Neuroprotective Effects of Phytochemicals in Neurological Disorders

EDITORS

Tahira Farooqui and
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Edited by Tahira Farooqui and Akhlaq A. Farooqui

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Phytochemicals hold a special, elite place in the nutritional landscape.

Joel Fuhrman, MD

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Preface

The medicinal properties and health benefits of plant products (seeds, fruits, leaves, stems, and roots) are attributed to their non-nutritive bioactive components, known as "phytochemicals," which are classified into primary and secondary metabolites. Primary metabolites (carbohydrates, lipids, amino acids, and proteins) are necessary for the growth and basic metabolism of all plants. Secondary metabolites (phytochemicals), on the other hand, are not essential, but they provide vegetables, fruits, and herbs with their flavor and color. They not only play crucial roles in the well being of plants by interacting with their ecosystems, but also protect them from pathogens and absorb ultraviolet (UV), preventing DNA and photosynthetic apparatus damage. Consumption of phytochemicals by animals produces antioxidant, anti-inflammatory, antimicrobial, antitumor, analgesic, neuroprotective, and antiplatelet effects. In addition, they induce antiaging effects and improve poor blood circulation. These effects are mediated through the regulation of various receptors, transcription factors, growth factors, inflammatory cytokines, protein kinases, protein phosphatases, and other enzymes (phospholipases and cyclooxygenases). In brain, receptors, transcription factors, growth factors, and enzymes modulate the signal-transduction pathways critical in controlling synaptic plasticity and inducing neurogenesis in the hippocampus. The ability of many phytochemicals to activate the extracellular signal-regulated kinase (ERK)1/2 and protein kinase B (PKB/Akt) signaling pathways is associated with the activation of the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), a transcription factor that plays an important role in memory formation. In recent years, the amount of research into phytochemicals has increased all over the world, and new terms such as "functional food" and "nutraceutical" have been introduced. There are several issues related to the use of phytochemicals, including concern about their dosage and activity and about the presence of contaminants.

Epidemiological studies have shown that incidences of neurological disorders among people living in Asia are lower than in the Western world. This may be due to the regular consumption of phytochemicals in the form of spices. Extensive research over the last 10 years has indicated that phytochemicals derived from various spices and oils (turmeric, black pepper, licorice, clove, ginger, garlic, green tea, and olive and flaxseed oils) target inflammatory and oxidative stress pathways and retard or delay the onset of neurological diseases. More than 7000 phytochemicals have been identified, which possess antiproliferative, anti-inflammatory, antioxidant, antiviral, and hypocholesterolemic properties. Unlike vitamins and minerals, phytochemicals are not necessary for

the maintenance of cell viability, but they play a vital role in protecting neural cells from the inflammation and oxidative stress associated with normal aging and brain diseases. Although many phytochemicals present in plant foods are poorly absorbed and undergo rapid excretion, they exert anti-inflammatory, antioxidant, and anticarcinogenic effects at realistic doses. Consumption of phytochemicals may also mediate neurohormetic response through the modulation of adaptive stress-resistance genes, which are responsible for encoding protein chaperones that favor resistance to cellular stress and modulate immune function. Thus, regular consumption of phytochemicals from childhood to adulthood may reduce the risk of age-related neurological disorders.

The chemical structures of phytochemicals are often used as "privileged structures" for the creation of synthetic analogues, which have improved pharmacological activities due to their optimized bioavailability and pharmacokinetic profile. Note that most studies on phytochemicals have been performed in animal models and cell-culture systems, and it is difficult to evaluate the significance of their effect in humans.

Information on the effects of phytochemicals on human health is scattered throughout the literature in the form of original papers and reviews, but few edited books. In this book, we provide the reader with a comprehensive and cutting-edge description of the metabolism of the molecular mechanism associated with the beneficial effects of phytochemicals in age-related neurological disorders, in a manner that is useful not only to students and teachers but also to researchers and physicians. The book has 29 chapters. Chapter 1 provides an introduction to the role of phytochemicals in protecting against neuroinflammation, which is typically associated with neurodegenerative diseases. Chapter 2 deals with the protective role of flavonoids in transgenic Alzheimer's disease (AD) mouse models. Chapters 3–15 describe the beneficial effects of phytochemicals (rich in flavonoids and polyphenols) against neurological disorders in model systems. Chapter 16 discusses the use of bee products (apitherapy) for the treatment of neurological disorders. Chapter 17 elegantly describes the mechanisms underlying the beneficial actions of polyunsaturated fatty acids (PUFAs) in brain diseases. Chapters 18–20 deal with the anti-inflammatory effects of resveratrol. Chapter 21 focuses on nobiletin, a flavonoid (an O-methylated flavone) that has the ability to rescue cognitive impairment in animal models. Chapters 22–25 discuss the potential neuroprotective effects of curcumin against brain diseases. Chapter 26 discusses polyphenols and protein misfolding. Chapter 27 describes the molecular mechanisms involved in the neuroprotective action of phytochemicals. Chapter 28 focuses on nutraceuticals (a food or a part of a food that provides health benefits, including the prevention or treatment of a disease) and their effect on cognitive dysfunction. Finally, Chapter 29 provides a perspective on the importance of phytochemicals in diet and on the direction for future research in phytotherapeutics. These topics fall in a fast-paced research area related to cell death in neurological disorders, which provides opportunities for target-based therapeutic intervention using phytochemicals. This book can be used as a supplemental text for a range of phytotherapeutics courses. Clinicians and pharmacologists will find it useful in understanding the molecular aspects of phytochemicals in chronic human diseases.

We have tried to ensure uniformity of presentation, as well as a logical progression of subject from one topic to another, and our authors have provided extensive bibliographies. For the sake of simplicity and consistency, a large number of figures showing the chemical structures of phytochemicals used for the treatment of chronic diseases and

signal-transduction pathways are also included. We hope that our attempt to integrate and consolidate the current knowledge on the molecular aspects of phytochemicals will provide the basis for more dramatic advances and developments in the area of the molecular mechanisms associated with the beneficial effects of phytochemicals in age-related neurological disorders.

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1

Use of Phytochemicals against Neuroinflammation

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1.1 Introduction

Neuroinflammation and oxidative stress are closely associated with the pathogenesis of neurotraumatic and neurodegenerative diseases, such as stroke and Alzheimer's disease (AD). During the inflammatory reaction, secretion of proinflammatory cytokines and chemokines amplifies and maintains inflammatory responses. It involves the enzymatic activity of cytosolic phospholipase A_2 ($cPLA_2$) and secretory phospholipase A_2 ($sPLA_2$), which release arachidonic acid from glycerophospholipids, and of cyclooxygenase (COX) and 5-lipoxygenase (5-LOX), which oxidize arachidonic acid to proinflammatory eicosanoids. This is followed by the formation of the prostaglandin D2 (PGD2) and of docosahexaenoic acid (DHA)-derived resolvins and protectins, which facilitate the resolution of inflammation. Acute neuroinflammation is a protective process that isolates the injured brain tissue from uninjured areas, destroys injured cells, and rebuilds the extracellular matrix. Without it, brain tissue would rapidly be damaged by the effects of injury and infections, including those of microbial, viral, and prion origin. Acute neuroinflammation involves the recruitment of lymphocytes, monocytes, and macrophages of the hematopoietic system and glial cells of the central nervous system (CNS). Microglia are recruited to the site of injury to protect and repair the injured tissue via the secretion of cytokines, chemokines, and lipid mediators such as resolvins and neuroprotectins, while astrocytes react by forming a glial scar. Chronic neuroinflammation, on the other hand, lingers for years, and causes damage to brain tissues. It is closely associated with the activity of microglia and astrocytes and with the assembly and activation of the inflammasome: a multiprotein oligomer consisting of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3). Once activated, the inflammasome binds to and appositions together many p45

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pro-caspase-1 molecules to induce their autocatalytic cleavage to p20 and p10 subunits. Caspase-1 then assembles into its active form (consisting of two heterodimers with a p20 and p10 subunit each), in order to carry out a variety of processes, including cleavage of pro-interleukin (IL)-1β into IL-1β, cleavage of pro-IL-18 into IL-18 to induce interferon gamma (IFN-γ) secretion, and activation of lipid biosynthesis [1]. Inflammasomes orchestrate the activation of precursors of proinflammatory caspases, which, in turn, cleave precursor forms of IL-1β, IL-18, and IL-33 into their active forms. These lead to further stimulation of PLA_2, COX-2, and LOX; generation of eicosanoids, lysophosphatidylcholine (lyso-PtdCho), and platelet-activating factor (PAF); production of reactive oxygen species (ROS), proteinases, and complement proteins; and a potent inflammatory response. Alterations in the expression of inflammasome mediators may lead to neurodegeneration in neurotraumatic, neurodegenerative, and neuropsychiatric diseases. Based on this, it has been suggested that regulation of the inflammasome machinery may be better than suppression of all inflammation for the treatment of inflammatory conditions [1,2].

An emerging approach to the alleviation of neuroinflammation involves the use of medicinal plants and herbs. Epidemiological studies have indicated that the incidence of neurological disorders among people living in Asia is lower than that in the Western world. This may be due to the regular consumption of phytochemicals in the form of spices. Extensive research over the last 10 years has indicated that phytochemicals derived from various spices e.g., turmeric, red pepper, black pepper, licorice, clove, ginger, garlic, coriander, cinnamon, target inflammatory and oxidative stress pathways and retard or delay the onset of neurological diseases. More than 7000 phytochemicals, which possess antiproliferative, anti-inflammatory, antiviral, and hypocholesterolemic properties, have been identified (Figure 1.1). Unlike vitamins and minerals, phytochemicals are not required for the maintenance of cell viability, but play a vital role in protecting neural cells from neuroinflammation and oxidative stress associated with aging and brain diseases. Roots, stems, leaves, fruits, and seeds contain phytochemicals such as terpenoids, phenolic compounds, glucosinolates, betalains, and chlorophylls. Although many phytochemicals in plant foods are poorly absorbed and undergo rapid excretion, they exert anti-inflammatory, antioxidant, and anticarcinogenic effects at realistic doses. The effects of phytochemicals are mediated by their ability to counteract, reduce, and repair damage resulting from oxidative stress and

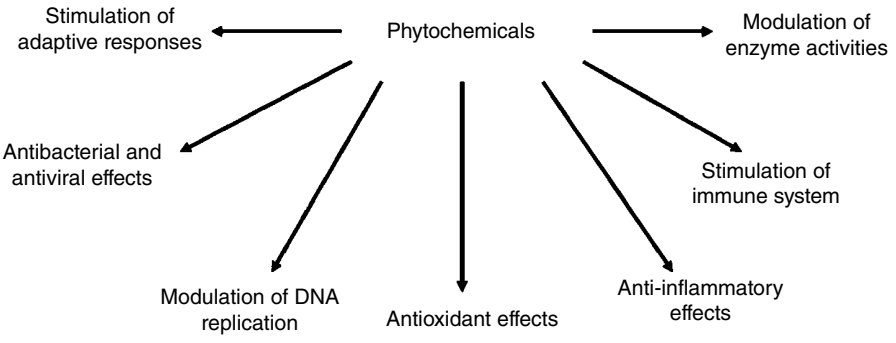

Figure 1.1 Effect of phytochemicals on various cellular activities.

neuroinflammation – processes that are modulated by the transcription factor, nuclear factor kappa B (NF-κB). Phytochemicals also stimulate the synthesis of adaptive enzymes and proteins that favor resistance to cellular stress [3].

1.2 Mechanism of Action of Phytochemicals

Plants and phytochemicals produce their beneficial effects not only through modulation of enzyme activities and regulation of gene expression, but also via the stimulation of adaptive cellular stress response pathways that protect cells against a variety of adverse conditions. Phytochemicals bind to neuronal cell-membrane or nuclear receptors as elective ligands and have signaling effects at concentrations much lower than is required for effective antioxidant activity [4]. They act on the NF-κB pathway to inhibit inflammation. NF-κB is predominantly localized in the cytoplasm in a complexed form that is inactive, but during oxidative stress it is released from the NF-κB–IκBα complex and migrates to the nucleus, where it initiates the transcription of a number of proinflammatory enzymes, including $sPLA_2$, COX-2, NADPH oxidase and inducible nitric oxide synthase (iNOS), as well as proinflammatory cytokines (tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6). The latter stimulate the activities of PLA_2 and sphingomyelinases through a feedback loop involving cytokine-mediated phosphorylation. Other potential mechanisms through which NF-κB induces neuronal death include the induction of death proteins and an aborted attempt to re-enter the cell cycle. Phytochemicals such as curcumin, resveratrol, *Ginkgo biloba* (GB) retard inflammation by preventing the migration of NF-κB into the nucleus. In addition, many phytochemicals block the activation of NF-κB by inhibiting a protein kinase. *In vitro* studies indicate that phytochemicals inhibit both serine/threonine protein kinase and protein tyrosine kinase, supporting the view that phytochemicals may inhibit IκB kinaseβ (IKKβ) in the cytoplasm and nucleus, leading to a reduction in NF-κB activity. Phytochemicals have also been reported to modulate age-related decline in memory by upregulating signaling pathways that control synaptic plasticity. They activate both the extracellular signal-regulated kinase (ERK) 1/2 and protein kinase B (PKB)/Akt signaling pathways and cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), a transcription factor that upregulates the expression of several neurotrophins that facilitate memory formation [5,6].

An important cellular antioxidant response that underlies the action of many phytochemicals is induction of antioxidative and anti-inflammatory enzymes through the cytoplasmic oxidative stress system (nuclear factor erythroid 2-related factor 2 (Nrf2)–kelch-like erythroid Cap'n'Collar homologue-associated protein 1 (Keap1)) (Figure 1.2) [7]. Under physiological conditions, Keap1 keeps the Nrf2 transcription factor in the cytoplasm, allowing it to be ubiquitinated and degraded by proteasomes, thus maintaining Nrf2 at low levels. This prevents Nrf2 from mediating the constitutive expression of its downstream genes. When cells are exposed to oxidative stress, a signal involving phosphorylation and/or redox modification of critical cysteine residues in Keap1 blocks the enzymatic activity of the Keap1–Cul3–Rbx1 E3 ubiquitin ligase complex, leading to a decrease in Nrf2 ubiquitination and degradation. As a result, free Nrf2 translocates into the nucleus, where it – along with other transcription factors (e.g., sMaf, ATF4, JunD, PMF-1) – transactivates the antioxidant response elements (AREs)

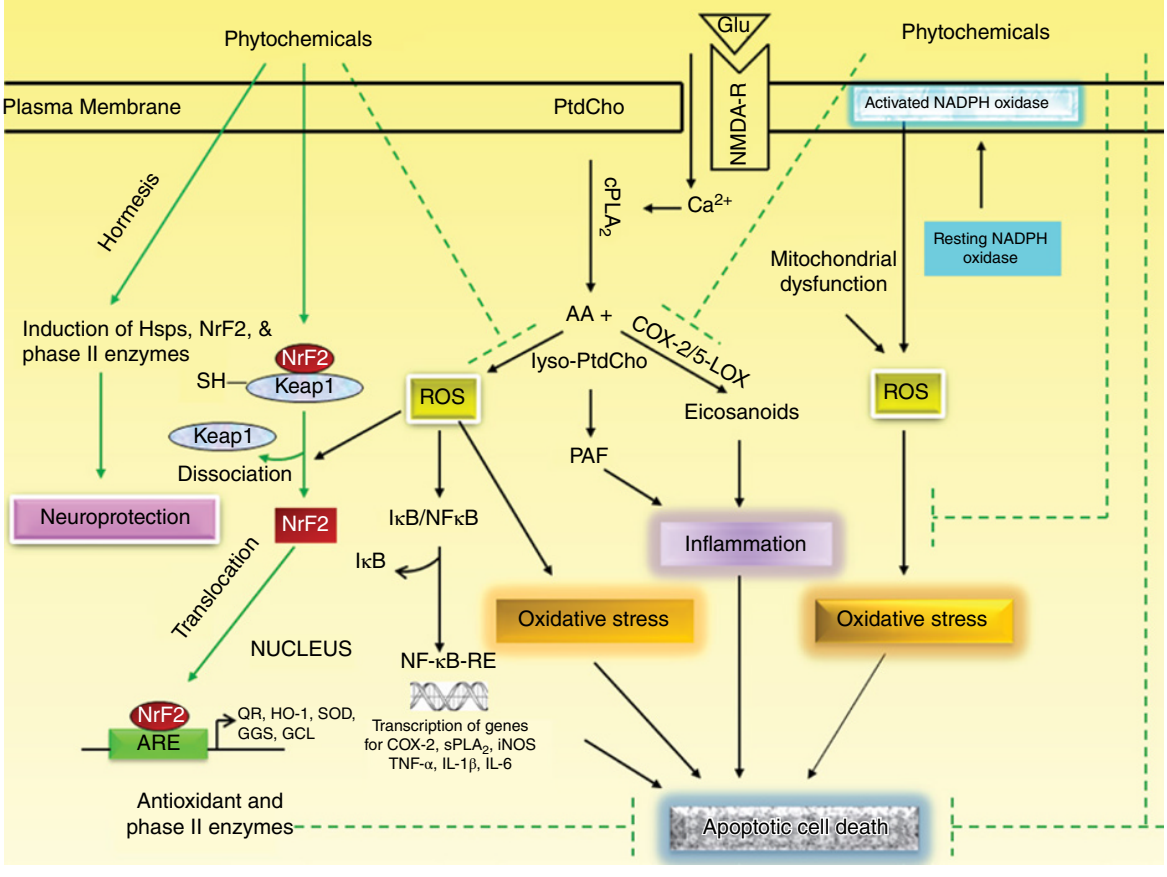

Figure 1.2 Hypothetical diagram showing the effects of phytochemicals on signal transduction processes in the brain. AA, arachidonic acid; COX-2, cyclooxygenase 2; $cPLA_2$, cytosolic phospholipase A_2; HO-1, hemeoxygenase 1; HSP, heat-shock protein; IL-1β, interleukin 1β; IL-6, interleukin 6; iNOS, inducible nitric oxide synthase; Keap1, kelch-like erythroid Cap'n'Collar homologue-associated protein 1; LOX, lipoxygenase; lyso-PtdCho, lyso-phosphatidylcholine; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PAF, platelet-activating factor; PM, plasma membrane; PtdCho, phosphatidylcholine; QR, quinine oxidoreductase; ROS, reactive oxygen species; SOD, superoxide dismutase; $sPLA_2$, secretory phospholipase A_2; TNF-α, tumor necrosis factor alpha; γ-GCL, gamma glutamylcystein ligase. (*See insert for color representation of the figure.*)