the phosphorylation of PI3K and Akt, the nuclear translocation of Nrf2, and the protein concentrations of SOD, HO-1, and GSH [81]. Anthocyanins diminished cell death by modifying the expressions of proapoptotic markers (cleaved caspase-3) and stress markers (MDA, H₂O₂, 8-OHdG) while enhancing the glycogen synthase kinase-3 beta (GSK3b), phosphorylation of PI3K and Akt, the nuclear translocation of Nrf2, the expression of HO-1, and GSH levels.

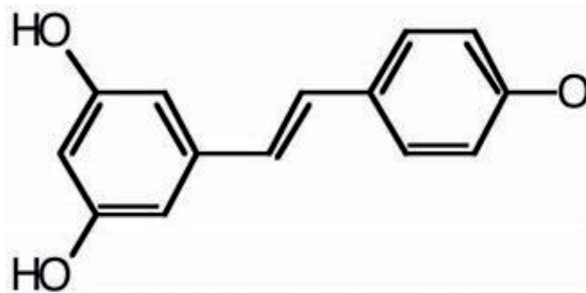


Figure 4.

Resveratrol whose chemical name is 3,5,4'-trihydroxy-trans-stilbene is a stilbenoid, a type of natural polyphenol, and a phytoalexin synthesized by numerous plants in response to injury or when the plant is under attack by pathogens, such as (viruses, bacteria or fungi).

5.1.3 Tea polyphenols, oxidative stress, neuroprotection

Tea polyphenols (TPs) attenuated OS in H_2O_2 -stimulated SH-SY5Y cells by activating the Keap1-Nrf2 signaling pathway and the TrkB/CREB/BDNF pathway [114]. Also in these experiments, TPs attenuated H_2O_2 -induced cell death, mitochondrial dysfunction and reduced elevated ROS and H_2O_2 concentrations. Moreover, TPs heightened the nuclear translocation of Nrf2 and the TrkB/CREB/BDNF signaling mechanism by activating the PI3K/Akt pathway, and thus, transcriptionally regulating the downstream expressions of HO-1, NQO1, SOD, GPx, and CAT in SH-SY5Y cells [114].

5.1.4 Isoflavone of fermented soy and neuroprotection

8-Hydroxydaidzein (8-OHD), an isoflavone of fermented soy, protected against neuroinflammation in LPS-stimulated BV2 microglial cells by stimulating Nrf2-antioxidant and Akt/NF-kB inflammatory signaling pathways. In BV2 microglial cells, 8-OHD inhibited the LPS-activated productions of NO, TNF- α , and IL-6 by suppressing gene expression [115]. Moreover, 8-OHD quenches ROS and promotes the nuclear translocation of Nrf2, and thus, upregulates the expressions of Phase II enzymes, such as HO-1, NQO1, and GCL [115]. 8-OHD also suppresses the LPS-stimulated phosphorylation of Akt and NF-kB-p65 attenuating LPS-induced prostaglandin E2 (PGE2) production without affecting COX-2 expression [116].

5.1.5 Rutin protection against neurotoxicity

A flavonoid found in buckwheat, rutin protected male albino SD rats from acrylamide or g-radiation-induced neurotoxicity by activating the PI3K/Akt/GSK-3b/NRF-2 signaling pathway (**Figure 5**) [118]. Rutin (**Figure 5**) increases the phosphorylation of PI3K, Akt, and GSK-3b and the nuclear translocation of Nrf2, suppressed MDA levels, GST activity, and the expressions of IL-1b and IL-6, and increased IGF1 and NGF levels [118]. The phytochemical rutin's mechanisms of action includes reduction of proinflammatory cytokines, increasing antioxidant enzyme activities, stimulation of the mitogen-activated protein kinase cascade, downregulation of mRNA expression of PD-linked and proapoptotic genes, upregulation of the ion transport and antiapoptotic genes, and restoration of the functions of mitochondrial complex enzymes [119]. Taken together, these suggest that they phytotherapeutic rutin may be a hopeful neuroprotective compound for the treatment of NDDs.

Rutin as neuroprotective agent has been seen to move from bench to the bedside as a phytotherapeutic [120] as well as the inhibition of neuroinflammation and

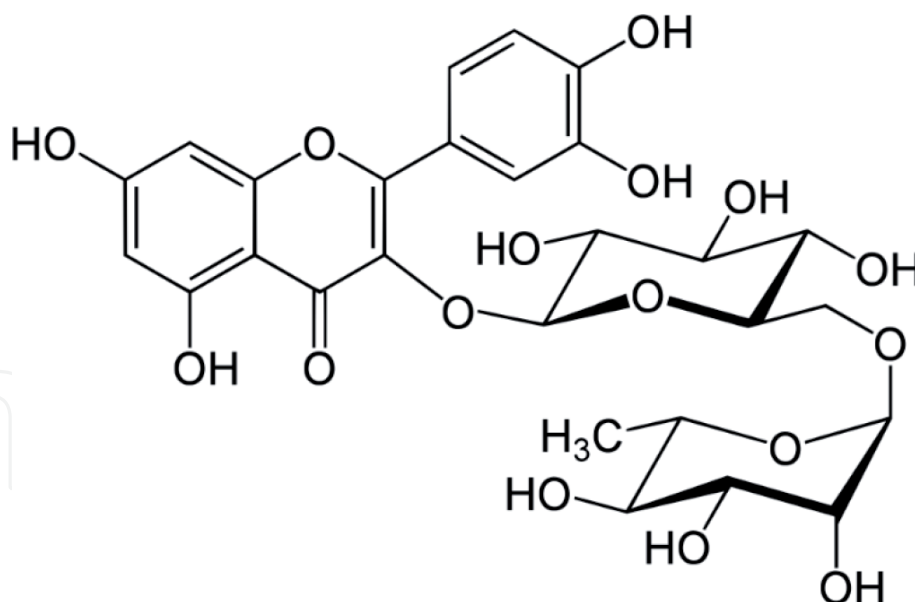


Figure 5.
 Rutin, also called rutoside, quercetin-3-O-rutinoside and sophorin, is the glycoside combining the flavonol quercetin and the disaccharide rutinose (α -L-rhamnopyranosyl-(1 \rightarrow 6)- β -D-glucopyranose) [117].

providing neuroprotection in subarachnoid hemorrhage through suppressing the RAGE-NF- κ B inflammatory signaling pathway [121].

Rutin has anti-inflammatory, antioxidant, anti-viral, anti-tumor and immune regulatory effects. Neuroprotective mechanisms of rutin for spinal cord injury has been reported to occur through anti-oxidation and anti-inflammation and inhibition of p38 mitogen activated protein kinase pathway [122].

5.2 Non-phenolic compounds, neuroprotection and lipid peroxidation

Numerous non-phenolics have been reported to exhibit neuroprotective effects against OS in models of AD and other neurodegenerative disorders [62].

5.2.1 Brassicaphenanthrene A, acerogenin A and neuroprotection

Isolated from *Brassica rapa*, Brassicaphenanthrene A protects HT-22 neuronal cells from glutamate-induced excitotoxicity and upregulates Nrf2-mediated HO-1 expression via PI3K/Akt and JNK regulatory pathways [123]. Acerogenin A, an isolate from the stem bark of *Acer nikoense* (Japanese traditional medicine) protected HT22 cells from glutamate-induced oxidative injury [124] through the stimulating the PI3K/Akt/Nrf2/HO-1 pathway. Acerogenin A diminished cell death by suppressing the production of ROS and increasing the nuclear translocation of Nrf2, the expression of HO-1, and the phosphorylation of Akt [124].

Polysaccharide extracts (PPE) of *Perilla frutescens* triggered PI3K/Akt and Nrf2-mediated HO-1/NQO1 pathways and protected against H₂O₂-induced OS in HT22 cells [125]. The PPE attenuates cell damage by suppressing the expressions of Bax, cytochrome C, and caspases-3, -8, and -9, and enhancing the expressions Bcl-2 and Poly [ADP-ribose] polymerase (PARP) while increasing MAPKs (p38, ERK, JNK), PI3K, Akt and p65 phosphorylation, decreasing NF- κ B concentration and enhancing the nuclear translocation of Nrf2 and the expressions of HO-1 and SOD [125].

3,3'-Diindolylmethane, a metabolite of indole-3-carbinol found in Brassicaceae family, attenuates OS in glutamate-induced HT-22 cells by activation of the TrkB/ Akt pathway [126]. 3,3'-Diindolylmethane metabolite moderates the expressions

of Bax, cytochrome c, cleaves caspase-3, and AIF (apoptosis-inducing factor), and improves Bcl-2 expression, the phosphorylation of TrkB, Akt, and CREB, and the expressions of HO-1, GCLC, NQO-1, and GPx. Scopolamine-treated mice improved cognitive deficits after 3,3'-Diindolylmethane administration [126].

Diallyl trisulfide, an organosulfur compound in garlic oil, stimulated the PI3K/Akt-mediated Nrf2/HO-1 signaling pathway and protected against OGD-induced neuronal injury [127]. Also, diallyl trisulfide inhibited the expressions of proapoptotic markers (cleaved caspase-3), OS markers (ROS and MDA), and increased the nuclear translocation of Nrf2, the expression of antioxidant enzymes (e.g., HO-1), and the phosphorylation of Akt [127] thus reducing lipid peroxidation potentials in brain injury.

Oxymatrine, isolated from the Chinese herb *Sophora flavescens* protected P7 SD rats from hypoxic-ischemic brain injury [128], through activating the Akt/GSK3b/HO-1/Nrf-2 signaling pathway. Moreover, oxymatrine increased the nuclear translocation of Nrf2, the phosphorylation of Akt and GSK3b, and HO-1 expression and attenuated the degree of neurological deficits [128].

6'-O-Galloylpaeoniflorin, a galloylated derivative of paeoniflorin isolated from peony root, protected an OGD-induced ischemic PC12 cell model and a CIRI male Wistar rat model against ischemic stroke through stimulating PI3K/Akt/Nrf2 pathway [129]. Also, 6'-O-galloylpaeoniflorin attenuated OS and neuroinflammation while improving neurological deficits, inhibiting apoptosis by suppressing the expressions of pro-apoptotic markers (cleaving caspase-3), inhibiting inflammatory cytokine (TNF- α , IL-1b), and MDA concentration. Nuclear translocation of Nrf2 and SOD expression increased through elevation of Akt phosphorylation [129].

Ginkgolides A, B and C are diterpenes isolated from *Ginkgo biloba* L. and defends PC12 cells from OGD/R-induced ischemic injury in adult male SD rats subjected to MCAO-induced acute cerebral ischemic injury [130]. They stimulate Akt/Nrf2 and Akt/CREB signaling pathways. These ginkgolides inhibit cell death by overwhelming the expressions of Bax and cleaved caspase-3, enhancing the phosphorylation of Akt and pCREB, and increasing the nuclear translocation of Nrf2 and HO-1 expression [130]. Also, ginkgolides protects against ischemic stroke in an OGD-induced SH-SY5Y cell ischemic model and MCAO-induced model of cerebral ischemic injury in male SD rats [131]. Ginkgolides suppress ROS production and increase Akt phosphorylation, the nuclear translocation and phosphorylation of Nrf2, and the expressions of HO-1, Nqo1, and SOD [131]. In the process lipid peroxidation associated damages are averted.

PC12 cells are protected against OGD/R-induced neuronal injury by **Protodioscin** which actuates the PI3K/Akt/Nrf2 pathway. This occurs through elevating the expressions of HIF-1 α , SOD, GPx, HSP70, and HO-1, the phosphorylation of PI3K and Akt, the nuclear translocation of Nrf2, and upregulating miR-124. As a result, OS is attenuated [132] and lipid peroxidation reduced.

Matrine, a quinolizidine alkaloid, derived from the herb *Radix Sophorae flavescentis*, protected rats from subarachnoid hemorrhage [133] through PI3K/Akt-mediated NF- κ B inhibition and Keap1/Nrf2-dependent HO-1 induction. The effects of matrine included inflammatory cytokines (TNF- α , IL-1b) and pro-apoptotic markers (Bax and cleaved caspase-3) expression suppression with enhanced pro-survival marker Bcl-2 ([133]. Also, matrine increased nuclear translocation of Nrf2 and HO-1 expression and lowered NF- κ B P65 expression by increasing the phosphorylation of Keap1, Akt, and I κ B- α [72] invariably attenuating lipid peroxidation.

Panax notoginseng saponins protected against blood-brain barrier (BBB) injury [134] by activating the PI3K/Akt/Nrf2 antioxidant signaling pathway. In LPS-stimulated cerebral microvascular endothelial cells BBB injury model,

saponins attenuated the creations of ROS and inflammatory cytokines (IL β 1b, TNF α), decreased NF β kB levels, and increased the nuclear translocation of Nrf2 HO-1 expression, and the phosphorylation of Akt [134].

6. Lipid peroxidation-induced inflammation and oxidation-mediated degenerative diseases

Degenerative disease is positioned as one of the most fatal group of diseases contributing to the mortality, poor quality of life, increasing economic problems of the sufferers with OS and inflammation being leading drivers of lipid peroxidation related pathology [135]. The most common degenerative diseases include rheumatoid arthritis (RA) [136], diabetes mellitus (DM) [137], and cardiovascular disease (CVD) [138]. Although a number of synthetic medications are used to treat these diseases, none of the current regimens are completely safe. Phytochemicals: polyphenols, carotenoids, anthocyanins, alkaloids, glycosides, saponins, and terpenes are potential sources of alternative medications to attenuate the oxidative stress and inflammation associated with degenerative diseases. Some of these active compounds have shown good promise for development into novel mediators for treating RA, DM, and CVD by targeting OS and inflammation.

6.1 Phytotherapeutics and degenerative diseases

Several synthetic regimens are used to attenuate oxidative stress and inflammation-mediated degenerative diseases, with most of them exerting considerable side effects when utilized in the treatment of CVDs [139], DM [140] and RA [141].

6.1.1 Cardiovascular diseases, oxidative stress and lipid peroxidation

CVDs are a group of diseases associated with complications of the heart and blood vessels invariably leads to coronary heart disease a major component of CVDs [135]. Lipid peroxidation associated major risk factors of CVDs include hypertension (HTN), hypercholesterolemia, diabetes, obesity, inflammation, smoking, consumption of alcohol, lack of exercise, and a familial history of heart diseases [142].

6.1.2 Pathogenesis of CVDs

Atherosclerosis occurs due to the accumulation of atherosclerotic plaques within the walls of the arteries is the major precursor of CVDs. Plaque formation originates from endothelial damage, followed by adherence of circulating monocytes and subsequent exposure to homocysteine, inflammation, increased platelet aggregation, and higher levels of oxidized low-density lipoprotein (LDL-ox) and ROS [143]. Moreover, increased serum triacylglycerols.

(TAG), cholesterol (C), increased plasma fibrinogen and coagulation factors, hyperglycemia, HTN and lipid peroxidation are crucial in the pathogenesis of CVDs [144].

6.1.3 Phytochemicals and CVDs

Polyphenols and other antioxidants from fruits, vegetables, and spices has the potential to lower CVD risks by attenuating oxidative stress and inflammatory mediators [135]. Fruit consumption in Japan protected against the risk

of CVDs [145], a higher consumption of fruits and vegetables correlated with a lower risk of all-cause mortality, predominantly cardiovascular mortality [146] while high-frequency consumption of fruits and vegetables lowered plasma C-reactive protein (CRP) and homocysteine concentrations, accordingly reducing inflammation a considered high risk factor of CVDs [147]. High fruit consumption level decreased HTN and blood glucose concentration which significantly decrease the risks of CVDs [148].

Polyphenolic extract from the apple has a significant effect on decreasing the serum total-C and LDL-C levels in healthy individuals with relatively high body mass index (BMI), which consequently limits CVD risk [149]. Consumption of banana decreases the oxidative modification of LDL, plasma lipids, and lipoproteins and thus ultimately aids in protection from atherogenesis due to its antioxidant properties [150]. Furthermore, blueberries, strawberries, and cranberries reduce cardiovascular risk factors of lipid peroxidation, inflammation, and regulate HTN due to the presence of high concentrations of anthocyanins and ellagitannins in their skin and flesh [151, 152]. Moreover, being good sources of polyphenols, berries have a high content of micronutrients such as folate, α -carotene, β -carotene, potassium, vitamin C, and vitamin E, which exhibit noteworthy antioxidant activities [153].

Citrus fruits such as mandarins, lemons, oranges, and grapefruits contain high quantities of flavanones (naringin and hesperidin stimulate nitric oxide in endothelium) that improve significant vascular functions and the lipid profile in coronary artery diseases patients [154, 155]. Pomegranate fruit juice and peel extracts have antihypertensive, anti-atherosclerotic, antioxidant, and anti-inflammatory effects because of polyphenolic compounds including anthocyanins, catechins, and tannins, contributing to the attenuation of CVD risk factors [156].

Polyphenol-rich peach and plum juice prevent against risk factors effects for cardiometabolic disorders by decreasing the expression of plasma proatherogenic and proinflammatory molecules, intercellular cell adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1, and nuclear factor kappa B (NF- κ B) and by decreasing foam cell adherence to aortic arches. Furthermore, peach and plum juice reduce plasma angiotensin II activity and the expression of its receptor Agtr1 in cardiac tissues. Peach and plum polyphenols act as peroxisome proliferator activated receptor- γ (PPAR γ) agonists [157]. An *in vivo* and *ex vivo* experiment watermelon improves lipid profiles and antioxidant capacity and decreases inflammation and alters gene expression for lipid metabolism and consequently reduce CVDs risk factors [158].

Sulfur-containing organic compounds (organosulphur) from garlic (*Allium sativum*), onion (*Allium cepa*), and cruciferous vegetables such as broccoli, cauliflower, cabbage, and Brussels sprouts exhibited cardioprotective effects facilitated by their antioxidant and anti-inflammatory properties [159]. Garlic's sodium 2-propenyl thiosulfate is suggested to block platelet aggregation through inhibition of ADP and platelet-activating factor (PAF) [160]. The onion key flavonoid, quercetin (3,3',4',5,7-pentahydroxyflavone), has anti-atherosclerotic properties and accumulate in the aorta tissue where its metabolites exert antioxidant and anti-inflammatory activities [161]. The bright red carotene and carotenoid pigment in tomato, lycopene, significantly reduces myocardial infarction (MI) in isoproterenol injected rats [162]. Supplementation of tomato and corn oil improves diastolic function, changes cardiac miRNA expression, and attenuates lipid hydroxy peroxidation and oxidative stress [163].

Ginger (*Zingiber officinale*) benefits in the treatment of CVDs exhibiting anti-inflammatory as well as antithrombotic properties by inhibiting the production of NO, inflammatory cytokines, cyclooxygenase (COX), and lipoxygenase (LOX) with

no or very few side effects as compared to nonsteroidal anti-inflammatory drugs (NSAIDs) [164, 165]. Ginger is known for its being an antioxidant, antiplatelet aggregation, positive inotropic, hypotensive, hypoglycemic and hypolipidemic in *in vitro*, *in vivo* studies and in human clinical trials [166].

Black pepper, and its active ingredient (piperine) influences significant decrease in the concentrations of free fatty acids, phospholipids, and triacylglycerols and an increase in the concentration of high density lipoprotein cholesterol (HDL), thus reducing the risk of atherosclerosis [167, 168].

7. Diabetes mellitus and lipid peroxidation

7.1 Pathogenesis from inflammation and lipid peroxidation

The pathogenesis of DM is closely associated with involvement of low-grade chronic inflammation and the activation of the innate immune system [169]. Excessive concentrations of glucose and free fatty acids initiate cellular OS in the pancreatic islets and insulin-sensitive tissues including adipose tissue, leading to the activation of c-Jun N-terminal kinase (JNK) and NF- κ B [170]. Increases in the adipocyte proinflammatory cytokines production including tumor necrosis factor alpha (TNF- α), interleukin (IL) 6, IL-1 β , leptin, resistin, and chemokines such as MCP-1, CC-chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 8 occurs when inflammatory signaling pathways start regulating protein phosphorylation and cellular transcriptional events. Accordingly, recruitment to immune cells such as monocytes to the adipose tissues contributes to tissue inflammation. Differentiation of monocytes into macrophages creates several inflammatory cytokines, further encouraging local inflammation. Moreover, the release of cytokines and chemokines from the adipose tissues into the circulation promotes inflammation in other tissues including the pancreatic β -islets [170] worsening diabetes mellitus status.

Inflammation-induced insulin resistance build up is further escalated by JNK and IKK β /NF- κ B which play important roles in inflammation. The stress kinase, JNK, normally phosphorylates the c-Jun component of the AP-1 transcription factor promoting insulin resistance. Phosphorylation of the serine residues in the insulin receptor substrate 1 (IRS-1) is involved [171]. Subsequently, counter-regulatory serine/threonine phosphorylation [172] inhibits insulin receptor signaling that normally occurs through a tyrosine kinase cascade [173]. The I κ B protein inhibitors of NF- κ B are the highly selected physiological substrates for IKK β . The NF- κ B is inhibited by I κ B α which when phosphorylated by IKK β undergoes proteasomal degradation releasing the former for translocation into the nucleus, where it promotes the expression of numerous target genes whose products induce insulin resistance. IKK β causes insulin resistance through the transcriptional activation of NF- κ B. Therefore, decreasing gene expression and improving insulin resistance may be achieved by administration of anti-inflammatory phytochemicals. Increasing adiposity is reported to upsurge inflammatory gene expression in the liver [174], which further increases the production of cytokines and chemokines aspects ameliorated by triterpenes phytotherapeutics [34]. Immune cells including monocytes and macrophages are recruited and/or activated, which leads to local insulin resistance processes that may be averted by anti-inflammatory triterpenes like Asiatic acid, maslinic acid or oleanolic acid.

Oxidative stress modifies the enzyme systems, impairs glutathione metabolism, causing lipid peroxidation and reducing vitamin C concentration and thus contributing to DM [175]. Actually, a mutual relationship exists between hyperglycemia

and oxidative stress in DM with hyperglycemia fueling glucose autooxidation, NADPH oxidase activity, oxidative phosphorylation, protein glycation, and the polyol pathway, which leads to ROS generation and OS [176]. Healthy cells are damaged functionally and structurally by ROS, losing cellular integrity leading to many pathophysiological conditions.

7.2 Phytochemical intervention in DM

Was it not for their side effects, numerous synthetic drugs groups and insulin groups possess antioxidative and anti-inflammatory potential that can be used in the treatment of DM. Resultantly, the pursuit for alternative and safer treatment regimens for DM management remains open for investigation.

7.2.1 Phytochemicals interventions in DM

In streptozotocin- (STZ) induced diabetic Sprague Dawley rats, the oral administration of **naringin** (4',5,7-trihydroxyflavonone-7-rhamnoglucoside) at 50 mg/kg/day reduces OS and increases fasting plasma insulin activity. Naringin, the foremost flavonoid in grapefruit juice, ameliorates OS and improves ATP synthesis in pancreatic β -cell mitochondria and upgrades the subsequent insulin secretion by β -cells [177]. Significant amelioration of β -cell dysfunction, insulin resistance and hyperglycemia, reduction of TNF- α , IL-6, CRP, increase in antioxidant enzyme activities, reduced NF- κ B expression, and upregulated adiponectin and PPAR γ expression have been observed through the application of naringin on diabetic Wistar albino male rats for 28 days. The positive alterations were obtained with naringin treatment at 25, 50, and 100 mg/kg/day. Furthermore, naringin effectively rescues kidney cells, β -cells, and liver cells from continued pathological modifications and oxidative damage [178].

Resveratrol (Figure 3), a phytochemical, exerts potent antioxidative, antidiabetic, and anti-inflammatory activities. In the liver and spleen of STZ-induced male Long-Evans rats (type 1 DM), resveratrol administration (0.1 or 1.0 mg/kg/day) for 7 days, significantly decreased OS (including manganese-superoxide dismutase expression, superoxide anion content, protein carbonyl concentration). Also, reduction in hepatic inflammation factors (NF- κ B and IL-1 β) and decreasing the TNF- α and IL-6 concentrations in spleen were observed [178].

Apples contain a principal phenolic compound called **Phlorizin** (PZ). Preexposure of PZ- docosahexaenoic acid ester (DHA) onto a lipopolysaccharide (LPS) stimulated macrophages inflammation model effectively reduced TNF- α , IL-6, and COX-2 protein concentrations compared with DHA alone. However, both PZ-DHA ester and DHA have the potential to inhibit NF- κ B activation a proinflammatory marker. Therefore, PZ-DHA ester has the potential to quench T2DM-associated inflammation [179] and ameliorate the disease.

Diabetes mellitus is associated with the glutathione concentration reduction demonstrating the critical role of OS in its pathogenesis. Pretreatment of Ins-1E pancreatic β -cells with the **flavonoid epicatechin** (present in green tea, grapes, and cocoa) prohibited tert-butyl hydroperoxide induced cell damage, ROS and p-JNK over expression. Over more, insulin secretion which indicates the protective potentiality of epicatechin against oxidative stress on β -cells is restored [180].

Pomegranate (*Punica granatum*) fruit contains flavonoids such as anthocyanins, flavonols, ellagitannins, gallotannins, and proanthocyanidins providing beneficial effect in T2DM by reducing lipid peroxidation and OS. Also effected is the increasing of enzymatic antioxidant activity, decreasing ROS, and preventing activation of PPAR γ and NF- κ B by pomegranate [181].

Anthocyanins, found in tart cherry, alter tissue PPAR γ activity affecting metabolism and inflammation. The intake of tart cherry reduces retroperitoneal IL-6 and TNF- α mRNA expression, NF- κ B activity, and plasma IL-6 and TNF- α concentrations while increasing retroperitoneal PPAR α and PPAR γ mRNA expression in Zucker fatty rat model of obesity and metabolic syndrome. The risk of T2DM development tend to decrease when systemic and local inflammation, metabolic syndrome and lipid peroxidation are reduced [182].

Adipose tissue LPS-induced macrophages infiltration increased adiposity and lipid peroxidation may lead to T2DM. In an *in vitro* inflammation model where the pathologic relationships between adipocytes and macrophages were mimicked, anthocyanin-rich fractions from blackberry-blueberry beverages inhibited NO and TNF- α the secretion and the phosphorylation of NF- κ B p65 [183] and lipid peroxidation tendency.

T2DM is associated with chronic, low-grade, systemic inflammation accompanied by an increased production of adipokines or cytokines by obese adipose tissue. Grape fruit (0.5 g/kg/ six weeks) treatment of diabetic db/db mice produced antihyperglycemic effects that were accompanied by reduced mRNA expression of proinflammatory genes such as COX-2, monocyte chemotactic protein-1, TNF- α , NF- κ B and reduced lipid peroxidation in the liver and epididymal adipose tissue [184].

The immunomodulatory effects of a mycelial submerged culture and broth of *Grifola frondosa* **mushrooms** on splenocytes and peripheral blood cells. Two weeks of intragastric administration of fermented mycelia, broth, or their combination (1 g/kg/day) into DM Wistar rats significantly decreased the 2-hour postprandial blood glucose level, the production of T-leukocyte-derived interferon gamma (IFN- γ), monocyte-derived IL-4 and IL-6, and T-splenocyte derived IL-4 which treatment significantly enhanced macrophage-derived TNF- α production [185] and possible decreased lipid peroxidation.

The administration of **fermented carrot juice** (by *Lactobacillus plantarum* NCU116) for five weeks in STZ-induced diabetic rats positively regulated the blood glucose concentration, hormone, and lipid metabolism, reestablished the antioxidant capacity, restored the morphology of pancreas and kidney, and upregulated the LDL receptor, cholesterol 7 α -hydroxylase (CYP7A1), GLUT4, and PPAR α and PPAR γ mRNA expression [186].

In diabetic male C57BL/6 J mice, (0.5 mg/kg) treatment for 4 months with **Sulforaphane (SFN)**, an isothiocyanate found in broccoli, significantly inhibited cardiac lipid accumulation and enhanced cardiac inflammation, OS, and fibrosis. By downregulating diabetes induced PAI-1, TNF- α , CTGF, TGF- β , 3-NT, and 4-HNE expression, SFN ameliorated lipid peroxidation potential. Also, SFN, upregulated nuclear factor (erythroid-derived 2-) like factor 2 (Nrf2) and its downside genes, NQO1 and HO-1 in rescuing DM sequelae. Of note, SFN diminished 4-HNE-LKB1 adducts and reversed the diabetes-induced inhibition of LKB1/AMPK and its downstream targets, including sirtuin 1, PGC-1 α , phosphorylated acetyl-CoA carboxylase, and carnitine palmitoyl transferase-1. Ultimately, SFN treatment of T2DM attenuate the cardiac OS-induced inhibition of the LKB1/AMPK signaling pathway, thereby preventing T2DM-induced lipotoxicity and cardiomyopathy [187].

Onion-derived quercetin derivatives are important flavonoids for improving diabetic conditions in both *in vivo* and *in vitro* models. Eight days of treatment with onion peel extract (1%) improved significantly glucose tolerance, liver and skeletal muscle glycogen content, and insulin receptor and GLUT4 expression in muscle tissues of STZ-induced DM in male Sprague Dawley (SD) rats. The OS-inducing dysregulations of SOD activity, increased free fatty acids plasma concentrations,

the formation of MDA, and IL-6 over expression in hepatic tissue, were significantly suppressed in this model of onion-derived quercetin treatment [188].

Traditional medicinal mushroom known as *Cordyceps militaris* are a source of **Cordycepin (3'-deoxyadenosine)**. Inhibition of NO, suppression of NF- κ B activation, and protein expression suppression of proinflammatory mediators that further inhibit the production of proinflammatory cytokines such as IL-1 β , IL-6, and TNF- α has been demonstrated in LPS-stimulated 263.7 cells treated with cordycepin. Over more, an elevated concentration of cordycepin reduced the T2DM-regulating genes such as 11 β -HSD1 and PPAR γ as well as the expression of costimulatory molecules such as ICAM-1 and B7-1/-2 [189].

Curcumin (a polyphenolic compound) in Turmeric (*Curcuma longa*) is the active ingredient possesses broad-spectrum biological activities such as anti-inflammatory, antioxidant, and antitumor. Reduction of OS and inflammatory responses and inhibition of prostaglandin E2 (PGE2) and NOS have been observed in the injured lungs of DM rats after administration of curcumin. As a mode of action, curcumin inhibited the stimulation of NF- κ B, a key player in inflammatory responses [190]. Eight weeks treatment of db/db mice with curcumin improved AMPK and PPAR γ expression and reduced NF- κ B protein levels [191].

Hyperglycemia-mediated OS of DM may induce neuronal injury. **Curcuminoids**, polyphenols of turmeric, displayed protective effects against OS in the brain of STZ-induced diabetic rats by restoring the normal concentrations of lipid peroxidation and nitrite content and endogenous antioxidant marker enzymes [192]. *De novo* synthesis of glutathione and the suppression of insulin receptor expression were achieved with the administration of curcumin which attenuated insulin-induced OS in hepatic stellate cells by stimulating the expression of glutamate-cysteine ligase [193]. Pretreatment with a novel curcumin analogue (B06) at 5 μ M significantly reduced the high-glucose-induced overexpression of inflammatory cytokines in macrophages through the inhibition of c-Jun N-terminal kinase/NF- κ B activation [194].

Administration of **ginger powder** (0.5%, 1%, and 5%) in STZ-induced inbred male Wistar/NIN rats for one month protected against DM effects by modulating antioxidant enzymes, glutathione and downregulating lipid and protein oxidation [195]. Combined **garlic bulb, ginger rhizome, turmeric rhizome** (200 mg/kg body weight) treatment for 28 uninterrupted days significantly alleviated hyperglycemia and dyslipidemia, increased insulin production, enhanced GSH, and decreased lipid peroxidation in nicotinamide and STZ-induced diabetic rats [196].

Diabetic encephalopathy is one of the more severe complications of DM characterized by severely reduced body weight. **Saffron** at 40 and 80 mg/kg significantly increased the body weight and serum TNF- α concentrations and decreased the blood glucose, glycosylated proteins, and advanced glycation end product (AGE) serum concentrations in DM encephalopathy rats. Additionally, saffron significantly increased the glutathione content, superoxide dismutase, and catalase but remarkably decreased the cognitive deficit and serum TNF- α , and it induced NOS activity in hippocampus tissue [197].

Administration of **Crocins**, an active constituent of saffron, significantly decreased MDA ($p < 0.01$) and xanthine oxidase ($p < 0.05$) activities while elevating glutathione ($p < 0.05$) concentration, thus ameliorating renal injury in STZ-induced rats [198]. **Safranal** is one of the components of the saffron plant which, in high-fat diet (HFD) and STZ-induced T2DM rats, treatment for a period of 4 weeks diminished OS caused by T2DM and reduced the inflammation by decreasing plasma and pancreas tissue the TNF- α and IL-1 β s concentrations [199].

The protective effect of **Onion** protected against OS *in vivo* where STZ-induced male diabetic Wistar rats administered 1 mL/day of *Allium cepa* solution (0.4 g

Allium cepa/rat) improved the fasting serum HDL concentration, alleviated hyperglycemia by diminishing SOD activities [200]. Another *in vivo* study also investigated the protective effects of onion against oxidative stress; 12 weeks of onion intake suppressed the diabetes-induced oxidative stress more effectively in STZ-induced diabetic rats [140]. Onion powder (7% w/w) administration suppressed the glutathione peroxidase, glutathione reductase, and glutathione S-transferase activities [201].

Mustard leaf (*Brassica juncea*) strongly inhibits the AGE formation and free radical-mediated protein damage oral ingestion by STZ-induced diabetic rats an EtOAc fraction (50 and 200 mg/kg body weight/day/10 days) reduced the serum glucose and glycosylated protein, superoxide and nitrite/nitrate concentrations. This suggests that the EtOAc fraction of mustard leaf has the capacity to attenuate damage caused by the oxidative stress involved in diabetes and its complications [202]. Brown mustard is a high source of Asiatic acid, a triterpene with an excellent antioxidant capacity, potent anti-inflammatory [203], antihyperglycemic [204], antihyperlipidemic [35], reduction of OS while rescuing malarial infection in SD rats.

8. Rheumatoid arthritis (RA) and phytochemical interventions

RA is an inflammatory, systemic autoimmune syndrome with primary degenerating articular structures involving, the cartilage (movable synovial joints- knees, shoulders, hands) and the bones (osteoarthritis and osteoporosis) as a result of pannus development over the joint surfaces (abnormal layer of fibrovascular or granulation tissues) [205]. great socioeconomic impact worldwide.

8.1 Pathogenesis of RA Arise from autoimmune inflammation and OS

The pathogenesis of RA involves A complex interplay between genetic and environmental factors leading to autoimmune inflammatory responses against the connective and synovial tissues of the joints [136]. Furthermore, increased ROS concentrations are actively involved in RA pathogenesis [206, 207]. Infiltration of the affected synovial tissues and promotion of the overexpression, release, and activity of proinflammatory cytokines [TNF- α , TNF-induced NF- κ B, vascular endothelial growth factor (VEGF), IL-1 beta (IL-1 β), IL-6, IL-8, and IFN- γ] by T cells, B cells, and macrophages are particular findings in patients with RA [208, 209].

Responding to the proinflammatory cytokines, synoviocytes (FLS) fibroblasts flourish and produce huge quantities of cytokines, matrix metalloproteinases (MMPs), and COX-2, which progressively degrade cartilage and lead to joint obliteration [210, 211]. Oxidative stress is involved in the disintegration of cartilage through Nrf2 or NFE2L2 dysregulation [212]. Activated Nrf2 binds to antioxidant response elements (AREs), resulting in the augmented expression of antioxidative enzyme [e.g., Heme oxygenase-1 (HO-1)] encoding genes [213, 214] which indicates both OS and inflammatory response are implicated in the RA pathogenesis. Resultantly, phytochemicals with anti-inflammatory capacities play a crucial role in the battle with RA.

8.2 Phytochemicals against OS and inflammation in RA

Side effects are common and unavoidable from synthetic regimens used for managing RA making alternative medicine and traditional medicine a viable source

for treating the disease. Phytochemicals attenuate OS and inflammation and relieve and protection from RA.

The clinical phenomenon in patients with RA involves osteoclastogenesis which is a process where bone tissues is destroyed by osteoclasts. **Polyphenols** extracted from **dried plums** extracted polyphenols inhibit osteoclastogenesis through suppressing TNF- α and NO synthase activity and by downregulating the transcription factor nuclear factor for activated T cells (NFATc1) [215]. **Cherry anthocyanins** reduce both OS (SOD and decrease serum MDA) and inflammatory mediators (decrease in TNF- α) in an SD adjuvant-induced RA rat model [216].

Resveratrol polyphenol confers significant protective effect against an aggressive RA rat model [217]. Anti-inflammatory and antioxidative resveratrol activities influenced reduction of specific rheumatoid biomarkers activities [serum rheumatoid factor (RF), MMP-3 and cartilage oligomeric matrix protein (COMP)], immunological biomarkers [IgG and antinuclear antibody (ANA)], immunomodulatory cytokines (TNF- α), and OS biomarkers [myeloperoxidase (MPO), CRP, and MDA] [217].

A natural polyphenol in mangoes, **mangiferin**, suppressed the expression of IL-1 β , IL-6, TNF- α , and receptor activator of NF- κ B ligand (RANKL) via the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and the inhibition of NF- κ B [218]. Mangiferin also exerts strong proapoptotic effects on human synovial-derived synoviocytes when protecting against joint degeneration in RA [219].

Kaempferol from grapefruits inhibits synovial fibroblast proliferation by suppressing inflammatory cytokine IL-1 β , inhibiting the phosphorylation of ERK-1/2, p38, and JNK, preventing the activation of NF- κ B, and reducing OS by impeding the production of MMPs, COX-2, and PGE2 in RA-derived synovial fibroblasts [220].

9. Conclusion

Lipid peroxidation resulting from OS and inflammation are mixed up in the pathogeneses of degenerative brain disorders, DM, RA. Propositions targeting these provides means to develop viable strategies to treat these diseases using phytochemicals. Cells are furnished with antioxidant defense systems to combat the effects of OS with the Nrf2 being the master regulator of redox homeostasis. The regulator triggers the antioxidant enzyme systems. Consequently, targeting Nrf2 appears to offer a means of controlling OS. However, attenuating OS alone may not confer satisfactory protection against these diseases, in which case, targeting the classical cell survival pathway, that is, the TrkB/PI3K/Akt pathway would be required to restore cellular function. These signaling pathways upregulate pro-survival factors but suppress their pro-apoptotic counterparts.

Phytochemical with pharmacological modulation capacity may coactivate TrkB signaling mediated cell survival and Nrf2-ARE antioxidant systems. The combination offers promise for the treatment of diseases connected with OS-associated brain degeneration, glucose homeostasis derangements, and rheumatoid arthritis.

Contextually, several phytotherapeutics have been reported to protect against neuronal injury by activating TrkB/PI3K/Akt and Nrf2 signaling systems, which suggests they could be utilized to design novel therapeutic agents for NDD, ischemic stroke, TBI, and brain aging.

Phytochemicals (for example, resveratrol, tea polyphenols etc.) have been shown to promote the regeneration capacity of neurons along with their protection by dual targeting TrkB/PI3K and Nrf2-ARE signaling [81, 114]. These may have a better chance of succeeding with AD subjects.

Generally, the preventive and curative action of phytotherapeutics against pathological conditions [116, 221] emanate from their ability to behave as antioxidant and oxidants and that they are electron donors and electron receivers under varying environments in a pluripotential capacity which allows them to influence reduction and oxidation reactions [13, 32, 34, 35]. The negative values of redox potential probably enable the active principles to act as an antioxidant and in turn scavengers of free radicals as they are oxidized in the process. Crucially, it has been observed that the relative efficacy of antioxidant activity of the *Salix aegyptiaca* phytochemicals tends to be similar to their relative order of redox potential.

Acetylsalicylic acid has been shown to have lowest redox potential and antioxidant activity suggesting that the phytochemicals such as gallic acid, quercetin, rutin and vanillin, other than salicylates contribute to the medicinal properties of *S. aegyptiaca*, indicating a possible synergistic activity necessitating whole plant approaches in the use phytotherapeutics [222].

The interesting connection between OS, inflammation, lipid peroxidation are closely linked to initiation and progression of various diseases [223] necessitating interventions with phytochemicals to combat, at molecular level, different aspects of the biological homeostasis bringing about pathophysiological conditions of cardiovascular diseases, DM, RA and brain degenerative disorders of the old. The phytotherapeutics triterpenes Asiatic acid, maslinic and oleanolic have pleiotropic functions rendering them potent interventions for OS-related disease and lipid peroxidation.

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