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The Immune Modulatory Effects of Yoga: Mechanisms and Health Implications Under Stress

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Abstract: Yoga, an ancient practice integrating physical postures, breath control, and meditation, has garnered increasing attention for its potential to modulate immune responses, particularly under conditions of stress. Chronic stress is known to disrupt immune function through the activation of the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-adrenal-medullary (SAM) system, and the hypothalamic-pituitary-gonadal (HPG) axis, leading to immune cell dysregulation and altered cytokine production. By influencing these pathways, yoga can mitigate the adverse effects of stress on the immune system. This review explores the mechanisms by which yoga exerts its immune-modulatory effects, including the reduction of stress hormones, the regulation of inflammatory cytokines, the enhancement of parasympathetic nervous system activity, and the improvement of immune cell function. Additionally, it examines the health implications of these effects, highlighting yoga's role in enhancing immune resilience and reducing the risk of stress-related diseases. Evidence from clinical studies and trials is synthesized to provide a comprehensive understanding of how yoga can be integrated into health management strategies to support immune health and overall well-being.

Keywords: Yoga, Immune modulation, Immune cell function, Health benefits, Stress management, Cytokine

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Introduction

Stress is a common condition, arising from physical threats or psychological distress, which triggers a range of chemical and hormonal reactions in the body. In mammals, these responses lead to increased delivery of oxygen and glucose to the heart and large skeletal muscles. This physiological change supports adaptive behaviors like the "fight or flight" response (Seal and Turner,2021; Kaluza, 2022). Consequently, various body systems, including the autonomic, cardiovascular, gastrointestinal and immune systems, may be impacted as part of this adaptive response to stress (zafar *et al*., 2021). The immune system is a network of glands, nodes, and organs that protect the body from bacteria, viruses, fungi, and other harmful organisms. To function optimally, the immune system requires a steady supply of energy and nutrients (Saghiv and Sagiv, 2020). However, toxins in the environment and in our food, poor diet, lack of or excessive exercise, and stress can all negatively impact its performance, leading to a decline in its effectiveness.

Elliot and Eisdorfer's taxonomy classifies stressors into five categories based on duration and course. Acute time-limited stressors involve short challenges like public speaking or mental arithmetic. Brief naturalistic stressors are short-term challenges that occur at specific life points, such as academic exams. Stressful event sequences arise from life-changing events, such as losing a spouse or experiencing a natural disaster, which lead to a series of challenges with an eventual end (Elliott and Eisdorfer, 1982; Alharthi *et al*., 2019). Chronic stressors pervade a person's life and require significant adjustments, such as living with a permanent disability or being a refugee. Distant stressors are past traumatic experiences, like child abuse or war trauma, that have long-lasting impacts on mental and physical health.

The immune system, comprising glands, nodes, and organs, protects the body from bacteria, viruses, fungi, and other harmful organisms. It needs a constant supply of energy and nutrients to function optimally (Pothiraj *et al*., 2024). Environmental toxins, poor diet, insufficient or excessive exercise, and stress can negatively impact the immune system, leading to a decline in its effectiveness. When the immune system does not function at optimal levels, the body becomes more susceptible to health problems. Stress-induced immune dysregulation has been shown to have significant health consequences, including reduced immune response to vaccines, delayed wound healing, reactivation of latent herpes viruses such as Epstein–Barr virus (EBV), and an increased risk of more severe infectious diseases (Dymanowska-Dyjak *et al*., 2024).

Bidirectional Signals: How Stress Influences Immune Responses

Bidirectional communication between stress and immune responses highlights the complex interplay between the nervous and immune systems. Stress can significantly impact immune function through various mechanisms. For instance, stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of cortisol, which suppresses immune cell activity (Fig. 1). Additionally, the autonomic nervous system releases catecholamines during stress, altering immune cell distribution and often leading to immunosuppression. Stress also influences cytokine production, typically shifting the balance toward pro-inflammatory cytokines, which can contribute to inflammatory and autoimmune conditions (Maier, 2003). Conversely, the immune system can affect stress responses. Immune cells release cytokines that signal the brain, influencing neurotransmitter systems and potentially affecting mood and behavior (Fig. 1). Direct neural routes, such as the vagus nerve, facilitate communication between the brain and immune system, allowing the brain to modulate immune function (Miller *et al*., 2013; Bjorklund *et al*., 2024). This bidirectional interaction has significant health implications, contributing to chronic diseases, mental health disorders, and increased susceptibility to infections.

How does stress "get inside the body" to affect the immune response? The immune system, a network of glands, nodes, and organs, protects the body from bacteria, viruses, fungi, and other harmful organisms. It requires a constant supply of energy and nutrients to maintain optimal

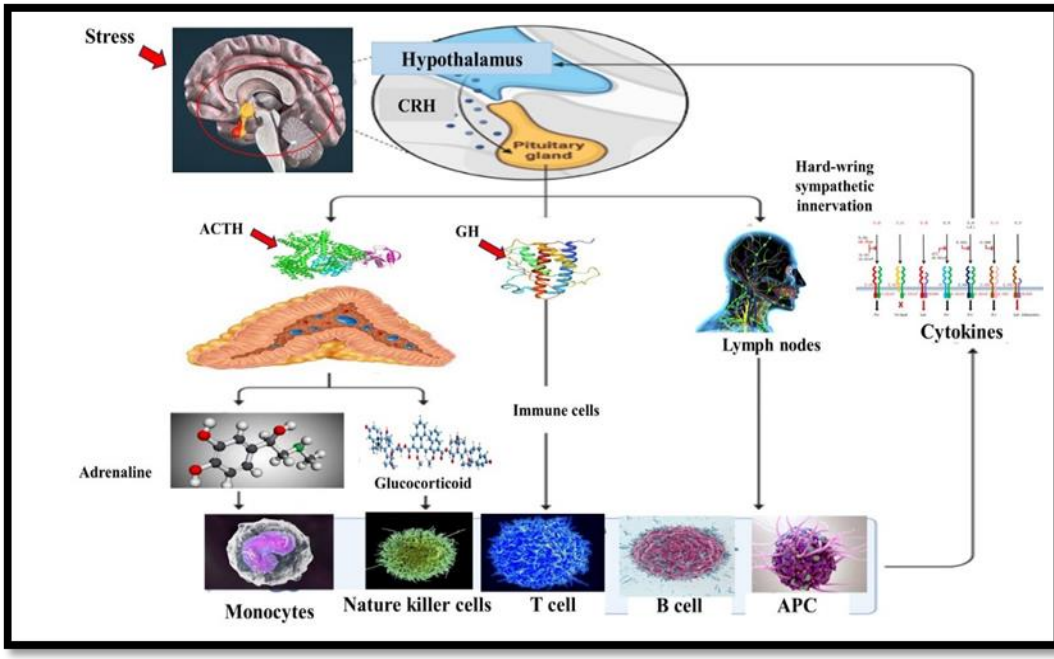

Fig. 1: Bidirectional communication between stress Immune System Interactions Under Stress.

function. However, environmental toxins, poor diet, lack of or excessive exercise, and stress can adversely impact the immune system, leading to a decline in its effectiveness (Miller *et al*., 2017). Stress affects the immune system through a complex network of bidirectional signals involving the nervous, endocrine, and immune systems. The key mediators of these interactions are neurotransmitters, neuropeptides, hormones, and cytokines.

Stress triggers neuroendocrine changes that significantly impact immune responses. When the body perceives stress, it activates the hypothalamic-pituitary-adrenal (HPA) axis, starting with the release of Corticotropin-Releasing Hormone (CRH) from the hypothalamus. CRH stimulates the pituitary gland to secrete Adrenocorticotrophic Hormone (ACTH), which in turn prompts the adrenal glands to produce cortisol (Fig. 2) (Herman *et al*., 2016). Elevated cortisol levels have multiple effects on the immune system, often leading to immunosuppression by inhibiting the activity and proliferation of immune cells like T-helper (Th) cells.

Additionally, stress influences the autonomic nervous system (ANS), particularly through the sympathetic nervous system, which releases catecholamines such as adrenaline and noradrenaline. These neurotransmitters can modulate immune responses by affecting the production and activity of cytokines, such as Interferons (IFN), Interleukins (IL), and Tumor Necrosis Factor (TNF). Chronic stress can shift the cytokine balance towards a pro-inflammatory state, which is mediated by Nuclear Factor (NF) pathways, contributing to inflammation and autoimmune disorders (Pondeljak and Lugovic-Mihiic, 2020).

Yoga is proposed to mitigate the adverse effects of stress on the immune system through several mechanisms. It may reduce the activity of the HPA axis, thereby lowering cortisol levels, and modulate the ANS by enhancing parasympathetic activity while reducing sympathetic drive (Mishra and Mishra, 2024). This balance can lead to a reduction in stress-induced cytokine production and promote a more anti-inflammatory cytokine profile. Yoga also positively affects the cardio-vascular system (CVS), enhancing overall health

Corticotropin	• Activates macrophages; inhibits IL-1 and IL-6 releasing hormone production
Adrenocorticotrophic Hormone	• Inhibits IFN-γ and IgG production; blocks macrophage activation by IFN-γ; amplifies B cell proliferation
Growth Hormone	• Activates macrophages; enhances H2O2 production
Gonadotropin	• Increases IL-2 receptor (IL-2R) expression; promotes T and B cell proliferation; enhances serum Ig hormone levels
Prolactin	• Increases T-cell proliferation, IFN-γ, IL-2R, and macrophage function
Thyroid-stimulating hormone	• Increases IL-2, GM-CSF, and Ig production
Luteinizing hormone	• Enhances IL-2-stimulated T-cell production
Oxytocin and vasopressin	• Increase IFN-γ production
Cortisol	• Inhibits IFN-γ, IL-2, IL-6, and TNF-α production; enhances IL-4 and TGF-β production; enhances immune cell expression of IL-1, IL-2, IL-6, and IFN-γ receptors
Estrogen	• Increases T-cell proliferation; enhances activity of the IFN-γ gene promoter
Progesterone	• Increases IL-4 production; enhances CD30 expression
Adrenaline	• Inhibits IL-1 and IL-2 production
Testosterone	• Increases IL-10 production
Thyroxine	• Activates T cells

Fig. 2: Hormones effect on Immune Response and cytokines.

and further supporting immune function. Through these mechanisms, yoga helps maintain a healthier immune response and mitigates the negative impacts of stress (Wadikar, 2019).

Regulation of Neuroendocrine System by Cytokines

Cytokines and their receptors are expressed centrally in the hypothalamus and anterior pituitary cells, where they play crucial roles in regulating pituitary development, cell proliferation, and hormone secretion (Fig. 3). These molecules act as immunoneuroendocrine modulators, transmitting signals that link stress (both peripheral and central) and inflammation with the hypothalamo-pituitary axes (Arora and Bhattacharjee, 2008; Konsman , 2023).

The first cytokine demonstrated to have neuroendocrine effects was interferon, which has been shown to increase steroidogenesis upon administration. Subsequently, several other cytokines such as IL-1, IL-2, IL-6, IFN-β, IFN-γ, leukemia inhibitory factor (LIF), and tumor necrosis factor-alpha (TNF-α) have been found to elevate plasma adrenocorticotropic hormone (ACTH) and glucocorticoid levels in both laboratory animals and humans (Arora and Bhattacharjee, 2008). IL-1, IL-2, IL-6, and TNF-α directly stimulate pituitary cells to produce ACTH and β-endorphins, contributing to the activation of the hypothalamo-pituitary-adrenal (HPA) axis. Additionally, IFN-γ upregulates glucocorticoid receptor expression in macrophages during immune system activation, demonstrating the bidirectional interaction between cytokines and the neuroendocrine system, where glucocorticoids exert their effects on immune cells (Arora and Bhattacharjee, 2008).

This intricate network of signaling pathways highlights the close relationship between the immune and neuroendocrine systems, with cytokines serving as key mediators in coordinating responses to stress and inflammation.

Effect of acute and chronic stress on immune System

The impact of stress on immune function is governed by two fundamental concepts. Firstly,

α-Endorphin	• Inhibits immunoglobulin production
Acetylcholine	• Stimulates T and NK cells and increases IFN-γ production
Angiotensin II	• Enhances IFN-γ production; proliferation of splenic lymphocytes; stimulates TNF-α, TGF-β, MCP-1
β-Endorphin	• Inhibits T cell proliferation; enhances IFN-γ production and NK cell-mediated cytotoxicity
Catecholamines	• Increase Ig production, inhibit T cells and NK cells in peripheral circulation
DHEAS	• Enhances IFN-γ and T-cell proliferation
Histamine	• Inhibits IL-12, TNF, and IFN-α and enhances IL-10 production
Inhibin	• Facilitates TGF-β-mediated immunosuppression in thymocytes
Activin	• Inhibits TGF-β-mediated immunosuppression in thymocytes
IGF1 and IGF2	• Enhances PBMC proliferation
Melatonin	• Enhances IL-1, IL-2, IL-6, TNF-α, and IFN-γ production
Met encephalin	• Enhances antigen-specific proliferation
Nerve growth factor	• Increases B-cell proliferation, IL-6 production, IL-2R expression, and IgA synthesis
Prostaglandin E2	• Inhibits IL-2 production
Serotonin	• Inhibits T cell proliferation, IFN-γ-induced HLA class II expression, increases NK cytotoxicity
Somatostatin	• Inhibits T-cell proliferation, IFN-γ production, Ig production
Substance P	• Increases T cell proliferation and IFN-γ production, causes MHC class II upregulation by IFN-γ
VIP	• Inhibits T cell proliferation and IL-12, enhances IL-5 and cAMP production

Fig. 3: Effect of various neuroendocrine factors on immune responses and cytokine levels.

chronic stress, often maladaptive in nature, typically harbors a significant psychological component, as physical stressors are swiftly resolved, while psychological and social strains may persist for prolonged durations. Modern neuroimaging techniques shed light on the intricate relationships between neural networks and cognitive, emotional, and mnemonic processes, emphasizing the close interplay between the mind and brain. Secondly, the intricate network of functional neuroendocrine-immune pathways underscores the intimate connection between the brain and the immune system (Schneiderman and Baum, 2018).

Stress affects immune domains, distinguishing between natural and specific responses, in alignment with the stressor's duration—acute versus chronic. Acute and time-limited stressors prompt an adaptive redistribution of immune cells, preparing the natural immune system for potential infection or injury. The efficiency of this adaptive process is optimized when the excess energy from fight-or-flight responses isn't channeled towards stress-related immune alterations. Consequently, acute stress boosts parameters of natural immunity with minimal time and energy investment required to combat invaders. Conversely, brief stressors, such as examinations, alter the potency of specific immunity, skewing it from cellular (Th1) immunity towards heightened humoral (Th2) immunity (Arora and Bhattacharjee, 2008; Schneiderman and Baum, 2018) .

Yoga as a Catalyst for Enhancing Immune Resilience against Stressors

The practice of yoga offers a proactive approach to managing stress, potentially mitigating the constant activation of the endocrine system and thereby enhancing immune function. Various psychoimmunological studies employing diverse strategies such as hypnosis, relaxation techniques, exercise, and cognitive behavioral therapies have demonstrated positive changes in perceived coping and self-efficacy (Jindani, 2014). Ancient cultures, particularly those of China and India, developed exercises with profound healing effects, notably Qi Gong and yoga, each characterized by meditative qualities, focused breathwork, and deliberate movement (Scrimgeour, 2023).

Yoga, deeply rooted in ancient Indian culture, encompasses physical, mental, and spiritual development. Unlike conventional exercise programs, yoga emphasizes the union of body, mind, and spirit. Hatha Yoga, the most commonly practiced form, comprises physical postures (asanas), breathing exercises (pranayama), and meditation (dhyana). Asanas stretch and strengthen the body while massaging internal organs, rejuvenating the nervous system, and enhancing joint mobility. Pranayama techniques regulate breathing, promoting slower and more refined respiration. Ultimately, yoga aims to cultivate tranquility of the mind (Sarkar, 2023).

Scientifically less replicable but widely studied for its stress-relieving effects, yoga has been associated with a myriad of benefits, including improved well-being, relaxation, concentration, self-confidence, and interpersonal relationships, as well as reduced irritability and increased attentiveness (Liskey, 2020). While scientifically rigorous studies are ongoing, many researchers report substantial benefits of yoga in alleviating stress and its effects, making it a promising approach for stress management. Yoga postures, particularly those involving twisting and compression, stimulate and rejuvenate immune organs and channels. Specific poses, such as inversions, forward bends, chest and lung openers, and restorative poses, offer targeted benefits for immune function. For instance, poses like Kurmasana (tortoise pose) support the thymus gland, while inversions and forward bends enhance sinus flow and lung function. Restorative yoga poses provide healing benefits during periods of low energy. Recognized even in the Western world, yoga serves as a complementary therapy for managing symptoms in various conditions, including cancer survivorship, aiding in the management of depression, anxiety, insomnia, pain, and fatigue (Arora and Bhattacharjee, 2008).

Yoga practice exerts a profound influence on the hypothalamus, particularly inhibiting the posterior or sympathetic area, thereby optimizing the body's responses to stress while restoring autonomic regulatory reflex mechanisms (Tolahunase *et al.*, 2021). While the activity of the parasympathetic system may increase or remain unaffected, yogic techniques are known to modulate emotional expressions by inhibiting fear, aggressiveness, and rage centers while stimulating rewarding centers in the brain, inducing a state of bliss and pleasure. Consequently, individuals practicing yoga and meditation exhibit lower anxiety, heart rate, respiratory rate, blood pressure, and cardiac output compared to controls (Ambhore and Joshi, 2009).

The impact of yogic practices on the hypothalamus extends to the anterior pituitary gland, leading to reduced production of adrenocorticotropic hormone (ACTH) and subsequently cortisol synthesis from the adrenal glands. This decrease in cortisol levels has been consistently observed across various studies. Additionally, Qi Gong training, a Chinese energy system incorporating meditative techniques, has shown to elevate CD4 T cells and the CD4/CD8 cell ratio while reducing anxiety and plasma levels of ACTH, cortisol, and aldosterone (Dong *et al.*, 2016). Overall, these findings underscore the ability of yoga to mitigate stress responses through multifaceted neuroendocrine pathways.

While comprehensive clinical trials evaluating the direct impact of Yoga on the immune system remain limited, numerous studies on yogic practices and similar techniques have demonstrated promising outcomes in immune-mediated disorders. For instance, HIV-positive individuals, participating in a ten-week cognitive behavioral stress management (CBSM) intervention, exhibited improvements in mood, with reductions in urinary cortisol and norepinephrine levels alongside increased serum Dehydroepiandrosterone-sulphate (DHEA-S) and testosterone levels. These changes in hormone production correlated with short-term increases in IgG antibody titers to herpes viruses and longer-term alterations in lymphocyte subpopulations, indicating potential immune system reconstitution. Further analysis revealed enhanced immune system reconstitution markers, such as CD4+CD45RA+CD29+ lymphocytes, at follow-up compared to controls (Arora and Bhattacharjee, 2008). These findings suggest that reductions in cortisol output and depressed mood during CBSM may mediate its effects on immune system reconstitution. The underlying mechanisms likely involve the modulation of the hypothalamic-pituitary-adrenal (HPA), hypothalamic-pituitary-gonadal (HPG), and sympathetic-adrenal-medullary (SAM) axes, with consequential impacts on immune function (Zefferino *et al*., 2021).

Meditation practices have been associated with increased melatonin levels and decreased serotonin levels. Studies have demonstrated a significant relationship between mind-body therapies, such as Transcendental meditation and visual imagery, and patient recovery from dermatomyositis, potentially mediated by influences on the humoral immune system. Cancer patients often experience compromised immune function, with immune factors being used to predict disease progression. Research has shown that lower distress levels predict longer disease-free intervals in breast cancer patients, while decreased natural killer (NK) cell activity predicts recurrence. Stress levels have been linked to diminished NK cell lysis, reduced response of NK cells to recombinant interferon-gamma (IFN-γ), and decreased proliferative response of peripheral blood lymphocytes in breast cancer patients post-surgery (Angka, 2021).

In terms of immune outcomes, the study found no changes in the numbers of lymphocyte subtypes (NK, T, or B cells), or overall lymphocyte numbers. However, post-intervention reductions in levels of interferon-gamma (IFN-γ), interleukin-10 (IL-10) – both associated with cancer-associated depression – and a notable increase in interleukin-4 (IL-4) levels were observed. IL-4, known for its role in growth inhibition and apoptosis in breast cancer cell lines, showed a 3-4-fold increase post-intervention (Carlson *et al*., 2003). While the extent to which these immunological changes translate into tangible improvements in health outcomes such as the incidence, severity, or duration of infectious or malignant diseases remains unclear, the preliminary evidence is promising. It is concluded that stress negatively impacts the immune system, making individuals more vulnerable to diseases. Managing stress, particularly chronic or long-term stress, through various relaxation techniques may help people overcome other co-morbidities associated with diseases and lead to a better quality of life even during stressful periods (Bock *et al*., 2024).

Conclusion

The present review underscores the profound impact of stress on the immune system, particularly highlighting the detrimental effects of chronic or long-term stress, which can heighten susceptibility to various diseases. It emphasizes the pivotal role of relaxation techniques in mitigating stress levels and enhancing overall well-being. While these techniques may not directly alter immune cell counts, they have demonstrated the ability to modulate cytokine levels associated with immune function. Notably, reductions in stress-related cytokines such as IFN-γ and IL-10, coupled with increases in immune-stimulatory cytokines like IL-4, suggest a favorable shift in immune activity. Integrative approaches that combine stress management techniques with conventional medical treatments hold promise in optimizing immune function, especially in individuals grappling with immune-related disorders like cancer. However, the review also underscores the need for further research to unravel the precise mechanisms underlying the immunological effects of relaxation techniques and their translation into tangible health benefits. This includes comprehensive investigations into the incidence, severity, and duration of infectious or malignant diseases in individuals practicing these techniques. In essence, while the preliminary evidence is encouraging, ongoing research endeavors are essential to fully harness the potential of relaxation techniques in bolstering immune health and overall quality of life.

Ethical Statement

This review paper adheres to the ethical guidelines for research and publication. The manuscript does not involve any studies with human participants or animals.

Author Contributions

Each author contributed equally to the research design, data analysis and manuscript preparation. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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