Journal of Phytonanotechnology and Pharmaceutical Sciences 4(2): 9-15, 2024

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2024.4.2.2

Journal of Phytonanotechnology and Pharmaceutical Sciences

Review Article : Open Access

Stress: Pathological pathways and role of nutraceuticals in its management

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Article Info

Article history
Received 16 April 2024
Revised 27 May 2024
Accepted 28 May 2024
Published Online 30 June 2024

Keywords
Stress
Nutraceuticals
Flavonoids
Inflammation
Neurotransmitter

Abstract

Stress is a ubiquitous element of modern life, significantly affecting both physical and mental health through various pathological pathways. This review examines the fundamental mechanisms of stress, including its disruption of the hypothalamic-pituitary-adrenal (HPA) axis and the induction of oxidative stress and inflammation mediated by cytokines such as IL-1, IL-6, and TNF-α. Despite these challenges, nutraceuticals hold the potential to mitigate stress's impact. This article explores the roles of polyphenols, flavonoids, adaptogens like *Rhodiola rosea* and *Withania somnifera*, omega-3 fatty acids, B vitamins, magnesium, and probiotics, highlighting their diverse mechanisms of action. These nutraceuticals exhibit antioxidant and anti-inflammatory properties, modulate neurotransmitter levels, and promote neurogenesis, offering a robust approach to combat stress-induced conditions. By providing a detailed overview of stress pathology and nutraceutical interventions, this review aims to enhance understanding of effective stress management strategies. Furthermore, it emphasizes the necessity of future research to fully realize the potential of nutraceuticals in reducing the adverse effects of stress on human health and well-being.

1. Introduction

In understanding the complexities of stress, various neurobiological pathways come into play, orchestrating responses that extend far beyond momentary challenges. The intricate interplay of the hypothalamic-pituitary-adrenocortical (HPA) axis, the limbic system, and the autonomic nervous system intricately modulate stress responses (McEwen *et al.,* 2010; Herman *et al.,* 1997; Sapolsky *et al.,* 2000; McEwen, 2000; de Kloet *et al.,* 2005). Chronic stress, characterized by prolonged activation of these pathways, can detrimentally impact health, contributing to allostatic load and increasing susceptibility to various diseases (Miller *et al.,* 2007; Juster *et al.,* 2010). Hans Selye's pioneering work in describing the 'general adaptation syndrome' laid the foundation for comprehending the multifaceted nature of stress and adaptation (Selye, 1950). Furthermore, the concepts introduced by Selye have evolved, encompassing the intricate bidirectional communication between the brain and the periphery, highlighting the role of glucocorticoids and other stress mediators (Charmandari *et al.,* 2005; Chrousos and Gold, 1992).

1.1 Stress

Stress, a multifaceted phenomenon, encompasses physiological and psychological responses to challenges or threats, that disrupting the body's equilibrium (Lupien *et al.,* 2009). It involves intricate interactions between the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-adrenal-medullary (SAM) axis, and the immune system (Dhabhar, 2014). The HPA axis orchestrates the release of glucocorticoids, particularly cortisol, which mobilize energy and modulate immune responses (Sapolsky *et al.,* 2000). Concurrently, the SAM axis triggers the release of catecholamines, facilitating immediate physiological responses (Goldstein *et al.,* 2010). Chronic stress dysregulates these systems, contributing to various health problems, including cardiovascular diseases and psychiatric disorders (McEwen, 1998). Moreover, stress-induced alterations in neural circuits, such as the prefrontal cortex and amygdala, underlie cognitive and emotional disturbances (Arnsten, 2009). Understanding stress mechanisms is crucial for developing interventions to alleviate its adverse effects and promote resilience.

1.2 Pathological pathways of stress

Pathological pathways involved in stress encompass a complex interplay of molecular changes and physiological responses (Eugeny *et al.,* 2019). Stress can lead to various diseases through mechanisms such as chronic low-grade inflammation, altered ion secretion, increased epithelial permeability, and dysregulation of the stress system (Li*et al.,* 2023). The stress response involves immediate and slower modes mediated by corticosteroid hormones acting on mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the brain, influencing adaptation, recovery, and homeostasis (Liu *et al.,* 2015). Chronic stress can result in failures of homeostasis, contributing to conditions like atherosclerosis, non-alcoholic fatty liver disease, depression, irritable bowel syndrome, and inflammatory bowel disease. Understanding the common pathways, such as chronic mild inflammation, AKT, and MAPK signallingnetworks, is crucial for unravellingthe pathogenesis of stress-related diseases and developing effective treatment strategies (Melanie *et al.,* 2008; Bellingrath *et al.,* 2017).

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1.2.1 Hypothalamic-pituitary-adrenal axis (HPA)

The hypothalamic-pituitary-adrenal (HPA) axis is a critical neuroendocrine system that governs the body's response to stress and regulates numerous physiological processes, including mood and emotional regulation.When stress is detected, the hypothalamus releases corticotropin-releasing hormone (CRH), which then stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH) (Hinds *et al.,* 2022). ACTH, in turn, triggers the adrenal cortex to secrete cortisol, a glucocorticoid hormone essential for managing stress by mobilizing energy resources and modulating immune response (Noorzaid *et al.,* 2023). Numerous studies have highlighted the HPA axis's pivotal role in stress responses, noting that the release of cortisol is a key component. Dysregulation of this axis is linked to several conditions, such as increased vulnerability to substance abuse during opioid abstinence, metabolic stress from specific diets, and heightened susceptibility to inflammatory diseases like colitis following early life stress (Muir *et al.,* 2022). These findings underscore the complex relationship between the HPA axis and stress-related physiological responses, emphasizing its importance in both normal stress adaptation and the development of various diseases.

1.2.2 Sympatho-adrenal-medullary (SAM) system

The sympatho-adrenal-medullary (SAM) system is essential in managing the body's response to stress, particularly psychological stress, and its effects on various physiological systems. Studies indicate that psychological stress triggers an increase in catecholamines such as adrenaline and noradrenaline, which can impact hair follicles and contribute to skin conditions like acne (Koji *et al.,* 2021). Additionally, the SAM system is closely linked with the hypothalamic-pituitary-adrenal (HPA) axis in mediating stress responses, with both systems being activated during stressful situations (Emolio *et al*., 2020). Research has also shown the SAM system's role in cardiac responses to mental stress, where sympathetic activation can lead to severe cardiac events and heightened cardiovascular risk, especially in individuals with panic disorder (Jayasinghe *et al.,* 2016). Moreover, studies on the relationship between cardiorespiratory fitness and SAM system reactivity reveal that fitness levels can affect physiological responses to psychological stress, with lower-fit individuals exhibiting higher dopamine reactivity. Understanding the patterns of co-activation between the SAM system and the HPA axis during stress responses offers valuable insights into the development of internalizing and externalizing problems in adolescents, highlighting the importance of examining SAM-HPA interactions during both stress reactivity and recovery phases (Martha *et al.,* 2019).

1.2.3 Inflammatory pathways

Stress can activate inflammatory pathways by triggering the production of pro-inflammatory cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumournecrosis factor-alpha (TNF-α). These cytokines are crucial in immune responses and can influence the hypothalamic-pituitary-adrenal (HPA) axis, creating a feedback loop that amplifies stress responses. Inflammatory pathways are significant in various stress-related conditions (Mario *et al.,* 2022; Juan *et al.,* 2021). Research indicates that stress exposure can activate innate NF-kB and NLRP3 inflammasome pathways, leading to inflammatory responses in different tissues. Additionally, the impact of psychosocial stress on immune pathways is increasingly recognized in immune-mediated skin conditions like atopic dermatitis and psoriasis, emphasizing the link between stress and inflammation. Furthermore, in Alzheimer's disease and mild cognitive impairment, oxidative stress and neuroinflammation play crucial roles, with genetic factors affecting biomarker levels and cognitive test outcomes. Polymorphisms in genes related to oxidative stress and inflammation are associated with these conditions. Understanding these inflammatory mechanisms in the context of stress can provide valuable insights for developing targeted treatments for various stress-related disorders (Taylor *et al.,* 2022; David *et al.,* 2023).

1.2.4 Interplay of different pathways of stress

The interplay between the HPA axis, SAM system, and inflammatory pathways orchestrates the body's response to stress, creating a complex network of interactions (Figure 1). When stress is perceived, the hypothalamus initiates the release of corticotropin-releasing hormone (CRH), stimulating the pituitary gland to release adrenocorticotropic hormone (ACTH), which in turn prompts the adrenal glands to produce cortisol. Simultaneously, the sympathetic nervous system activates the adrenal medulla, leading to the release of adrenaline and noradrenaline. These hormones mobilize energy resources and prepare the body for immediate action. Additionally, stress triggers the release of pro-inflammatory cytokines, which can influence the HPA axis and exacerbate stress responses. This intricate interplay regulates various physiological processes, including metabolism, immune function, and cardiovascular activity, highlighting the interconnectedness of these pathways in the body's adaptive response to stress.

2. Role of nutraceuticals in stress management

2.1 Polyphenols

Polyphenols, abundant in various plant-based foods, are renowned for their potent antioxidant properties, which combat oxidative stress and inflammation, consequently ameliorating the effects of stress.

2.1.1 Resveratrol

Resveratrol, found notably in grapes and berries, activates the SIRT1 pathway, which enhances mitochondrial function and diminishes oxidative stress (Baur and Sinclair, 2006; Howitz *et al.,* 2003). Through SIRT1 activation, resveratrol promotes cellular stress resistance by deacetylating and activating PGC-1α, a pivotal regulator of mitochondrial biogenesis and antioxidant defense (Lagouge *et al.,* 2006; Park *et al.,* 2012).

2.1.2 Epigallocatechin gallate (EGCG)

EGCG, a catechin present in green tea, manifests neuroprotective and anti-inflammatory effects (Panickarand Anderson, 2011). By modulating the NF-κB pathway, EGCG reduces the production of pro-inflammatory cytokines while enhancing antioxidant enzyme expression through the Nrf2 pathway (Thimmulappa*et al.,* 2002; Smith and Luo, 2004).

2.2 Flavonoids

Flavonoids, a diverse group of phytonutrients, exert robust antioxidant and anti-inflammatory effects.

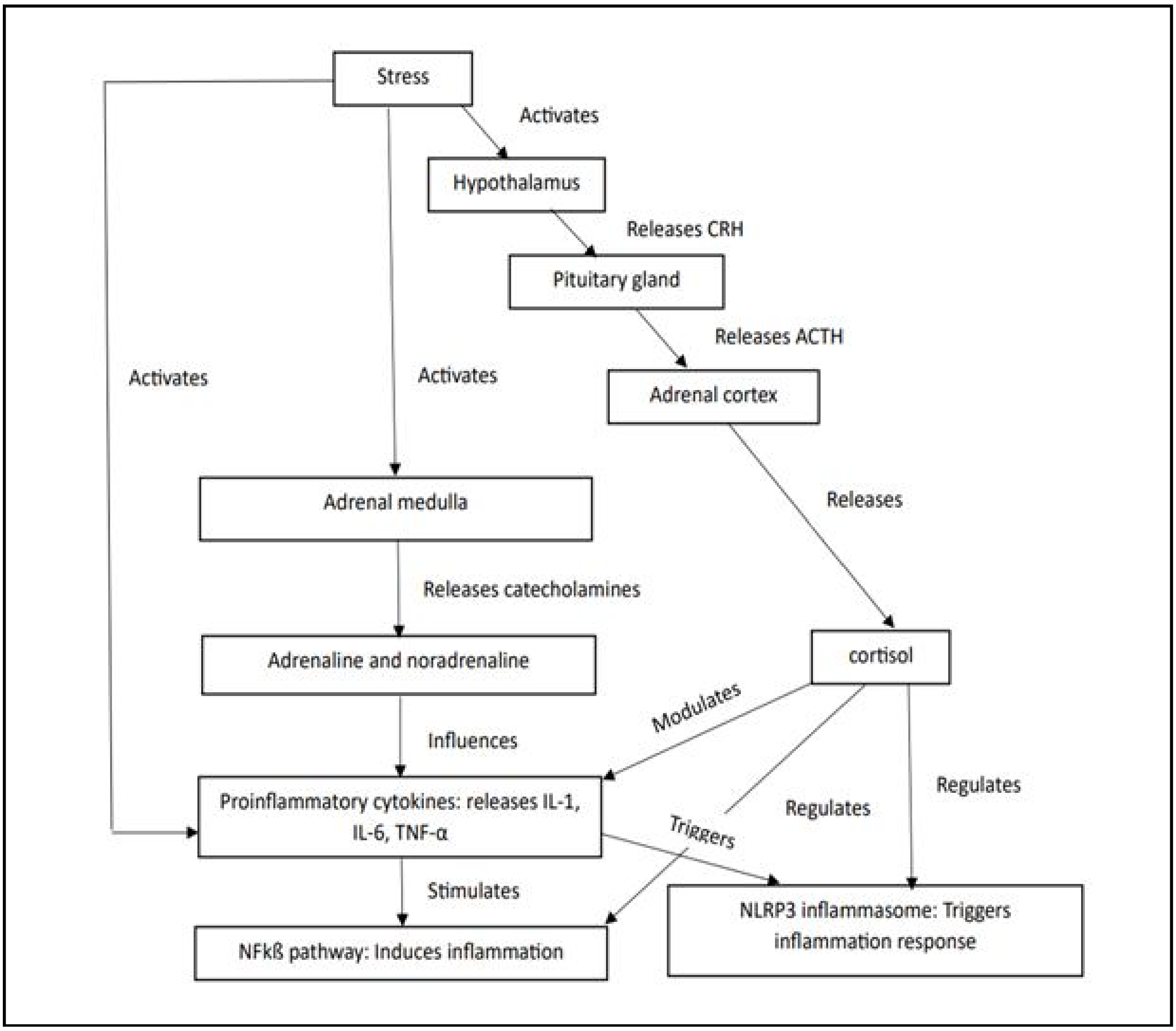

Figure 1: Interplay of pathological pathways of stress.

2.2.1 Quercetin

Quercetin, abundant in apples and onions, combats oxidative stress and inflammation (Di Carlo *et al.,* 1999). Through scavenging reactive oxygen species (ROS) and activating the Nrf2 pathway, quercetin enhances antioxidant defencesand inhibits the NF-κB pathway, thereby reducing pro-inflammatory cytokine production (Reay *et al.,* 2010; Cho and Leung, 2007).

2.2.2 Luteolin

Luteolin, found in celery and green peppers, possesses neuroprotective and anti-inflammatory properties (Kim *et al.,* 2015). By modulating the NF-κB and MAPK pathways, luteolin inhibits pro-inflammatory cytokine production while enhancing antioxidant defencesthrough Nrf2 pathway activation (Xu *et al.,* 2014).

2.3 Adaptogens

Adaptogens, natural substances aiding the body's adaptation to stress, exert a normalizing effect on bodily processes.

2.3.1 *Rhodiola rosea*

Rhodiola rosea, an adaptogenic herb, enhances stress resilience by modulating cortisol levels and improving mood (Darbinyan *et al.,* 2000). Through HPA axis modulation, it reduces cortisol production while increasing serotonin and dopamine levels, thereby enhancing mood and cognitive function (Spasov *et al.,* 2000; Olsson *et al.,* 2009).

2.3.2 Ashwagandha

Ashwagandha (*Withania somnifera*) alleviates stress and anxiety by modulating the HPA axis and bolstering antioxidant defenses (Chandrasekhar *et al.,* 2012). By decreasing cortisol levels and increasing endogenous antioxidants such as superoxide dismutase (SOD) and glutathione peroxidase, ashwagandha confers stress resilience (Archana and Namasivayam, 1999; Bhattacharya *et al.,* 2000).

2.4 Triterpenoid saponins

Triterpenoid saponins modulate stress responses through their anti-inflammatory and neuroprotective properties.

2.4.1 *Ginkgo biloba*

Ginkgo biloba flavonoids and terpenoids enhance cerebral blood flow, reduce oxidative stress, and improve cognitive function (Kennedy and Scholey, 2003; Ahlemeyer andKrieglstein, 2003). By enhancing endothelial nitric oxide synthase (eNOS) activity and scavenging ROS, they protect neurons from oxidative damage, thereby enhancing cognitive function and mood (Ude *et al.,* 2013; Weinmann *et al.,* 2010).

2.4.2 Astragalus

Astragalus saponins bolster immune function and reduce inflammation, safeguarding against stress-induced immune suppression and oxidative damage (Cho and Leung, 2007; Liu and Sun, 2006). By enhancing immune cell proliferation and activity and inhibiting pro-inflammatory cytokine production, astragalus saponins support immune health and stress resilience (Block and Mead, 2003; Panossian and Wikman, 2010).

Table 1: Nutraceuticals and their role in stress management

S.No.	Phytochemicals	Mechanism of action	References
		Polyphenols	
1.	Resveratrol	Activates the SIRT1 pathway, enhancing mitochondrial function and reducing oxidative stress.	Park *et al.,* 2012
2.	Epigallactocatechingallate	Modulates NF-κB pathway, reducing pro-inflammatory cytokine production and enhancing antioxidant enzyme expression through Nrf2 pathway activation.	Smith and Luo, 2004
		Flavonoids	
3.	Quercitin	Scavenges ROS inhibits NF-κB pathway and enhances antioxidant defencesthrough Nrf2 pathway activation.	Cho and Leung, 2007
4.	Luteolin	Modulates NF-κB and MAPK pathways, inhibiting pro-inflammatory cytokine production and enhancing antioxidant defencesthrough Nrf2 pathway activation.	Xu *et al.,* 2014
		Adaptogens	
5.	*Rhodiola rosea*	Modulates cortisol levels, and enhances mood and cognitive function by HPA axis modulation.	Olsson *et al.,* 2009
6.	Ashwagandha	Modulates HPA axis, reduces cortisol levels, and bolsters antioxidant defences.	Bhattacharya *et al.,* 2000
		Triterpenoid saponins	
7.	*Ginkgo biloba*	Enhances cerebral blood flow, reduces oxidative stress, and improves cognitive function.	Weinmann *et al.,* 2010
8.	Astragalus	Bolsters immune function, reduces inflammation, and supports stress resilience.	Cho and Leung, 2007
		Other nutraceuticals	
9.	Omega-3 Fatty acids	Modulate neurotransmitter systems, reduce inflammation, and promote cognitive health.	Su *et al.,* 2015
10.	B-vitamins	Support cognitive health and alleviate stress by modulating neurotrans-mitter systems.	Bottiglieri *et al.,* 2000

2.5 Other nutraceuticals

Additional nutraceuticals, aside from the major categories, exhibit significant anti-stress properties.

2.5.1. Omega-3 fattyacids

Omega-3 fatty acids, notably eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found in fish oil, reduce inflammation and enhance neuronal function (Su *et al.,* 2015; Grosso *et al.,* 2014). By modulating neurotransmitter systems and inhibiting pro-inflammatory mediators, omega-3s alleviate stress and promote cognitive health (Bloch and Hannestad, 2012; Freeman *et al.,* 2006).

2.5.2. B Vitamins

B vitamins, particularly B6, B9 (folate), and B12, are essential for neurotransmitter synthesis and homocysteine regulation (Bottiglieri *et al.,* 2000; Morris, 2008). By supporting neurotransmitter synthesis and reducing homocysteine levels, B vitamins alleviate stress and enhance mood.

3. Conclusion

This paper explores the pathways of stress, emphasizing the complex interaction between physiological responses and neural circuitry. By clarifying the role of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis, and their effects on cognitive and emotional functioning, it highlights the multifaceted nature of stress-related disorders. Additionally, the examination of nutraceutical therapeutics presents promising strategies for stress management, providing a comprehensive approach to modulate oxidative stress, inflammation, and neuroplasticity. With increasing awareness of the mind-body connection, incorporating nutraceutical interventions into clinical practice offers significant potential for enhancing resilience and improving mental well-being.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Ahlemeyer, B. and Krieglstein, J. (2003). Neuroprotective effects of *Ginkgo biloba* extract. Cellular and Molecular Life Sciences CMLS, **60**(9):1779-1792.

Archana, R. and Namasivayam, A. (1999). Antistressor effect of *Withania somnifera*. J. Ethnopharmacol., **64**(1):91-93.

Arnsten, A. F. (2009). Stress signalling pathways that impair prefrontal cortex structure and function. Nature Rev. Neurosci., **10**(6):410-422.

Azwan, K.; Firdous, J.; David, P. R.; Sari, D. K. and Muhammad, N. (2023). Diets that have potential to stimulate the hypothalamic-pituitary-adrenal (HPA) axis in Sprague Dawley rats. Sumatera Med. J., **6**(2):77-92.

Baur, J. A. and Sinclair, D. A. (2006). Therapeutic potential of resveratrol: The *in vivo* evidence: Nat. Rev. Drug Discov., **5**(6):493-506

Bellingrath, S. and Kudielka, B. M. (2017). Biological pathways to stress-related disease vulnerability in educators. Educator stress: An Occupational Health Perspective, pp:77-100.

Bhattacharya, S. K.; Bhattacharya, D.; Sairam, K. and Ghosal, S.(2000). Anxiolytic-antidepressant activity of *Withania somnifera* glycowithanolides: An experimental study. Phytomedicine, **7**(6):463-469.

Bloch, M. H. and Hannestad, J. (2012). Omega-3 fatty acids for the treatment of depression: Systematic review and meta-analysis. Mol. Psychiatry, **17**(12):1272-1282.

Block, K. I. and Mead, M. N.(2003). Immune system effects of echinacea, ginseng, and astragalus: A review. Integrative Cancer Therapies, **2**(3):247-267.

Bottiglieri, T.; Laundy, M.; Crellin, R.; Toone, B. K.; Carney, M. W. and Reynolds, E. H.(2000). Homocysteine, folate, methylation, and monoamine metabolism in depression. J. Neurol. Neurosurg. Psychiatry., **69**(2):228-232.

Chandrasekhar, K.; Kapoor, J. and Anishetty, S.(2012). A prospective, randomized double-blind, placebo-controlled study of safety and efficacy of a high-concentration full-spectrum extract of Ashwagandha root in reducing stress and anxiety in adults. *Indian* J. Psychol. Med., **34**(3):255-262.

Charmandari, E.; Tsigos, C. and Chrousos, G.(2005). Endocrinology of the stress response. Annu. Rev. Physiol., **67**:259-284.

Cho, W. C. and Leung, K. N. (2007). *In vitro* and *in vivo* immunomodulating and immunorestorative effects of *Astragalus membranaceus*. J.Ethnopharmacol., **113**(1):132-141.

Chrousos, G. P. and Gold, P. W. (1992). The concepts of stress and stress system disorders: Overview of physical and behavioral homeostasis. JAMA, **267**(9):1244-1252.

Coppen, A. and Bolander-Gouaille, C.(2005). Treatment of depression: Time to consider folic acid and vitamin B12. J. Psychopharmacol., **19**(1):59-65.

Darbinyan, V.; Kteyan, A.; Panossian, A.; Gabrielian, E.; Wikman, G. and Wagner, H.(2000). *Rhodiola rosea* in stress induced fatigue: A double-blind cross-over study of a standardized extract SHR-5 with a repeated low-dose regimen on the mental performance of healthy physicians during night duty. Phytomedicine, **7**(5):365-371.

David, V.; Gregoriè, K.; Andreja, E.; Saša, È.; Katja, G. and Vita, D.(2023). Genetic polymorphisms in oxidative stress and inflammatory pathways as potential biomarkers in Alzheimer's disease and dementia. Antioxidants, **12**(2):316.

de Kloet, E. R.; Joëls, M. and Holsboer, F. (2005). Stress and the brain: From adaptation to disease. Nature Rev. Neurosci., **6**(6):463-475.

Dhabhar, F. S.(2014). Effects of stress on immune function: The good, the bad, and the beautiful. Immunologic Research, **58**(2-3):193-210.

Di Carlo, G.; Mascolo, N.; Izzo, A. A. and Capasso, F. (1999). Flavonoids: Old and new aspects of a class of natural therapeutic drugs. Life Sciences, **65**(4):337-353.

Emilio, E. R. R.; José, Y. and Rigoberto, S. (2020). Fisiología del estrés y suintegración al sistemanervioso y endocrino, Reviews, **32**:61-70.

Eugeny, Y. G. and Natalia, V. Z. (2019). Cellular stress and general pathological processes. Curr. Pharm. Des., **25**(3):251-97.

Felipe, B. A.; Graziano, P. and Helena, M. T. B. (2021). The role of HPA axis and allopregnanolone on the neurobiology of major depressive disorders and PTSD. Int. J. Mol. Sci., **22**(11):5495.

Freeman, M. P.; Hibbeln, J.R.; Wisner, K. L.; Davis, J.M; Mischoulon, D.; Peet, M.; Keck, Jr, P. E.; Marangell, L. B.; Richardson, A.J .; Lake, J. and Stoll, A. L. (2006). Omega-3 fatty acids: Evidence basis for treatment and future research in psychiatry. J. Clin. Psychiatry, **67**(12):1954.

Gareau, M.G.; Silva, M.A. and Perdue, M. H. (2008). Pathophysiological mechanisms of stress-induced intestinal damage. Curr. Mol. Med., **8**(4):274-81.

Goldstein, D. S. and Kopin, I. J. (2010). Evolution of concepts of stress. Stress, **13**(2):175-185.

Grosso, G.; Pajak, A.; Marventano, S.; Castellano, S.; Galvano, F. and Bucolo, C. (2014). Role of omega-3 fatty acids in the treatment of depressive disorders: A comprehensive meta-analysis of randomized clinical trials. PloS One, **9**(5).

Herman, J. P. and Cullinan, W. E. (1997). Neurocircuitry of stress: Central control of the hypothalamo-pituitary-adrenocortical axis. Trends in Neurosciences, **20**(2):78-84.

Hinds, J.A. and Edwin, R.S. (2022). The role of the hypothalamus-pituitary-adrenal (HPA) axis in test-induced anxiety: Assessments, physiological responses, and molecular details. Stresses, **2**(1):146-55.

Jayasinghe, S. U.; Lambert, G. W.; Torres, S. J.; Lambert, E. A.; Eikelis, N. and Turner, A. I. (2016). Hypothalamo-pituitary adrenal axis and sympatho-adrenal medullary system responses to psychological stress were not attenuated in women with elevated physical fitness levels. Endocrine, **51**:369-79.

Juan, M.C; Zhantao, Y. and Agustín, G. R.(2021). Heat stress-mediated activation of immune-inflammatory pathways. Antibiotics, **10**(11):1285.

Juster, R. P.; McEwen, B. S. and Lupien, S. J.(2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav. Rev., **35**(1):2-16.

Kennedy, D. O. and Scholey, A. B.(2003). *Ginkgo biloba*: Effects on memory and cognition. CNS Drugs, **17**(5):325-340.

Kim, H. K.; Choi, S. Y. and Lee, H. Y.(2015). Luteolin prevents lipopolysaccharide-induced neuroinflammation in BV2 microglia. Cell. Mol. Neurobiol., **35**(1):523-531.

Koji, Mizuno; Hiroaki, Sakaue; Keita, Kohsaka; Hidetomo, Takeda; Nobukazu, Hayashi and Takashi, Sato.(2021). An increase in normetanephrine in hair follicles of acne lesions through the sympatho-adrenal medullary system in acne patients with anxiety. J. Dermatol., **48**(8):1281-1285.

Lagouge, M.; Argmann, C.; Gerhart-Hines, Z.; Meziane, H.; Lerin, C. and Daussin, F.(2006). Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. Cell, **127**(6):1109-1122.

Lawrence, T. (2009). The nuclear factor NF-κB pathway in inflammation. Cold Spring Harbor Perspectives in Biology, **1**(6):a001651.

Li, X.; Teng, T.; Yan, W.; Fan, L.; Liu, X.; Clarke, G.; Zhu, D.; Jiang, Y.; Xiang, Y.; Yu, Y.; Zhang, Y.; Yin, B.; Lu, L.; Zhou, X.F. and Xie, P. (2023). AKT and MAPK signallingpathways in the hippocampus revealthe pathogenesis of depression in four stress-induced models. Translational Psychiatry, **13**(1):200.

Liu, Q. Y. and Sun, L. R. (2006). The immunomodulatory and anti-inflammatory effects of Astragalus polysaccharide and its mechanism. Chin. J. Immunol., **22**(5):505-507.

Liu, Y. Z.; Wang, Y. X. and Jiang, C. L. (2017). Inflammation: The common pathway of stress-related diseases. Front. Human Neurosci., **11**:273283.

Lupien, S. J.; McEwen, B. S.; Gunnar, M. R. and Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nat. Rev. Neurosci., **10**(6):434-445.

Maes, M.; Leonard, B. E.; Myint, A. M.; Kubera, M. and Verkerk, R. (2011). The new '5-HT' hypothesis of depression: Cell-mediated immune activation induces indoleamine 2,3-dioxygenase, which leads to lower plasma tryptophan and an increased synthesis of detrimental tryptophan catabolites (TRYCATs), both of which contribute to the onset of depression. Progress in Neuro-Psychopharmacology and Biological Psychiatry, **35**(3):702-721.

Mario, F. J.; Anthony, J. C. and Allan, H. Y.(2022). Neuroendocrine and stress pathways in bipolar disorders. In: Biomarkers in bipolar disorders, Academic Press, 313-330.

Martha, E. W.; Amanda, B.; John, E. L.; Jason, J. B.; Celina, M. J.; Jarl, A. A.; Sarah, E. D. P. and Ashley, M. (2019). Coactivation of SAM and HPA responses to acute stress: A review of the literature and test of differential associations with preadolescents' internalizing and externalizing. Dev. Psychobiol., **61**(7):1079-93.

McEwen, B. S. (2000). The neurobiology of stress: From serendipity to clinical relevance. Brain Res., **886**(1-2):172-189.

McEwen, B. S. and Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease. Annals of the New York Academy of Sciences, **1186**(1):190-222.

Messaoudi, M.; Lalonde, R. and Violle, N. (2011). Assessment of psychotropic-like properties of a probiotic formulation (*Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175) in rats and human subjects. Br. J. Nutri., **105**(5):755-764.

Miller, A.H.; Maletic, V. and Raison, C. L.(2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. Biol. Psychiatry, **65**(9):732-741.

Miller, G. E.; Chen, E. and Zhou, E. S.(2007). If it goes up, must it come down? Chronic stress and the hypothalamic-pituitary-adrenocortical axis in humans. Psychol. Bull., **133**(1):25-45.

Mittal, M.; Siddiqui, M. R.; Tran, K.; Reddy, S. P. and Malik, A. B. (2014). Reactive oxygen species in inflammation and tissue injury. Antioxidants and Redox Signaling, **20**(7):1126-1167.

Morris, M. S.(2008). The role of B vitamins in preventing and treating cognitive impairment and decline. Advances in Nutrition, **3**(6):801-812.

Muir, R. Q.; Klocke, B. J.; Foote, J. B.; Jennings, M.; Molina, P. A.; Kellum, C. E.; Pollock, J. S. and Maynard, C. L.(2022). Early life stress induced hypothalamic-pituitary-adrenal (HPA) axis dysfunction promotes chronicity of experimental colitis in mice. The FASEB Journal, **36**.

Munhoz, C. D.; Lepsch, L. B.; Kawamoto, E. M.; Malta, M. B.; de Sá Lima, L. and Avellar, M. C. W. (2006). Chronic unpredictable stress exacerbates lipopolysaccharide-induced activation of nuclear factor-κB in the frontal cortex and hippocampus *via* glucocorticoid secretion. J. Neurosci., **26**(14):3813-3820.

Olsson, E. M.; von Schéele, B. and Panossian, A. G. (2009). A randomized, double-blind, placebo-controlled, parallel-group study of the standardized extract SHR-5 of the roots of *Rhodiola rosea* in the treatment of subjects with stress-related fatigue. Planta Medica, **75**(2):105-112.

Panickar, K. S. and Anderson, R. A.(2011). Mechanisms and therapeutic effects of high-phenolic foods on neurodegenerative diseases. Adv. Nutr., **2**(4):384-392.

Panossian, A. and Wikman, G.(2010). Evidence-based efficacy of adaptogens in fatigue, and molecular mechanisms related to their stress-protective activity. Curr. Clin. Pharmacol., **5**(3):198-219.

Park, S. J.; Ahmad, F.; Philp, A.; Baar, K.; Williams, T. and Luo, H.(2012). Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. Cell, **148**(3):421-433.

Reay, J. L.; Kennedy; D. O. and Scholey, A. B. (2010). Single doses of panax ginseng (G115) reduce blood glucose levels and improve cognitive performance during sustained mental activity. J. Psychopharmacol., **19**(4):357-365.

Sapolsky, R. M.; Romero, L. M. and Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. Endocrine Rev., **21**(1):55-89.

Selye, H. (1950). Stress and the general adaptation syndrome. Br. Med. J., **1**(4667):1383-1392.

Smith, R. E. and Luo, Y.(2004). Elevation of antioxidant and detoxification enzymes by oxalic acid in rat and mouse tissues. J. Biochem. Mol. Toxicol., **18**(3):131-140.

Spasov, A. A.; Wikman, G. K.;Mandrikov, V. B.; Mironova, I. A. and Neumoin, V. V.(2000). A double-blind, placebo-controlled pilot study of the stimulating and adaptogenic effect of *Rhodiola rosea* SHR-5 extract on the fatigue of students caused by stress during an examination period with a repeated low-dose regimen. Phytomed., **7**(2):85-89.

Su, K. P.; Matsuoka, Y. and Pae, C. U. (2015). Omega-3 polyunsaturated fatty acids in prevention of mood and anxiety disorders. Clin. Psychopharmacol. Neurosci., **13**(2):129-137.

Taylor, J.; Li, Q.; Sreeskandarajan, S.; Budunova, I.; He, Z.; Kang, J.; Gudjonsson, J.E.; Patrick, M.; Lam, C. and Tsoi M. (2022). Roles played by stress-induced pathways in driving ethnic heterogeneity for inflammatory skin diseases. Front. Immunol., **13**:845655.

Thimmulappa, R. K.; Mai, K. H.;Srisuma, S.; Kensler, T. W.; Yamamoto, M. and Biswal, S. (2002). Identification of Nrf2-regulated genes induced by the chemopreventive agent sulforaphane by oligonucleotide microarray. Cancer Res., **62**(18):5196-5203.

Ude, C.; Schubert-Zsilavecz, M. and Wurglics, M. (2013). *Ginkgo biloba* extracts: A review of the pharmacokinetics of the active ingredients. Clin. Pharmacokinetics, **52**(9):727-749.

Weinmann, S.; Roll, S.; Schwarzbach, C.; Vauth, C. and Willich, S. N. (2010). Effects of *Ginkgo biloba* in dementia: Systematic review and meta-analysis. BMC Geriatrics, **10**:14.

Xu, H.; Yu, X.; Qu, S. C. and Sui, D. Y.(2014). Luteolin protects against collagen-induced arthritis in rats by inhibiting angiogenesis and pro-inflammatory cytokines. Inflammation, **37**(6):2041-2048.

Citation **Sara Khan, MohammadIrfan Khan, Badruddeen, Juber Akhtar, Mohammad Ahmad, Nitin Ranjan Gupta, Anas Islam and Asad Ahmad (2023). Stress: Pathological pathways and role of nutraceuticals in its management. J. Phytonanotech. Pharmaceut. Sci., 4(2):9-15. http://dx.doi.org/10.54085/jpps.2024.4.2.2.**