

# Strategies to Overcome Neuroendocrine Immune Deficits in Aging: Role of Neuroendocrine-Immune Modulators and Bioactive Plant Extracts

Yaşlanmada Nöroendokrin Bağışıklık Problemlerinin Üstesinden Gelmede Stratejiler: Nöroendokrin-Bağışıklık Düzenleyiciler ve Biyoaktif Bitki Özüleri

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## Abstract

The neuroendocrine immune network functions in a delicate balance during health and the ability to maintain this balance through disease affects the outcome of the disease. During aging, there is a general decline in each of these systems that reflects on their synergistic functions and affect homeostasis leading to age-associated diseases including cancer, autoimmunity and degenerative diseases. Immunomodulation by estrogen through cyclic menstrual variations and precipitous decline during reproductive aging, facilitates the development of several female-specific age-associated diseases such as autoimmunity, osteoporosis, cardiovascular diseases and hormone-dependent cancers. Centrally and peripherally, norepinephrine released from sympathetic innervation of lymphoid organs plays a key role in naïve T-cell regulation. Hypothalamic catecholaminergic networks play a crucial role in endocrine regulation and indirectly affect immune functions during health and disease. Immune mediators such as cytokines can cross the blood brain barrier and bind to central neurons eliciting sickness behaviour and facilitate reprogramming of energy reserves to be used to fight the disease. Monoamine oxidase inhibitors like deprenyl and synthetic drugs like donepezil have been shown to exert positive effects on the age-associated decline in the neuroendocrine-immune network by delaying peripheral degeneration and increasing immune functions. Similar beneficial effects have been observed *in vitro* and *in vivo* in rats treated with Brahmi (*Bacopa monnieri*) and Noni (*Morinda citrifolia*). Comparative analysis of the strategies for reversing age-associated immunosenescence using synthetic drugs and natural remedies have shown significant immunomodulatory effects in middle-aged and old rats through modulation of MAPK and NF-κB signaling cascades.

**Keywords:** Immunosenescence, deprenyl, Brahmi, Noni, donepezil

## Öz

Nöroendokrin bağışıklık ağı vücut sağlığının korunmasında bulunduğu hassas denge ile bu sağlığın korunmasında önemli bir rol oynar. Yaşlanma sırasında, bu sistemlerin ve aralarındaki sinerjik işlevlerin etkinliğinin azalması ile, kanser, otoimmünite, osteoporoz, kalp-damar hastalıkları ve hormona bağlı kanserler ile dejeneratif hastalıklar gibi sağlık problemleri ortaya çıkabilmektedir. Östrojenin menstrüasyon sırasındaki dögüsel farklılıkları ve üreme sistemindeki yaşlanmaya bağlı olarak otoimmünite, osteoporoz kalp-damar hastalıkları ve hormona bağlı kanserler gibi hastalıklar meydana gelmektedir. Norepinefrinin lenfoid organların innervasyonu ile salınımı ile gerek periferik olarak gerek ise santral olarak etki göstermekte, aktive olmamış T lenfositlerinin düzenlenmesinde çok önemli roller oynamaktadır. Hipotalamus kökenli katekolaminergic ağ, endokrin sistemin düzenlenmesinde ve bu sistemin sağlık ve hastalıklarda söz konusu olan ve bağışıklık sistemi ile ilgili işlevlerinde vazgeçilmez bir rol oynar. Bağışıklık sisteminde etkin sitokinler gibi maddeler, kan-beyin engelini geçip beyindeki sınırları etkileyerek hastalıkların hastalarda meydana getirdiği değişiklikleri oluşturmada ve enerji kaynaklarının hastalık ile savaşılmalarını kolaylaştırmak üzere görev yapmaktadır. Monoamin oksidaz inhibitörü deprenil ve donepezil gibi yapay ilaçların nöroendokrin-bağışıklık ağına oluşan yaşa bağlı değişikliklere periferik sistemde olan bozulmayı azaltarak olumlu etki gösterdiği bildirilmiştir. Züfa otu (*Bacopa monnieri*) ve hint dutunun (*Morinda citrifolia*) *in vitro* ve *in vivo* olarak sıçanlarda yukarıda bahsedilene benzer yararlı etkiler gösterdiği gözlemlenmiştir. Yaşa bağlı bağışıklık yaşlanması ile oluşan etkilerin bazı yapay ilaçlar ve doğal maddeler ile sıçanlarda MAPK ve NK-κB sinyal yollarını etkileyerek bağışıklığı düzenlediği bildirilmiştir.

**Anahtar Kelimeler:** Bağışıklık-yaşlanma, derenil, züfa otu, hint dutu, donepezil

## Introduction

The neuroendocrine-immune network is a complex interdependent system in which each of the individual players: the nervous system, the endocrine system and the immune system; influence the outcome of the other.<sup>[1-3]</sup> The interdependence of these three super systems

is so complex that each of these systems is crucial for the regulation of the other systems. Centrally, neuroendocrine outflow can alter immune reactivity through hormones, direct innervation of lymphoid organs and be regulated by endocrine mediators (hormones) and immune mediators (cytokines) that can cross the blood-brain barrier.<sup>[2–4]</sup> Gonadal hormones such as estrogen can alter immune reactivity by binding to specific receptors on immune cells leading to proliferation and exert feedback regulation of the central hypothalamo-pituitary axis and aid in the maintenance of homeostasis in healthy individuals.<sup>[5–7]</sup> Aging, however, tilts the balance and affects homeostasis leading to derangements in the synergistic functions of the neuroendocrine-immune network that preclude the development of age-associated degenerative diseases and cancer.<sup>[8]</sup>

### Potential targets for Reversing neuroendocrine-immune deficits in Aging:

#### Loss of Compensatory Mechanisms (Antioxidant systems and Tropic factors)

Aging leads to dysregulation in the intracellular processes due to cumulative damage caused by free radicals over a lifetime leading to gradual decline in physiological functions. This damage is characterised by accelerated lipid peroxidation, malondialdehyde formation, and loss of membrane integrity by binding to proteins in the cell membrane, affecting their structure and functions.<sup>[9–10]</sup> In immune effector cells from secondary lymphoid organs such as spleen, the age-associated increase in the levels of lipid peroxidation and consequent accumulation of protein carbonyl compounds promote the formation of protein cross links, enzyme dysfunctions that disrupt normal cellular functions.<sup>[11]</sup> In sympathetic nerve fibers, the generation of free radicals, reactive oxygen and nitrogen species due to dysregulation in inflammatory processes during aging may contribute to age-associated degeneration.<sup>[12]</sup> Peripherally and centrally, aging also leads to a deficiency in the synthesis of target-derived growth factors, including nerve growth factor, (NGF) and brain derived growth factor (BDNF) in specific regions of the brain and in human peripheral blood mononuclear cells.<sup>[13]</sup> Decline in these growth factors lead to impaired binding to immune cells such as mast cells, eosinophils, T and B lymphocytes which can directly affect synaptic plasticity of sympathetic neurons in the periphery.<sup>[13,14]</sup>

#### Immunosenescence:

Age-associated loss of immune functions characterised as immunosenescence includes significant decline in innate and adaptive immune functions, defective hematopoiesis in the bone marrow, involution of the thymus, and alterations in the subset population and functions of immune effector cells in the periphery.<sup>[8]</sup> These age associated changes accompany chronic oxidative stress, inflammation and impaired homeostasis leading to reduced immunocompetence in both innate and acquired immunity.<sup>[3]</sup> Decline in innate immune functions play a crucial role in age-associated disease pathogenesis through impairments in the functions of phagocytic, chemotactic and cytotoxic immune effector cells including neutrophils, monocytes and macrophages through altered signalling pathways.<sup>[15]</sup> Age-associated increase in NF- $\kappa$ B signalling leads to increased proinflammatory cytokine expression including TNF- $\alpha$ , thereby promoting inflammatory processes.<sup>[13,16]</sup> Also, there is a concomitant decrease in the population of naïve T-cells and CD8<sup>+</sup> cell number leading to impaired interactions with B-cells in the secondary lymphoid organs in the elderly.<sup>[17]</sup> These deficits contribute to alterations in T-cell activation, subset populations and cytokine production leading to insufficient responsiveness to novel antigens and impaired memory responses to exposed antigens setting the stage for the onset and progression of age-associated diseases.<sup>[12]</sup> At the molecular level, age-associated impairments in activation of MAPK cascades and decreased ERK expression may contribute to decreased immune functions in stimulated T-cells.<sup>[13,18]</sup>

#### Peripheral Neurodegeneration:

Peripherally, regulation of neuroendocrine-immune responses is through sympathetic noradrenergic innervation of the primary (bone marrow and thymus) and secondary lymphoid organs (spleen, and lymph nodes). These nerve fibres play a crucial role in the sustenance of naïve T cells and influence immune functions through the release of norepinephrine which binds to specific receptors on immune cells.<sup>[19]</sup> Physically the presence of these nerve fibres have been extensively characterised in both primary and secondary lymphoid organs where they are found to be in synaptic association with immune effector cells such as lymphocytes.<sup>[2–4,20]</sup> Adrenergic signalling in lymphocytes is dependent on several factors such as type of T-cell subset involved, type of activation, expression and presence of co-stimulatory molecules like CD86, time of engagement, extent of AR expression and responsiveness.<sup>[21,22]</sup> During aging, the sympathetic noradrenergic innervation in the

peripheral lymphoid organs declines concomitant with decreased/impaired T-cell responses and functions.<sup>[19,20,23,24]</sup> Primarily, sympathetic denervation is the result of age-associated decline in compensatory mechanisms including antioxidant machinery, accumulation of free radicals and loss of target-derived growth factors.<sup>[13,25,26]</sup> Decline in sympathetic noradrenergic innervation in females is much earlier when compared to males implicating the role of estrogen in earlier denervation in females.<sup>[24]</sup>

### Endocrine dysfunctions: Estrogen

In females, estrogen plays a crucial role in upregulating antioxidant enzyme activities and suppressing free radical generation at the physiological levels and promote longevity.<sup>[27]</sup> Loss of physiological levels of estrogen in conditions such as ovariectomy leads to increased oxidative stress, inhibition of chemotactic index, lymphocyte proliferation and natural killer cell activity while estrogen supplementation reversed cellular oxidative distress and immunosuppression.<sup>[28]</sup> Estrogen can bind to specific estrogen receptors on lymphocytes that are differentially expressed based on immune cell type: ER $\alpha$  is predominantly expressed on CD4<sup>+</sup> T cells and may influence the maturation and differentiation in the thymus while ER $\beta$  is expressed on B cells and may alter lymphopoiesis in the bone marrow.<sup>[6,7]</sup> Estrogen induced immunomodulation is implicated in the predominant female-specific autoimmune diseases, hormone-dependent cancer, osteoporosis, and cardiovascular diseases.<sup>[6,7]</sup> Estrogen alters humoral immunity and alters the pathogenesis of certain female-specific diseases while it augments Th1 cytokine production and CD4<sup>+</sup> T cell proliferation in autoimmune diseases.<sup>[29-31]</sup> In a concentration and receptor-subtype dependent manner, 17 $\beta$ -estradiol treatment enhanced proliferation of T lymphocytes and IFN- $\gamma$  production through p-ERK 1/2, p-CREB, and p-Akt, enhanced antioxidant enzyme activities and NO production.<sup>[32]</sup> Immune functions are significantly altered during the various stages of estrous/menstrual cycle influencing T and B cell proliferation, and humoral functions due to cyclic variations in circulating gonadal hormones.<sup>[13]</sup> Estrogen significantly alters the influence of adrenergic agonists on immune functions thereby shedding a new light on its crucial role in neuroimmunomodulation in the periphery.<sup>[32,33]</sup>

### Deficits in central neurons:

Neuroendocrine-immune deficits in the secondary lymphoid organs may be influenced by decline in

hypothalamic catecholaminergic neuronal activity, loss of peripheral sympathetic noradrenergic (NA) innervation and norepinephrine (NE) release.<sup>[4,8]</sup> Chronic low grade inflammation during aging is observed in several brain areas through upregulation of the NF- $\kappa$ B family of transcription factors, apart from proinflammatory cytokines, and pathogen-associated molecular patterns, all of which contribute to central neurodegeneration.<sup>[34,35]</sup> In the hypothalamus, there is an increased expression of NF- $\kappa$ B-induced proinflammatory cytokines such as TNF- $\alpha$  with age, thereby causing diminished gonadotropin-releasing hormone secretion.<sup>[34,35]</sup> Similarly, in the medial basal hypothalamus, an age-related increase I- $\kappa$ B and NF- $\kappa$ B expression was found to influence gonadotropin functions and affect innate immunity through cross-talks between the neurons and the microglia.<sup>[36]</sup> Tyrosine hydroxylase expression declines in specific brain areas in women (striatum, medial basal hypothalamus) and men (prefrontal cortex) with age.<sup>[35,37]</sup> This is associated with impaired cognitive functions due to loss of gray matter, decreased synaptic and spine density, and loss of dendritic arborization along with a reduction in Tyrosine hydroxylase and cortical dopaminergic activity.<sup>[37]</sup> Age-associated loss of neurotrophin such as NGF are implicated in the development of neurodegenerative diseases as they are crucial to the survival of neurons by promoting growth and plasticity.<sup>[38]</sup> Decline in NGF production, NGF receptor expression, nitric oxide (NO) production and acetyl choline release are concomitant with degeneration of cholinergic fibres in Alzheimer's disease pathology.<sup>[39]</sup> Metabolic deficits due to chronic inflammation lead to increased load of reactive oxygen species as a result of mitochondrial dysfunction leading to neurodegeneration.<sup>[40]</sup>

### Reversing neuroendocrine-immune deficits through synthetic drugs and natural supplements

Strategies to reverse neuroendocrine-immune deficits in healthy aging have included a host of synthetic drugs and natural supplements involving biologically active phytochemicals.<sup>[8]</sup> The health benefits derived from these molecules range from antioxidant properties, anti-inflammatory properties, immunostimulatory properties, and neuroprotective functions in a host of age-associated diseases including hypertension, diabetes, cancer and degenerative diseases.<sup>[8,18,19,23]</sup> The concept of healthy aging is fast evolving and it is now crucial to understand if supplementation of phytochemicals and synthetic

drugs in early life have the potential to arrest or delay the aging process and thereby increase the average lifespan.<sup>[8,23]</sup> Among synthetic drugs, deprenyl and donepezil have been widely studied for their neuro-regenerative, immunostimulatory and cognitive benefits while Brahmi and Noni have been widely used in traditional medicine for cognitive health, immunostimulation and anti-inflammatory benefits.<sup>[8,23]</sup> Understanding how each of these modulate the neuroendocrine-immune network to revert the age-associated deficits and restore homeostasis would help explore the potential of these drugs as a strategic tool to promote healthy aging.

### Deprenyl

Deprenyl is a monoamine oxidase-B inhibitor that influences dopamine reuptake by central neurons and improves dopaminergic tone in patients with Parkinson's disease.<sup>[41]</sup> Deprenyl treatment reversed neural-immune dysfunctions in aging through increased norepinephrine release, improved immune functions, enhanced growth factor production and reversion of hippocampal, splenic and ganglionic nerve fibres.<sup>[42,43]</sup> Daily treatment of old (21 months) male F344 rats with 0.25 or 1.0 mg deprenyl/kg body weight (BW) through intraperitoneal route for 9 weeks showed significant increase in Tyrosine hydroxylase+ nerve fibres in the splenic white pulp and around the central arteriole concomitant with an increase in splenic norepinephrine content.<sup>[43]</sup> *In vitro* treatment of rat cortical astrocytes with selegiline (10pM-1nM) another irreversible monoamine oxidase-B inhibitor, significantly enhanced the expression of NGF thereby protecting against glutamate-induced excitotoxicity.<sup>[42]</sup>

In the spleen, deprenyl enhanced norepinephrine content, con A-induced T-cell proliferation, natural killer cell cytotoxicity, expression of nerve growth factor and tyrosine hydroxylase and enhanced antioxidant enzyme activities, concomitant with the restoration of sympathetic noradrenergic nerve fibres.<sup>[43,44]</sup> Young (3 month old) rats sympathectomised with 6-hydroxydopamine (6-OHDA) and treated intraperitoneally with 0.25, 1.0, 2.5 and 5.0 mg deprenyl/kg for 30 days showed significant increase in NA innervation and splenic NE content.<sup>[43]</sup> Deprenyl treatment (1.0 and 2.5 mg/kg BW for 10 days) of young (3 month old) female Wistar rats significantly enhanced the activity of Catalase (CAT), expression of p-TH, NGF, p-NFkB, p-ERK and p-CREB in the spleen.<sup>[44]</sup>

*In vitro*, deprenyl enhanced nerve growth factor expression in central neurons: cortical, hippocampal cultures and increased CNTF expression in astrocyte cultures.<sup>[45]</sup> A mixed population of flat and process bearing (PB) astroglia from post natal (day 2 or 5) rat cerebral cortex in culture showed significant increase in CNTF m-RNA expression and total process length in PB astrocytes by treatment with L-deprenyl ( $10^{-8}$ M- $10^{-11}$ M) following mechanical injury.

Deprenyl treatment (1.0 and 2.5 mg/kg BW for 10 days) of young (3 month old) female Wistar rats significantly enhanced CAT activity in the Frontal cortex, medial basal hypothalamus (MBH) and Striatum, glutathione peroxidase (GPx) activities in the MBH, striatum, heart and mesenteric lymph nodes (MLN), thereby restoring the compensatory machinery lost due to aging and help revert neuroendocrine-immune homeostasis.<sup>[44,46]</sup>

### Donepezil

Donepezil is a reversible acetylcholinesterase inhibitor used in the treatment of patients with Alzheimer's and Parkinson's-associated dementia.<sup>[47,48]</sup> Donepezil significantly enhances antioxidant enzyme activities in neuronal cells and splenic lymphocytes thereby improving both cognitive and immune functions in Alzheimer's and Parkinson's disease.<sup>[49,50]</sup> In an oxygen glucose deprivation model of rat pheochromocytoma cells, pre-treatment with acetyl cholinesterase inhibitors like Huperzine A and Donepezil, showed improved survival and reduced biochemical and morphologic signs of toxicity possibly by alleviating disturbances of oxidative and energy metabolism.<sup>[49]</sup> In another *in vitro* study, splenic lymphocytes from young, middle-aged and old rats treated with Donepezil showed significant increase in splenocyte SOD, GPx, GST activities, NO production, p-ERK and p-CREB expression and decreased lipid peroxidation.<sup>[50]</sup>

Clinically, donepezil treatment in patients with Alzheimer's disease has shown to alter the expression of beta chemokines in peripheral blood mononuclear cells, release of IL-1 $\beta$  and IL-6 from lymphocytes, and plays a regulatory role by altering the neural-immune network through modulation of neuroinflammatory pathways.<sup>[51-53]</sup> Neuroimmunomodulation and reversal of cognitive and functional deficits by donepezil may be attributed in part to the significant modulation of antioxidant enzyme functions and nerve growth factor-expression as shown by several *in vitro* studies using PC12 cells and splenocytes.<sup>[49,54]</sup> *In vitro* treatment of rat PC-12 cells with Donepezil



potentiated NGF-induced neurite outgrowth in a dose-dependent manner.

Peripherally, *in vitro* incubation of splenocytes with Donepezil (5, 10, 25, 50 and 100 mg/ml) significantly enhanced p-ERK and p-CREB signalling cascades and enhanced antioxidant functions possibly through CREB-mediated co-activation of ARE.<sup>[50]</sup> Centrally, Donepezil enhanced the hippocampal expression of IGF and p-ERK, activate hippocampal Trk neurotrophin receptors in mice, and enhances adult hippocampal neurogenesis.<sup>[55–57]</sup> *In vivo*, oral administration of donepezil to wild type mice for 4 weeks increased the hippocampal IGF-1 expression through the expression of calcitonin gene-related peptide (CGRP) and PKA signalling pathway.<sup>[55]</sup> Intraperitoneal administration of donepezil (3 mg/kg body weight) to adult mice showed autophosphorylation of hippocampal TrkA and TrkB neurotrophin receptors and increased p-CREB and Akt Kinase expression.<sup>[56]</sup> Adult rats orally administered with donepezil (0.5, 2.0 mg/kg BW) showed that donepezil can modulate hippocampal neurogenesis by enhancing neuronal survival in the dentate gyrus, through p-CREB signalling pathway.<sup>[57]</sup>

### ***Bacopa monnieri***

*Bacopa monnieri*, popularly known as Brahmi is characterised in Ayurveda as a natural remedy for memory impairment and cognitive decline.<sup>[58,59]</sup> Centrally, Brahmi mediates its beneficial effects by enhancing the activity of antioxidant enzymes including superoxide dismutase, CAT and GPx in the rat frontal cortex, striatum and hippocampus.<sup>[60,61]</sup> Treatment of rats with standardized extract of *Bacopa monnieri* (5 and 10 mg/kg) containing 82% Bacoside A administered orally for 14 and 21 days, increased SOD, CAT and GPx activities in frontal cortical, striatal and hippocampal areas.<sup>[60]</sup> In another study, rats pre-treated with alcoholic extract of *Bacopa monnieri* (20 and 40 mg/kg) for 3 weeks showed significant protection against 6-OHDA-induced loss of neurobehavioral activity (rotarod, locomotor activity, grip test, forced swim test, radial arm maze), decline in striatal GSH, CAT and SOD and increased lipid peroxidation and decreased GSH activity in the substantia nigra.<sup>[61]</sup>

Peripherally, brahmi enhanced splenocyte cytokine production (IL-2 and IFN- $\gamma$ ) and reversed their age-associated decline and increased antibody production (IgA and IgG), while bacoside-A the active ingredient enhanced T-lymphocyte proliferation.<sup>[50,61–63]</sup> In a longitudinal study

lower doses of brahmi treatment reversed the age-related decrease in Con A-induced IL-2 and IFN- $\gamma$  production by the splenocytes, enhanced splenocyte CAT, GPx and GST activities and increased the expression of NO, p-ERK, p-CREB and p-Akt in splenocytes.<sup>[50]</sup> In another study, Sprague Dawley rats fed with a diet supplemented with 1% Brahmi for 4 weeks showed significant increase in circulating levels of IgA and IgG, and increased expression of Con A and LPS-induced IFN- $\gamma$  and IL-2.<sup>[62]</sup> Interestingly, splenocytes treated with Bacoside-A, one of the phytoactive component found in Brahmi significantly enhanced Con-A-induced proliferation in rats while brahmi extract reduced it.<sup>[63]</sup>

Betulinic acid, another active ingredient found in Brahmi, suppressed LPS-induced IL-6 production in PBMCs through NF- $\kappa$ B signalling pathway, suggesting that its age-associated benefits may be from suppression of proinflammatory pathways.<sup>[64–66]</sup> *In vitro* treatment of PBMCs with triterpenoid and bacoside-enriched methanolic fractions of *Bacopa monnieri* significantly inhibited LPS-activated TNF- $\alpha$ , IL-6 and nitrite production through modulation of proinflammatory mediators.<sup>[65]</sup> Long-term treatment (3 months) of old Wistar rats on bacoside-enriched extract significantly attenuated age-associated neuroinflammation in the rat brain cortex by reversing age-dependent increase in pro inflammatory cytokines, iNOS expression, total nitrite and lipofuscin content.<sup>[66]</sup> Brahmi treatment also reversed age-associated deficits in antioxidant functions, nerve growth factor and tyrosine hydroxylase expression and age-related increase in lipid peroxidation both peripherally and centrally.<sup>[44,50,60,61]</sup> Treatment of 3 month old female Wistar rats with Brahmi significantly enhanced CAT activity, NO, p-TH, NGF, and p-NF- $\kappa$ B expression in the spleen.<sup>[44]</sup> Centrally Brahmi and bacoside treatments inhibit inducible nitric oxide synthase (iNOS) thereby preventing neuronal apoptosis, while in the periphery, age-associated decline in lymphocyte NO production is reversed by Brahmi treatment thereby increasing their functional ability through vasodilation and immune cell trafficking.<sup>[50,66–68]</sup> Intravenous treatment with brahmi extract (20–60 mg/kg BW) reduces the blood pressure in anaesthetised rats by releasing NO from the endothelium and modulating vascular smooth muscle Ca (2+) homeostasis.<sup>[68]</sup> The neuroprotective, immune enhancing and anti-inflammatory properties are mediated through p-ERK, MAPK signalling pathways, p-CREB, PKA and

C pathways, p-Akt through PI3K, and NF- $\kappa$ B signalling cascades.<sup>[50,65,69–70]</sup>

### *Morinda citrifolia*

*Morinda citrifolia* (Noni) has been a staple in Asian folk medicine for a number of centuries.<sup>[71]</sup> Phytochemicals in the roots, barks, and fruits including a variety of anthraquinones, iridoids, fatty acid glycosides and alcohols are crucial players in the functional benefits derived from Noni.<sup>[71–73]</sup> *In vitro* treatment of draining lymph node lymphocytes with Noni fruit juice significantly enhanced Con A-induced proliferation and IL-2 production and antioxidant activities.<sup>[74]</sup> *In vivo*, Noni treatment of old (16–17 months) male F344 rats treated with 5 ml/kg body weight of 5%, 10% and 20% of NFJ, twice a day, by oral gavage reversed age-associated decline in splenic lymphocyte proliferation, cytokine production (IL-2 and IFN- $\gamma$ ) through enhanced p-ERK and p-Akt expression and decreased proinflammatory cytokine (IL-6) production and I $\kappa$ B- $\alpha$  and NF- $\kappa$ B (p50 and p65) expression.<sup>[18,75,76]</sup> Beneficial effects of Noni supplementation may be through significant increase in antioxidant enzyme activities including CAT and glutathione-s-transferase (GST) concomitant with a decline in the extent of lipid peroxidation in old rats.<sup>[75]</sup> *In vivo*, treatment with noni extract and its bioactive component damnacanthol suppress inflammatory cascades through decreased expression of proinflammatory cytokines, cyclooxygenase-2 (COX-2), and iNOS.<sup>[77]</sup> Centrally, *Morinda citrifolia* treatment enhanced the expression of brain derived neurotrophic factor (BDNF) in mouse model of streptozotocin-induced memory impairment.<sup>[78]</sup> Noni and its bioactive compounds such as damnacanthol mediate the inhibition of LPS-induced NF- $\kappa$ B expression through decreased proinflammatory cytokine production, inhibition of cyclooxygenase-2 (COX-2), and iNOS targeting the inflammatory process.<sup>[78]</sup> The expression of target derived growth factors such as tyrosine hydroxylase and nerve growth factor were enhanced in old rats treated with Noni thereby reversing the age-associated deficits in compensatory mechanisms.<sup>[76,78]</sup>

### Conclusions

Integrative functioning of the nervous system, the endocrine system and the immune system is crucial for the maintenance of homeostasis during healthy aging. Loss of compensatory mechanisms including antioxidant enzymes and trophic factors due to general decline with age,

onset of immunosenescence, cognitive decline, endocrine deficits and loss of sympathetic noradrenergic innervation of the lymphoid organs contribute to the dysregulation of the neuroendocrine-immune network leading to the development and progression of age-associated diseases including degenerative diseases, infectious diseases, autoimmunity, and cancer. Both synthetic drugs and phytochemical compounds exert beneficial effects in aging by compensating for the age-associated decline in the neuroendocrine-immune network through increased antioxidant enzyme activities, enhanced expression of growth factors, hormones, and intracellular signaling molecules, direct regeneration of nerve fibers, decreased inflammation or enhanced cell-mediated immune functions. Understanding how each of these molecules can help modulate the complex interplay between the neuroendocrine-immune networks during health and disease may be the key to longevity.

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