Phytopharmaceuticals for Brain Health
Dedication

Dedicated to my well-respected and beloved parents, Maulana Abdul Subhan and Farida Begum, for always giving me inspiration; and my two beloved young sons, Ehtesham Suhail and Mujtaba Suhail, for helping me by their cute smiles and being patient while I was working on this esteemed book.

Shahnaz Subhan

Dedicated to my beloved husband, Debasis Bagchi, and our only daughter, Dipanjali Bagchi, and my mother, Bakul Bardhan.

Manashi Bagchi
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Preface

Research studies have demonstrated that appropriate nutrition, in conjunction with mental, social, and physical activities, may have a greater benefit in maintaining or improving brain health. Diet and appropriate nutrition, cognitive activity, social engagement, and regular physical exercise can significantly help in improving brain health with advancing age and potentially reduce the risk of cognitive decline.

Nutraceuticals and functional foods work against neurodegenerative diseases, which are associated with exacerbated oxidative stress in the central nervous system. The fundamental “neurohormesis” principle will also be discussed in this book.

Advancing age can exhibit health-related challenges that may take a toll emotionally, financially, and physically. Furthermore, regular stress and environmental pollution are challenging problems. There is no easy or quick solution. Recently, at the International Conference of Alzheimer’s Association in 2014, a two-year clinical trial on older adults at the risk of cognitive impairment demonstrated that a combination of physical activity, proper nutrition, cognitive training, social activities, and management of heart health risk factors slowed cognitive decline.

Research studies with a number of phytopharmaceuticals and medicinal plants demonstrated the efficacy of huperzine A, berry anthocyanins, *trans*-resveratrol, *Bacopa monniera*, *Centella asiatica*, *Curcuma longa*, flavonoids tocochromanols, and palm oil in boosting brain health and physical well-being. A chapter is dedicated to autism treatment with psychotherapy, nutrition and dance movement, a challenging and upsetting problem of the millennium.

Also, consumption of marine fishes and general seafood has been recommended for long-term nutritional intervention to preserve mental health and delay neurodegenerative processes, and to sustain cognitive health in humans. Omega-3 and omega-6 polyunsaturated fatty acids and antioxidants prevent the initiation and progression of many neurological disorders. Several phytochemicals have shown promising results against free-radical-promoted neurodegenerative processes and cognitive impairment.

Overall, this book will bring a classic scenario of neurological problems and their possible amelioration using novel nutraceuticals and functional foods.
About the Editors

Shahnaz Subhan, PhD, is a chief scientific officer at Applied Biodiversity Company, LLC, in Jersey City, New Jersey. She has been working as a researcher and academician with 20 years of experience in plant, medical, and microbial biotechnology. She is also working for the Jersey City Board of Education, New Jersey. Previously, she was an assistant professor at the Amity University in Noida, India, where she taught courses in biotechnology and worked almost 10 years in the same university. She was awarded a Young Scientist Fellowship in India for a government-funded major scientific project by DST. During her tenure in Amity University, she also got a short-term postdoctoral fellowship at The Institute for Molecular Medicine, California. She holds a PhD in botany (plant biotechnology) from the University of Delhi at Delhi, India, and a master’s degree in botany with major in microbial molecular genetics and microbial ecology and a BSc in botany (honors) with zoology and chemistry from the University of Delhi at Delhi, India.

Her research areas include the following: plant and medical biotechnology, phytochemistry, applied microbiology, and environmental sustainability. She has published in various peer-reviewed and leading journals, including Plant Cell Report, Journal of Medical Science, Asian Journal of Chemistry, British Biotechnology, Journal of Food Process Technology, International Journal of Pharma and Bioscience, CRC Press/Taylor & Francis, etc. She has also presented several research papers in international conferences. She has more than 20 years of experience in research, teaching, and supervising hundreds of undergraduate and postgraduate biotechnology and science students. Under her supervision, PhD thesis was also awarded to a PhD student in 2011.

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Manashi Bagchi, PhD, FACN, earned her PhD degree in chemistry in 1984. Dr. Bagchi is currently the chief scientific officer of Dr. Herbs LLC, Concord, California. Dr. Bagchi is also a consultant for Cepham Research Center, Piscataway, New Jersey, and Purity Products, Plainview, New York. Dr. Bagchi served as associate professor in the Creighton University School of Pharmacy and Health Professions, Omaha, Nebraska, from September 1990 to August 1999. Later, she served as the director of research at InterHealth Nutraceuticals, Benicia, California, from September 1999 to July 2009. Dr. Bagchi is a member of the Study Section and Peer Review Committee of the National Institutes of Health, Bethesda, Maryland. Her research interests include free radicals, human diseases, toxicology, carcinogenesis, anti-ageing and anti-inflammatory pathophysiology, mechanistic aspects of cytoprotection by antioxidants and chemoprotectants, regulatory pathways in obesity and gene expression, diabetes, arthritis, and efficacy and safety of natural botanical products and dietary supplements. She is a member of Society of Toxicology (Reston, Virginia), New York Academy of Sciences (New York, New York) and Institute of Food Technologists (Chicago, Illinois). She is a fellow and currently a board
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Section I

Pathophysiology
1 A Hidden Etiological Nemesis of Chronic Neurodegenerative Diseases

Bernard W. Downs and Manashi Bagchi

To find a solution, you must first be able to (accurately) state the problem.

Albert Einstein

1.1 DEFINING THERAPEUTIC PARADIGMS:
HISTORICAL OVERVIEW

Neurodegenerative disorders rank among the most disruptive, challenging, and burdensome maladies for which afflicted individuals, their loved ones and medical institutions contend. There are more published reports on the genetic influences predisposing neurodegenerative disease than can be referenced here. A simple literature search will inundate the researcher with a plethora of publications. However, while there is no lack of competent scientific opinion, a complete understanding of
the causes and effective treatments of neurodegenerative disorders, such as early onset Alzheimer disease (EOAD), among others, remains elusive. For example, a recent review paper (as of the writing of this chapter in 2016) is focused on exploring new avenues in translational research and therapeutic discoveries in EOAD [1]. The researchers conclude by commenting on the relevance of re-investigating EOAD patients as a means to explore potential new avenues for translational research and therapeutic discoveries. Translational research can help uncover genetic targets for therapeutic interventions. Although immensely valuable, similar to translational research in cancer, for example, unraveling and understanding molecular genetics continue to be inadequate to effectively eradicate this terrible disease. And, unfortunately, while continued research in this direction could illuminate therapeutic benefits, pursuing a pharmacological premise will not likely reveal a cure, as the disease is not caused by a drug deficiency.

Pharmacological interventions for some neurodegenerative disorders have met with frustrating side effects. For example, in regard to Parkinson disease, dyskinesia is a well-documented pathological development following L-DOPA therapy [2,3]. Other conditions present codisorders, which have met with even more severe results using pharmaceuticals. One such case is a report of a 38-year-old man diagnosed with multiple sclerosis (MS) in 2007. In that year, the man took part in a study examining the comparative effects of fingolimod (0.5 or 1.5 mg daily), interferonβ-1a (Avonex, Biogen Idec, Cambridge, UK), and placebo on MS [4]. The man was given fingolimod, a sphingosine-1-phosphate receptor modulator that sequesters lymphocytes in lymph nodes, preventing them from contributing to an autoimmune reaction. This mechanism of action reduces circulating lymphocytes, which is contraindicated in herpes simplex virus (HSV) infection. Based on evidence to be presented later in this chapter, the authors suggest that herpes viruses are an etiological factor in a large number of MS cases and other chronic neurodegenerative diseases. In fact, suppressing or weakening immune competence and responsivity could amplify HSV activation and the severity of HSV infection.

In the case of the present discussion, over the course of the next seven years, in a progressive and increasing manner, the man’s health deteriorated. In April 2014, he was admitted to the emergency department with loss of consciousness, fever, and epileptic seizures. Cranial computed tomography showed a hypodense area in the right temporal lobe. Diagnosis of HSV-1 encephalitis was made by polymerase chain reaction (PCR) analysis of cerebral spinal fluid. Blood count indicated lymphocytopenia; lymphocytes were low. His medical history indicated a previous herpes labialis. Antiviral therapy with intravenous acyclovir was initiated immediately at the day of presentation at the standard dose. Cranial magnetic resonance imaging showed signs of nonhemorrhagic encephalitis in both hemispheres. After 34 days, he was referred to a neurologic rehabilitation center. At discharge, he was alert but showed signs of right dominant tetraparesis (i.e., muscle flaccidity and loss of muscle control in four limbs). He was unable to speak due to a tracheal cannula and received an Expanded Disability Status Scale (EDSS) score of 9.5 (ranging from 0 to 10, with higher scores indicating increasing disability; 10 being death from MS). When he began the study seven years earlier, his EDSS score was 2.5. Follow-up examinations in the next nine months showed clinical worsening and progressive brain atrophy accentuated in the
postencephalitic regions. Prior to onset of HSV-1 encephalitis, he had not shown any evidence of immunologically relevant comorbidities during continuous follow-up in the MS outpatient clinic since 2007. This lack of “evidence” regarding the severity of the disease is most likely a “stealth” capability of the herpes virus. The comprehensive study of viral gene structure since the 1990s has revealed that virtually every class of animal virus has incorporated into its genome the machinery to thwart, suppress, neutralize, or evade the mitochondrial “danger alarm system” [5–8]. So, the lack of “obvious” evidence in this case, and others not cited here, is one reason why this chapter is entitled “A Hidden Etiological Nemesis of Chronic Neurodegenerative Diseases.” Rather than treating the patient based only on obvious symptoms, the physician should incorporate therapies based on the proposition of existing comorbidities, even when symptomatic signs are not obvious.

The man had not received corticosteroids or other immunomodulatory treatments apart from fingolimod. The only comedications were bupropion (Wellbutrin, GlaxoSmithKline AG, Münchenbuchsee, Switzerland) and, occasionally, methylphenidate (Ritalin, Novartis Pharma AG, Basel, Switzerland). Both bupropion and methylphenidate are dopamine and norepinephrine reuptake inhibitors. As impairments in brain function increased in severity, medications were most likely prescribed to reduce severe symptoms of attention-deficit/hyperactivity disorder (ADHD), depression, anxiety, sleep disturbances, etc. The long-term effect of these drugs and this therapeutic approach are subjects for another chapter at another time. However, interested clinicians and researchers can do a PubMed search of “Downs B” (one of the authors) and/or “Blum K” for extensive research and publications on reward deficiency syndrome (RDS).

It should also be noted from other research reports that fingolimod treatment of MS lowers varicella-zoster virus-specific immunity (VZV; a herpes virus) [8]. This suggests that subclinical VZV reactivation, demonstrated by PCR detection of VZV DNA in the saliva, is higher among MS patients treated with fingolimod compared with healthy controls.

Not to overstate the obvious, impaired immunity is to be avoided when fighting any herpes virus. While following Standard of Care procedures, these therapeutic interventions apparently intensified and accelerated HSV-related pathological progression and neurodegeneration.

1.2 REORIENTATION OPPORTUNITIES

Some very important questions need to be asked to determine whether the collective “we” are heading in the right direction. After so many years of intensive research on so many chronic degenerative diseases, why does the incidence of these diseases continue to rise? Why are so many people afflicted and so many people continue to suffer so much? It seems that we haven’t put a noticeable dent in the incidence of neurodegenerative diseases. We have identified the functional impairments in many of the neurodegenerative diseases. However, we have not identified the causes of these impairments. A simple age-old premise has been ignored. If you want to know how to solve a problem, you must first be able to accurately state or define the problem. For the most part, medical technocracy is focused on relieving suffering
with pharmacological interventions that reduce obvious symptoms. This approach generally does not effectively identify and/or address the underlying cause or causes. More unfortunate, is that in reality, pharmacologically speaking, in terms of chronic disease, the big money is not in the cure; it is in the “ongoing” treatment.

Another challenge of the pharmacological approach is the “reductionist” paradigm. This paradigm is based on the need to reduce the active substance to a single “active ingredient,” reduce the biochemical transaction to a single mechanism of action, reduce the targeted benefit site to some single loci, and reduce the outcome to a single “primary” benefit. For many years, the National Institutes of Health would not award grants for research on multi-ingredient nutraceutical formulas as, they asserted, it would not be possible to determine the “active ingredient” (a pharmacological requirement). As a result of this paradigm, almost all of the nutraceutical research performed since the passing of the Dietary Supplement Health and Education Act in 1994 has been on single ingredients with a well-defined “active molecule.” Hence, the default supposition is that the higher the concentration of the active ingredient is, the more beneficial the product will be. This was the perspective that spurred the meteoric rise of mega-dosing therapy of single ingredient nutritional products, i.e., vitamin C, B vitamins, oligomeric proanthocyanidins (OPCs), etc. A natural result of this paradigm was the birth of the evidence-based proprietary ingredient market.

Dietary supplement manufacturers and marketers constructed condition-specific finished product formulas by combining ingredients backed by research on or for specific conditions.

1.3  PARADIGM ‘SHIFT’ BEGINS

The emergence of “Integrative Medicine” has opened up another dimension of therapeutic opportunities for physicians using natural products. Over the ensuing years since the passage of the Dietary Supplement Health Education Act in 1994, nutraceutical research produced a plethora of products with sufficient scientific validation that health professionals could more confidently apply them in a clinical setting. However, the vast majority of physicians view evidence-based applications through the “lens” of a classically trained reductionist perspective with condition-specific symptomatic assessments. The primary difference from drugs was that the natural “remedies” were less biologically impacting than drugs and that natural products should be devoid of drug-like side effects, even in significantly higher amounts. Natural products and nutraceuticals were just being substituted for drug applications, e.g., glucosamine for joint health, red yeast rice to lower cholesterol, curcumin to reduce inflammation, chromium to promote insulin sensitivity, St. John’s Wort for depression, and the list is almost endless. This ingredient/condition-focused approach catapulted the rise of “condition-specific” objectives with natural product formulations.

The holistic principle should be that the “orchestra of nutrition” goes into the body and “plays the symphony of biology,” simultaneously and synergistically supporting the structure and function of all the cells, tissues, and organs in the systems of the body.
The experienced physician must have the wisdom of an artful conductor in constructing natural product and lifestyle protocols that address underlying etiological factors and arrest disease pathologies. But most physicians still focus on reducing symptoms to relieve suffering and improve comfort and functionality, which is their logical primary healthcare objective. While providing measurable improvements in symptomatic relief, very often, with this approach, the actual cause still remains elusive and unaddressed. Most physicians are trained to evaluate health status or the severity of illness from a symptomatic assessment and a blood chemistry, although genetic factors are beginning to gain attention for greater diagnostic accuracy. At the very least, a great need to expand the investigation to identify converging etiological cofactors is warranted. Such an investigation would ultimately lead to an imminent paradigm shift in diagnostic and treatment therapies.

1.4 MOST WELL-KNOWN ETIOLOGICAL FACTORS

Numerous papers have been published on the known primary causes of chronic neurodegenerative diseases. Investigators should be cognizant that multiple etiological factors frequently converge to manifest pathological symptoms. In addition to memory and neuromuscular tests and the results of a complete blood count, allergy panels, and other technical analyses, the clinician generally identifies the most obvious symptoms in their diagnostic evaluation. However, once obvious pathologies and symptoms have been identified, the quest for other etiological factors can be overlooked or diminished. Many times, the converging etiological factors are in fact the result of a sequela of etiological events, which is beyond the scope of generally recognized evaluation criteria. The sequence in which these events occur, the severity of each factor, and the underlying chronicity of each factor are important in determining treatment solutions.

For example, inflammation is probably the most noted etiological factor contributing to neurodegenerative pathologies. One of the authors (MB) has published extensively on the role of oxidative stress and damage, inflammation, and antioxidants in various pathologies, including neurological disorders and various stages of neoplastic processes and carcinogenesis including detoxification of carcinogenic metabolites [9–16]. This type of original research into reducing oxidative damage and inflammatory events in brain tissue has been foundational to spurring research by other authors on this topic as well [17].

While oxidative-induced inflammatory mechanisms are a significant etiological factor and occupy a significant amount of attention in the quest for various types of therapeutic interventions in neurodegenerative disorders, another well-known etiologic aspect involves imbalances in neurotransmitter function. Research in this area was the first to disclose a common genetic predisposition to the constellation of conditions categorically termed “reward deficiency syndrome” (RDS) [18]. In subsequent research, the authors further validated that dysfunction of the D2 dopamine receptors leads to aberrant substance seeking behavior with substances such as alcohol, drugs, tobacco, food, and other related behaviors (i.e., pathological gambling, Tourette’s syndrome, and attention deficit hyperactivity disorder, etc.). They provide
further evidence that variants of the D2 dopamine receptor gene are important common genetic determinants of RDS [19].

Addressing dopamine resistance/insufficiency is a primary target in disorders such as attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), addictions, obsessions, compulsivity, impulsivity, anxiety, posttraumatic stress disorder, Parkinson’s disease (PD), and many more. These types of conditions fall under the RDS rubric, a subject of much research and on which one of the authors (BD) and others have also published [2,3,19–22]. Fortunately, nutraceutical interventions are available to optimize gene expression, rebalance the brain, and enhance brain reward, especially in people with a genetic predisposition to excessive reward seeking behaviors.

1.5 NEW INSIGHTS INTO NEURODEGENERATIVE DISEASE (HIDDEN NEMESIS)

Another area that merits intense etiological research pertains to microbial and viral factors, specifically investigating the role of the herpes virus in neurodegenerative disease pathologies. This area of investigation will potentially reveal not only the viral causes and exacerbating viral factors but also effective natural solutions that have the ability to improve the quality of life for people suffering from chronic neurodegenerative disorders. Revelations in this area will add an important dimension of holistic therapeutic interventions, especially for nutraceutical-based “systems biology” modalities.

Numerous authors have reported on the herpetic etiology of various neurodegenerative diseases (i.e., Alzheimer’s disease [AD], MS [and acquired demyelinating syndrome], amyotrophic lateral sclerosis [ALS], PD, encephalitis, etc.) [23–33].

As already mentioned, you must first be able to accurately state or define the problem before you can effectively solve the problem. Unless interventions for neurodegenerative diseases include an antiviral therapeutic strategy that also boosts innate immune competence, they will not completely address or reverse the pathological process. Regardless of whether the intervention is pharmacological or natural, limited or one-dimensional therapeutic interventions can at best only attempt to manage symptoms and reduce suffering during the irrevocable progressive decline characteristic of the disease. Keep in mind that deteriorating health is the macrosystem manifestation of an increase in anaerobic metabolism, an increase in anaerobic infections (various microbes), and weakened immune competence. In addition to providing systemic nutritional support, inclusion of an antiviral strategy is mandatory.

The big question is how to arrest herpetic viral progression implicated in chronic neurodegenerative disorders.

HSV infection results in lifelong infection, which can be asymptomatic or present with recurrent lesions [6,32–34]. The herpes virus resides as a long-term underlying presence. Moreover, a growing body of evidence points to chronic bacterial and viral coinfections as potential etiological factors in neurodegenerative diseases, including AD, PD, and ALS. The chronic activation of inflammatory processes and host immune responses cause chronic damage resulting in alterations of neuronal function and viability. Viral and microbial agents have been reported to produce molecular hallmarks of neurodegeneration, such as the production and deposit of
misfolded proteins, oxidative stress, deficient autophagic processes, synaptopathies, and neuronal death. Chronic cycles of pathogen replication within the central nervous system (CNS) overburden already weak immune competence, alter neuronal function, and produce premature apoptosis and cell death [5]. The authors’ notion is that while microbial infections appear as coinfectious agents with herpes, such microbial species initiate further weakening of an already fragile immune system, enabling opportunistic activation and more severe infection of the herpes virus. Such a scenario is also believed to be common for Lyme disease, for example [35]. Excessive stress apparently increased immune suppression, activating and intensifying both types of infections. Stress from any source exerts overburdening effects on an already fragile or challenged immune system.

1.6 NUTRACEUTICAL INTERVENTIONS

Reducing the severity and/or incidence of active HSV infection with a combination of nutraceutical products holds significant potential. Pharmacological perspectives that influence natural approaches for the most part confine therapeutic approaches to single-ingredient, single-mechanistic tactics. Therefore, the synergistic effect of multifaceted multifactorial strategies is highly recommended. The proposed strategic objectives should include the following:

1. Inhibiting the herpes virus from binding to a cell receptor site
2. Boosting immune competence
3. Reducing factors that weaken immune competence and promote herpetic activation

1.7 HERPETIC THERAPEUTIC NUTRACEUTICALS (HERPECEUTICS)

L-Lysine (an essential amino acid)
Botanicals providing specific phytosaccharides (more on this later)
Para amino benzoic acid (PABA)
Geopropolis (from stingless bees [*Scaptotrigona postica*])
Multinutrient Complex (vitamins, minerals, phytonutrients, phospholipids)

There are numerous other ingredients that could be included. However, what is being presented in this chapter is a foundational baseline. The clinician should use this information as a starting point and diligently investigate other products to expand treatment options.

1.7.1 L-LYSINE

In order to replicate, the herpes virus requires the amino acid L-arginine, another amino acid common in foods and necessary to human life. Lysine is thought to interfere with the absorption of arginine in the intestine and inhibit viral severity. Moreover, the antiviral cell danger response is strongly regulated by the posttranslational state of lysines on histones and immune effector proteins like the double-strand
RNA binding protein, known as RIG1 (retinoic acid inducible gene 1), and the mitochondrial antiviral sensor. Lysine ubiquitination is a necessary prestep for oligomerization of RIG1, required for efficient binding to the mitochondrial antiviral sensor and interferon induction [36].

Although L-lysine efficacy as an antiharperetic agent is the subject of some controversy, the majority of results from numerous studies (in vitro and in vivo) on a range of population sizes and over various time frames confirm dose-dependent inhibitory effects of L-lysine (with and without low-arginine diets) against the incidence, recurrence, duration, and/or severity of HSV infection. Dosages range from 500 mg OID to 1000 mg TID [37–42]. A scant few studies report the failure of L-lysine to exert antihperetic effects [43]. Dosage levels in this research were low, population size was small, and duration of the study period was short. When dosage levels are more robust, population sizes and duration of the study period are shown to be less influential. The conclusion is that L-lysine, in a dose-dependent manner, has been shown to exert beneficial antihperetic effects. The potential therapeutic benefits of L-lysine should be synergistically amplified when it is combined with other products and therapeutic strategies.

1.7.2 Phytosaccharides

Another therapeutic nutraceutical approach with significant potential is to inhibit the herpes virus from binding to a cell receptor site. If the herpes virus is unable to bind to a cell receptor, its infectious potential remains impotent. Various phytosaccharides have been shown to prevent binding of HSV to receptors, thereby reducing severity and duration of HSV infection.

The mannose receptor (MR) was shown to be an important receptor for the non-specific recognition of enveloped viruses by dendritic cells (DCs) and the subsequent stimulation of interferon alpha (IFN-α) production by herpes viruses binding to that site. The MR binds several monosaccharides, including fucose, N-acetylglucosamine, and mannose, with high affinity [44,45]. Six different monosaccharides were shown to reduce the frequency of HSV-induced interferon-alpha-producing cells in a dose-dependent manner. The research demonstrated that most sugars had inhibitory effects at high concentrations (0.50 mM). However, fucose had the greatest inhibitory effect, followed by N-acetylgalactosamine (Gal-N-Ac) and N-acetylglucosamine (Glc-N-Ac). While the MR has been identified as an important receptor target for phytosaccharides, no receptor with specificity for both Glc-N-Ac/Man and Gal-N-Ac has yet been identified. These results suggest either a novel receptor with both mannose and galactose specificities or that more than one receptor with different specificities is involved in the stimulation of IFN-α synthesis by HSV and are therefore specific targets for competitive monosaccharide binding [46]. Thus, the MR probably serves as a critical link between innate and adaptive immunity to viruses, especially given the role of the MR in antigen (Ag) capture by DC and the importance of IFN-α in shaping immunity [46]. Therefore, supplying various phytosaccharides can evidently preferentially occupy the MR and block HSV binding. A number of monosaccharides, including fucose, mannose, galactose, N-acetylglucosamine, and N-acetylgalactosamine, exerted a strong inhibitory activity against HSV-1 and -2, with no cytotoxicity [47].
Various botanicals from fucoidan species of brown seaweed to pine cone extracts to aloe vera and others can provide a range of the phytosaccharides mentioned that have been shown to inhibit HSV binding. Caution should be exercised with fucoidan seaweed to ensure that it is free of heavy metals and other contaminants common to the marine environment. In the case of aloe vera, the inner gel is saccharide rich [48]. If the aloe vera being used is not fresh, the nutraceutical product being purchased should use a water or CO₂ extraction as many standard chemical solvent extraction methods break glycosidic bonds and eliminate or significantly reduce the presence of valuable monosaccharides. The same is true for pine cone extracts. Many ancient peoples made pine cone tea as a remedy for various maladies.

One type of aloe vera gel (99% H₂O) exhibited a significant inhibitory effect, one hour after a Vero cell line was infected with HSV-1, of 0.2%–5% on viral growth. The gel could be a useful topical treatment for oral HSV-1 infections without any noticeable toxicity [49].

While this chapter is examining therapeutic nutraceutical strategies to reduce chronic neurodegenerative diseases, owing to the nutritional value of aloe in this instance, certainly, other collateral beneficial effects could be expected. To demonstrate the broader benefit of aloe, we present evidence of its in vitro and in vivo effects on bone health. A quote from the study abstract is presented.

“In an animal study, mandibular right incisors of male Sprague–Dawley rats were extracted and an acemannan treated sponge was placed in the socket. After 1, 2, and 4 weeks, the mandibles were dissected. Bone formation was evaluated by dual energy X-ray absorptiometry and histopathological examination. The in vitro results revealed acemannan significantly increased bone marrow stromal cells (BMSC) proliferation, VEGF, BMP-2, alkaline phosphatase activity, bone sialoprotein and osteopontin expression, and mineralization. In-vivo results showed acemannan-treated groups had higher bone mineral density and faster bone healing compared with untreated controls. A substantial ingrowth of bone trabeculae was observed in acemannan-treated groups. These data suggest acemannan could function as a bioactive molecule inducing bone formation by stimulating BMSCs proliferation, differentiation into osteoblasts, and extracellular matrix synthesis. Acemannan could be a candidate natural biomaterial for bone regeneration” [50]. This data is presented as just one example to confirm the premise that these nutraceuticals are not pharmaceuticals or other type of medications. They are exerting multisystem benefits that are entirely nutritional-type therapeutic effects.

The authors suggest that researchers in the field of glycobiology expand legitimate scientific efforts to investigate and better define the inhibitory interaction of various saccharides against viral and bacterial species underlying many chronic degenerative diseases, especially the herpes virus. But, researchers should maintain a perspective of the structural and functional value of the nutraceuticals and their synergistic benefits when combined with other nutraceuticals that can “play the symphony of biology.”

It is also important to note that with the advent and advancing technologies of agribusiness and food treatment/processing practices, societal evidence indicates that our food supply is apparently falling short of supplying the requisite nutrition to sufficiently support optimal health. The collective “we” are not curtailing the escalating juggernaut of chronic degenerative diseases. And, the existing healthcare system
is and will continue to be woefully inadequate to keep pace with the increasing incidence of chronic degenerative diseases, especially of the neurological disorders.

1.7.3 **Geopropolis (Propolis from Brazilian Stingless Bees S. postica)**

This is one of the first studies investigating the potential effects of geopropolis against HSV-1. In cell culture, the results showed that hydromethanolic extracts of geopropolis (HMG) from stingless bees significantly reduced the number of copies of HSV-1 genomic DNA in the supernatant and in the lysate cell. All concentrations tested against HSV-1 through pre-, post-, and virucidal treatment were found to be effective in inhibiting HSV-1 viral replication. Quantification of viral DNA from herpes virus showed reduction of about 98% in all conditions and concentrations tested of the HMG extract. This indicates that geopropolis inhibited the events in early infection, such as viral binding and viral entry into cells as well as the viral replication [51]. To reiterate, while the scientific community readily uses pharmacological nomenclature, perspectives, and explanations, the effects demonstrated are not pharmaceutical-type actions. These effects have been attributed to various bioflavonoids and glyconutrient molecules within the geopropolis. But this approach would be more accurately presented as a whole food extract.

1.7.4 **PABA**

PABA demonstrated virucidal effects in a culture of the cell-free virus-containing material. It reduced the death rate of laboratory mice infected with experimental herpetic encephalitis (via intraperitoneal contamination) by an average of 40%. PABA increased the mean life-span of the same species of mice with experimental herpetic encephalitis, also significantly decreasing the virus titer in the mouse brain. In the same study, PABA exhibited a significant ability to potentiate the antitherpetic action of acyclovir (Zovirax, acycloguanosine) in the infected cultures when acyclovir was used in inactive concentrations [52].

While individual studies on single ingredients are by no means a conclusive therapeutic edict or a reductionist recommendation, they add another dimension of therapeutic options to the arsenal of nutraceutical products (already discussed) that reduce herpetic infections that exacerbate chronic neurodegenerative diseases. A new hope for an improved quality of life is presented.

1.7.5 **Multinutrient Complex**

In a *JAMA* paper published in 2002, researchers stated that “suboptimal intake of some vitamins, above levels causing classic vitamin deficiency, is a risk factor for chronic diseases common in the general population, especially the elderly.” They also stated that “it appears prudent for all adults to take vitamin supplements” [53]. While this is a well-intentioned recommendation, the significant exponential increase in the consumption of dietary supplements over the last 30 years has not put a dent in the incidence of chronic degenerative diseases. Moreover, the number one health malady in the United States is digestive problems, and they are increasing. The implication
from these factors is that consumed food and supplements are achieving suboptimal absorption at best. Health is progressively eroding on a societal scale. The informed consumer should seek out multivitamin/mineral supplements that provide nutrition that gets in, i.e., gets absorbed into the body’s tissues. Dietary supplements are not all the same. Consumers should ask dietary supplement companies to supply research published in peer-reviewed scientific literature to validate the effectiveness of their products.

Other nutraceuticals having some antitherpetic validation are

– Monolaurin
– Zinc

(The reader is encouraged to investigate the benefits of these ingredients to augment others mentioned in this chapter.)

1.8 CONCLUSION
A preponderance of evidence presented in this chapter confirms that chronic viral infections, specifically various herpes viruses, are important but overlooked etiological factors in chronic neurodegenerative diseases. Clinicians should not wait for the emergence of obvious symptoms to add nutraceutical products to

1. Bolster immune and metabolic competence
2. Inhibit the herpes virus from binding to a cell receptor site
3. Reduce factors that weaken immune competence and promote herpetic activation

We have revealed a little recognized etiological nemesis (i.e., herpes viruses) that demands therapeutic inclusion to more competently understand and effectively address chronic neurodegenerative diseases. There are nutraceutical products that have been shown to be effective in reducing the incidence, severity, duration, and recurrence of the herpes virus. Nutraceuticals and therapeutic strategies mentioned in this chapter are intended to convey valuable information regarding the biological building materials (nutritional/nutraceutical products) that are either unavailable or inadequate from standard American dietary practices and require supplementation. These nutraceutical products should be used in concert with other cofactors mentioned to bolster protection against the scourges of chronic neurodegenerative diseases.

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**Nutrition and Dance Movement Psychotherapy as Positive and Effective Interventions for Autism in Cyprus**


