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The Effects of Mindfulness-Based Therapies on Epigenetic Modifications and Gene Expression: A Review

I.U. KUMARAGE*[1],
[1]*Department of Molecular Biology & Biotechnology, Faculty of Science, University of Peradeniya, Sri Lanka*
**Corresponding Author: I. U. Kumarage*

ABSTRACT: Mindfulness is the conscious awareness of the present moment, with an open and non-judgmental mind. In recent years, mindfulness meditation practices have seen a significant expansion, gaining popularity, with a marked increase in research dedicated to exploring its health effects. These mindfulness-based therapies (MBT) include a range of practices, encompassing both sitting methods (mindfulness meditation, Vipassana, Zen), and moving approaches (Yoga, Tai Chi, and Qigong). Epigenetic mechanisms provide a way to control gene expression without changing the underlying DNA sequence, enabling the genome to adjust its functions to varying environmental conditions. Moreover, these changes in epigenetics and gene expression can serve as markers of different biological processes associated with health and diseases. Stress, stress-related disorders, cancers, and many other diseases have been often associated with changes in epigenetic mechanisms, and different MBT acts as promising additions to conventional therapeutic interventions, preventing diseases and improving health. Recent research studies have focused on unraveling the molecular and epigenetic mechanisms influenced by different MBTs, as these practices show positive outcomes through physiological and biochemical activities. This review summarizes the recent developments related to the molecular and epigenetic effects of Mindfulness therapies, emphasizing their clinical advantages in reducing the burden of various diseases.

Keywords: – Epigenetic Markers, Inflammatory Pathway, Meditation, Stress, Therapeutic Effect

I. INTRODUCTION

Meditation has been employed as a spiritual and therapeutic technique for over 5,000 years [1]. Various philosophical, spiritual, and psychological frameworks emphasize how the quality of consciousness profoundly influences the maintenance and enhancement of one's state of well-being [2]. Mindfulness is known as the ability to live with an open and nonjudgmental awareness toward all experiences in the present moment. Also, it is widely recognized for its positive impact on both mental and physical health, mitigating negative emotions, and enhancing an individual's capacity to adapt to adverse or stressful situations [3,4]. Thus, lifestyle therapies, such as MBT, are receiving more and more attention [5]. MBT, deeply rooted in Eastern traditions, has found its way into Western lifestyles and clinical practices. Presently, nearly 20% of the population actively engages in various forms of MBT [6]. Metacognitive awareness is strengthened through mindfulness training, allowing individuals to alter their perspective and reduce emotional reactivity [7].

Mindfulness Training encompasses practices such as meditation, yoga, Tai Chi, and various physical and mental activities. Growing evidence suggests that these practices are becoming promising complementary methods to conventional therapeutic interventions [8,9]. Numerous studies indicate that engaging in MBTs has the potential to alleviate symptoms associated with stress in various health conditions. These conditions range from psychological disorders such as mood and anxiety disorders to inflammatory diseases, aging, and even cancer. It is likely that alterations in the level of humoral, immune, and neurological factors may play a role in related outcomes. However, the molecular mechanisms driving the positive effects of MBT are not well understood [9]. Analysis of peripheral human tissues, including blood and saliva, has revealed that engaging in different forms of meditation practices can lead to a reduction in the stress hormone cortisol levels and reactive oxygen species (ROS), while also promoting the production of anti-inflammatory cytokines, endorphins, and neurotrophins [10,11]. Furthermore, some researchers have explored the influence of meditation on these effector molecules back to alterations in the expression of associated genes and more recently, to specific mechanisms that control gene expression [12,13]. Therefore, the above findings suggest a fascinating concept that MBT may exert its influence on the body through epigenetics [9].

The term 'epigenetics' refers to the set of heritable biochemical changes that control gene expression without changing the DNA sequence [14]. Environmental and lifestyle factors profoundly influence the functioning of genomes, interacting with genetic information. And epigenetic modifications form the molecular basis of gene-environment interactions, ultimately influencing the range of human phenotypes [9, 4]. Epigenetic modifications can be classified into 3 major categories: DNA methylation, histone modification, and small non-coding RNAs. DNA methylation involves the addition of methyl groups onto cytosines, which induces chromatin condensation, making the DNA inaccessible to the transcriptional machinery, ultimately resulting in the silencing of gene expression. The modification of histone through acetylation loosens chromatin, allowing for increased gene activity. Conversely, histone deacetylation tightens chromatin, establishing closed domains with suppressed gene activity. The stability and accessibility of mRNAs to the translation machinery can be regulated by microRNAs, which can affect the synthesis of proteins [15].

As well as phosphorylation of the cytosine-guanine dinucleotide units (CpG islands) is another type of modification, and these CpG sites are the major sites of these epigenetic changes [16]. These epigenetic alterations can potentially function as indicators of various biological processes in health and illnesses. Similarly, MBTs have been observed to induce epigenetic effects, highlighting their direct impact on DNA and chromosome structure [17]. This review aims to explore the epigenetic impacts of different MBTs, emphasizing their significance as complementary approaches alongside traditional medical interventions, and provide a summary of the recent studies on this aspect.

II. MINDFULNESS

Mindfulness is the practice of being fully present in the current moment with a non-elaborative and non-judgmental focus. And it involves recognizing and welcoming every thought, feeling, and sensation in the field of attention as they are [4]. In the practice of mindfulness, the cycle of getting distracted and then refocusing your attention is a continual occurrence. The goal is to enhance consciousness of the present moment, progressing towards subtler layers and strengthening the stability of attention [18]. The term mindfulness, originating from the Pali word sati (Sanskrit: smrti), essentially signifies the practice of "remembering." In the context of Buddhism, it refers to maintaining a sharp mental concentration on an object of consciousness at any given moment [19]. Mindfulness is like a miracle that instantly brings our distracted minds back, allowing us to fully experience each passing minute of our life [20].

In Buddhist contexts, mindfulness is one aspect of a comprehensive system of integrated spiritual teachings, practices, and beliefs meant to help the practitioner gain a profound understanding of suffering's nature and cause, as well as achieve spiritual liberation. In contrast, mindfulness practices have been adopted in Western secular settings as a means of treating individuals facing diverse physical and psychological issues, and existing research predominantly centers on evaluating its efficacy in improving these conditions and exploring the mechanisms that drive such improvements [18]. In Western cultures, there has been a growing trend of embracing it [21], and as a result, they have integrated a wide range of mindfulness practices originating from Eastern traditions to increase self-awareness and promote better health [9]. In Western approaches, there is typically less focus on concepts like 'non-self' and 'impermanence' compared to the traditional teachings of Buddhism [20].

III. DIFFERENT MINDFULNESS PRACTICES

It is believed that mindful states of awareness can be incorporated into everyday activities and are not limited to formal meditation practice. Furthermore, as mindfulness is regarded as a natural attribute of human consciousness, individuals who lack formal training are believed to display varying degrees of mindfulness [2]. Widely used mindfulness practices include a range of meditation techniques, encompassing seated practices such as mindfulness meditation, Vipassana, and breathing attention, as well as moving practices such as yoga, Tai Chi, and Qigong. All of these have as their common objective reaching a mental state of silence, which has favorable effects on emotional control and well-being [9]. All across the world, these therapies are used to improve health and disease prevention, and as a supplement to conventional medical treatments [17].

Static methods such as mindfulness meditation, vipassana, and breathing techniques are well-known ways to cultivate mindfulness in everyday life [22]. In mindfulness meditations, attentional control is acquired by directing focus toward internal events (such as breath, thoughts, emotions, bodily sensations) and external factors (such as sights and sounds) in the present moment, all while cultivating a nonjudgmental attitude [21]. This group of mindfulness meditation includes Mindfulness-Based Stress Reduction (MBSR), Mindfulness-Based Cognitive Therapy (MBCT), Zen Buddhist meditation, and other mindfulness meditation practices [1]. In breathing techniques, attention is directed towards the breathing rate, rhythm, and volume. Breathing techniques

are frequently employed to reduce physiological reactions to stress, potentially by enhancing the parasympathetic response [23].

Movement-based meditations like Yoga, Tai Chi, and Qigong are considered a fusion of mindfulness techniques and physical activities [22]. Yoga has a long history that stems from ancient Indian philosophy, spanning thousands of years. The conventional practice of yoga includes the practice of physical postures (Asanas), breath control techniques (Pranayama), and meditation exercises (Dyana), and these components encourage mental, physical, and spiritual harmony [21]. Asana enhances relaxation, flexibility, and heightened body awareness, and Pranayama centers around employing breathing techniques to attain a state of mental peace. The practice of Dhyana or meditation promotes mental stability, emotional balance, and an overall improvement in the quality of life [24]. Tai chi and qigong represent ancient Chinese therapeutic practices, which involve a combination of physical movements, controlled breathing, and attentional training to alleviate symptoms of diseases and promote overall health. While these activities and yoga have many similarities, one key difference is that these practices emphasize physical movement as a crucial element [21]. Tai chi involves gradual body postures that flow continuously from one to the next, improving physical alignment, flexibility, mental focus, and well-being [25]. Qigong and tai chi differ primarily in that tai chi is a martial art that provides self-defense and is externally focused, whereas qigong cannot provide self-defense and is an internally focused technique [26].

IV. EPIGENETICS

Epigenetic mechanisms provide a means to regulate gene activity independently of changes to the DNA sequence, enabling genes to adjust to varying environmental conditions [27]. Epigenetic information can be either passed down from one generation to the next or acquired during an individual's lifetime. Epigenetic alterations may be triggered by exposures occurring before and during pregnancy, affecting both parental germ cells and the developing fetus. In addition to this, an individual's lifestyle or environment may also alter their epigenetic makeup [15]. Epigenetic mechanisms, including DNA modifications, histone modifications, and microRNAs, refer to biochemical changes occurring at the DNA level [28], and they are subjected to spatial and temporal regulation [22]. An important feature of these modifications is their potential for dynamic reversibility. In contrast to epigenetic modifications, genetic changes in the DNA strand resulting from mutation, transposition, and recombination are rarely fully reversible within a specific cellular system [27].

4.1 DNA modifications

The two main epigenetic DNA modifications that target carbon atoms of cytosine bases of cytosine-guanine pairs, which are frequently found in CpG-islands, are methylation, which involves adding a CH_3 group, and hydroxymethylation, which involves the addition of a CH_2OH group [29]. In addition, various forms of DNA base modifications have been identified, but their cellular functions remain less understood, and their occurrence is also less frequent [27]. DNA methyltransferases are the enzymes responsible for adding methyl groups covalently to the fifth carbon of cytosine, and DNA methylation occurs at approximately 70%–80% of CpG dinucleotides [29]. The functional impact of an epigenetic modification depends significantly on its location within the gene structure, which comprises regulatory elements and the gene body. As an example, CpG methylation occurring in promoters, enhancers, and transcription starting sites tends to lead to transcriptional silencing, reducing the gene's expression, while a reduction in methylation (hypomethylation) of the same regions tends to elevate the transcription rate of the genes [30]. Individuals' environment, including factors such as dietary habits, stress level, and exercise, have the potential to increase or decrease the methylation in the genome, and consequently, this can lead to a decrease or increase in the activity of the corresponding genes [22].

4.2 Histone modifications

Histones are nuclear proteins that associate with DNA to form the nucleosome and are essential for packaging DNA into chromosomes [31]. Histones exert both positive and negative influences in gene expression regulation, primarily controlled by post-translational modifications occurring on specific amino acid residues [32]. Various histone modifications involve enzymatic acetylation, methylation of lysines and arginines, phosphorylation of serines and threonines, ubiquitination, and sumoylation of lysine [33]. The process of adding an acetyl group to histones (on N-terminal tails) is carried out by lysine acetyltransferases, while histone deacetylases are involved in the removal of acetyl groups from histones. Histone acetylation typically results in the relaxation of chromatin structure, and this conformation exposes DNA, enabling transcription to take place [29], and histone deacetylation tightens chromatin, thereby suppressing transcription [15].

4.3 MicroRNAs

MicroRNAs (miRNAs) are a class of short noncoding RNA molecules that play a crucial role in the regulation of gene expression post-transcriptionally [34]. miRNAs participate in the RNA interference (RNAi) pathway, where they interact with the untranslated regions (UTRs) of mRNA molecules to inhibit protein translation or induce the degradation of the mRNA [35]. MicroRNAs play crucial roles in diverse physiological and pathophysiological functions, including cell signaling, cardiovascular diseases, and carcinogenesis [34]. For example, virtually every cancer cell exhibits the control of gene expression mediated by miRNAs, and there are variations in the miRNA expression profiles of these cells as well [35]. Thus, miRNA expression patterns can be utilized as biomarkers for various diseases [36].

V. EPIGENETICS OF STRESS

Several research studies have identified a correlation between modifications in epigenetic markers and both physiological and psychological stress [9]. Stress is described as external or internal stimuli that disrupt the body's capacity to maintain a stable state of balance across the organ systems [37]. Psychological stress, comprising depression, anxiety, and anger is commonly linked to several physical diseases and is becoming more widely acknowledged as a risk factor for the onset and progression of disease [22]. The neuroendocrine system and autonomic nervous system (ANS) are the key regulators of stress responses, and they act as important mediators between emotional stress and diseases. Chronic stress can lower the levels of heart rate variability, suppress levels of certain anabolic hormones like DHEA or insulin-like growth factor, which can increase insulin levels and visceral fat, and testosterone that plays a vital role in endocrine balance suppressing catabolic and sympathetic stress responses [18]. Acute and chronic stress seems to elevate oxidative stress levels [38].

Alterations in epigenetic markers have been observed in the brains of individuals experiencing depression. According to some studies, individuals experiencing depression exhibited reduced DNA methylation levels in the brain-derived neurotrophic factor (BDNF) gene that encodes BDNF, a protein that supports nerve cell growth and survival, potentially influencing depression [39]. Brain specimens associated with early-life adverse experiences and various conditions, including post-traumatic stress disorder (PTSD), exhibit altered whole genome methylation profiles [9]. Dysregulation of the hypothalamic-pituitary axis (HPA) is a potential consequence of chronic stress [18]. The gene expression of hormones regulated by the HPA axis is upregulated in response to stress. Certain alterations include elevated levels of catecholamines and cortisol production and transcription of pro-inflammatory molecules. These alterations aim to maximize the body’s ability to recover from stress and thereby regain homeostasis [37]. Prolonged stress can induce changes in the methylation pattern of the SKA2 gene, influencing the HPA axis and increasing the risk of completing suicide [40]. Modifications in the methylation and histones of the glial cell-derived neurotrophic factor (GDNF) contribute to the modulation of stress responses in mice [41]. According to some studies, The CpG sites of the corticotropin-releasing factor (CRF) gene undergo methylation changes in reaction to chronic stress and depression [42].

5.1 Hypothalamic–pituitary–adrenal (HPA) axis, Stress and Epigenetics

The principal element of the neuroendocrine network that responds to both internal and external stimuli is the HPA axis. The proper functioning of the HPA axis is essential for the well-being of both the mind and body [43]. The HPA axis governs the secretion of hormones, among them the glucocorticoid steroid cortisol, commonly recognized as the “stress hormone” [44]. Glucocorticoids (GCs) are crucial for maintaining proper brain function and regulating the body's responses to both stress and environmental stimuli. About one in six people will experience depression during their lifetime, and according to some sources, elevated levels of glucocorticoid (GC) hormones and the overactivity of the hypothalamic-pituitary-adrenal (HPA) axis may contribute to the development of depression [45]. Activating glucocorticoid receptors (GR) serves to terminate the stress response, contributing significantly to the regulatory feedback loop of the HPA axis [44]. NR3C1, the GR gene, is involved in regulating the immune system's development and metabolism, as well as in the control of the HPA axis. Increased rates of DNA methylation within the GR gene have been observed in response to psychological stress [37].

A meta-analysis encompassing more than 900 individuals born to mothers who experienced perinatal psychosocial stress demonstrated notable DNA methylation at 5 consecutive CpG sites within NR3C1. This gene is believed to play a role in aberrant neurobehavior and cortisol reactivity in newborns [46]. As well as offspring born to women exposed to intense psychosocial stress often exhibit increased NR3C1 methylation and reduced birth weight [47]. It has been found that females who experienced traumatic events in their childhood and encountered stressful situations in adolescence demonstrated increased NR3C1 methylation rates [48]. FKBP5, a major regulatory protein of the HPA axis, binds to the GR and modulates the GR sensitivity in

response to stressors, leading to regulation of the HPA axis [49]. Genetic variability, particularly at the FKBP5 gene, influences the differential responses to similar stressors among individuals and why some people are more predisposed to illness rather than adaptation [50].

5.2 Inflammatory Pathway and Stress

Inflammation can be defined as the body's innate immune response to potentially harmful stimuli, such as injuries, metabolic stress, and pathogens [51]. Inflammatory processes contribute to the development of various chronic illnesses, such as diabetes, bowel and cardiovascular diseases, cancer, and arthritis. In response to inflammatory stimuli, intracellular signaling pathways are triggered, leading to the generation of inflammatory mediators [52]. Stress responses trigger the activation of the inflammatory pathway. Therefore, Stress-related psychopathology and stressors have been consistently linked to inflammation [53]. The focus in MBTs research has predominantly been on transcription factors associated with stress and inflammation. The synthesis of the nuclear factor kappa B (NF-κB), a key transcription factor, is initiated by the activation of the Sympathetic Nervous System (SNS) during stressful conditions [12]. One molecular linkage between psychosocial stress and changes in organ function is established by the activation of this transcription nuclear factor NF-κB [54]. NF-κB converts stress signals into inflammation by changing the activity of genes responsible for producing inflammatory cytokines [55].

5.2.1 Inflammatory markers

Inflammatory markers could serve as indicators for the potential development of inflammatory diseases. Upon the activation of inflammatory cells, inflammatory cytokines such as IL-1β, IL-6, TNF-α, inflammatory proteins, and enzymes are produced, and these molecules are potential biomarkers for disease diagnosis, prognosis, and therapeutic decision-making [52]. Inflammation is facilitated and inhibited by pro- and anti-inflammatory cytokines, respectively. IL-1β, IL-6, IL-8, IL-12, IFN-γ and TNF-α are proinflammatory cytokines while IL-4, IL-10 and TGF-β are anti-inflammatory cytokines [56]. C-reactive protein (CRP), haptoglobin, serum amyloid A, and fibrinogen are Inflammatory proteins in the blood [57], and enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), NADPH oxidase (NOX), and reactive oxygen species (ROS) are other inflammatory markers [52]. Findings indicate that the predominant stress hormones glucocorticoids and catecholamines exert an inhibitory effect on proinflammatory cytokine production and a stimulatory effect on anti-inflammatory cytokines [58]. However, prolonged stress induces adaptive changes in the body to the continuous release of stress hormones, becoming less responsive to their anti-inflammatory effects [12]. Stress can also increase the level of IL-6, INF-γ, and CRP [59].

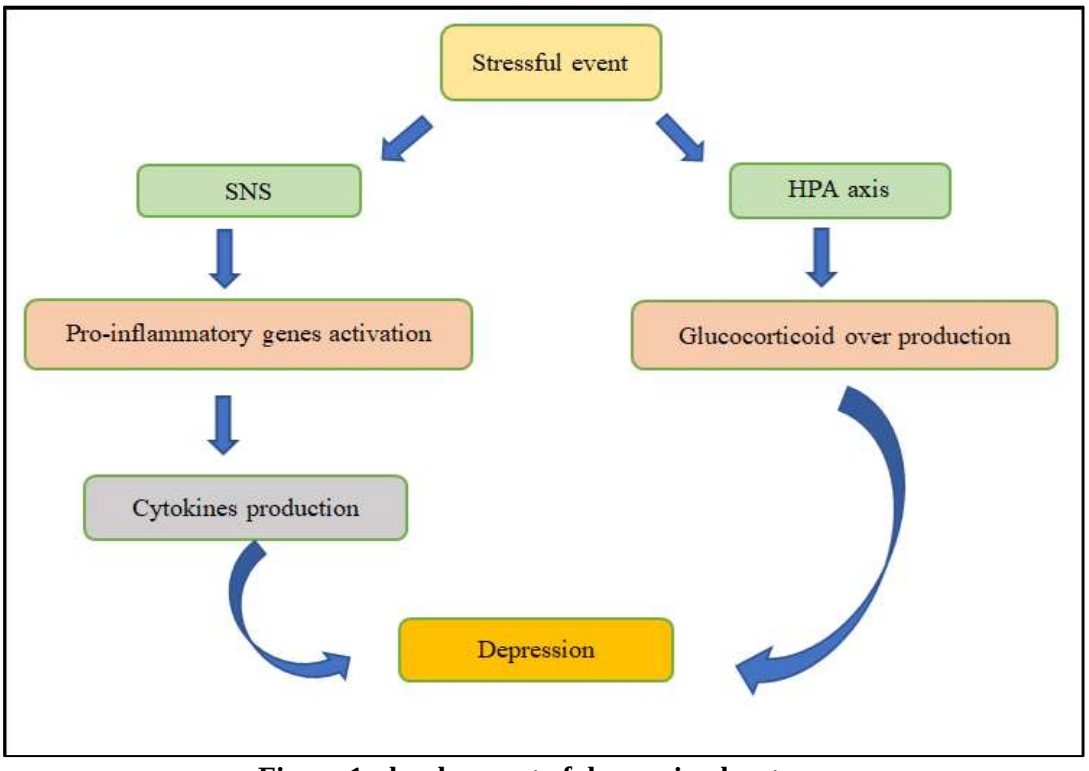

Figure 1: development of depression by stress

VI. EFFECTS OF SITTING (STATIC) MEDITATIONS

The molecular aspects of sitting meditations have been extensively studied in research. Their influence extends to the regulation of numerous metabolites, biomarkers like hormones, and neurotransmitters. As well as immune and neuroendocrine factors affected by stress play a crucial role in the development and progression of diseases [9]. Many studies have demonstrated that meditation can improve health through several interrelated pathways, such as the HPA axis, which produces glucocorticoids, and the autonomic nervous system (ANS), which balances sympathetic and parasympathetic activity. These pathways are important upstream regulators of immune response, gene expression, and normal functioning of the central nervous system [59].

According to the study by Chaix and his colleagues, after engaging in intensive meditation for one day, a reduction in the expression of the pro-inflammatory protein cyclooxygenase-2 (COX2) was noted, and also the team observed that the epigenetic change of this gene was achieved by altering the activity of particular regulatory transcription factors rather than through methylation changes. Furthermore, the most significant alteration in methylation resulting from the meditation intervention was observed in the TBKBP1 gene, a participant in the TNF-α/NF-κB pathway, which is activated in blood cells when exposed to acute and chronic psychological stress conditions. As well as the study also discovered differential methylation in TNFSF13B (B-cell activating factor), PRF1 that code for the perforin protein, PHF21A (PHD finger protein 21A), and SAP18 (Sin3A-associated protein 18kDa), associated with chromatin remodeling and epigenetic regulation [60].

The study conducted by Dutcher and his colleagues detected a notable decrease in the expression of pro-inflammatory genes of the NF-κB transcription control pathway in samples of peripheral blood cells collected from highly stressed call center workers after a 30-day digital mindfulness training intervention, indicating that mindfulness stress reduction interventions exert a beneficial effect on the health of stressed workers [61]. Another study reveals the changes in the expression of genes related to chromatin modulation and inflammation after month-long meditation practice. In the study, participants in the retreat exhibited a notable downregulation of the TNF pathway. Moreover, increased methylation and suppression of TBKBP1 and TNFSF13B genes, which play key roles in the TNF and NF-kB pathways, were observed [62].

Another research study conducted by Mendioroz and the team demonstrated an association between telomere length and DNA methylation levels in long-term meditators, particularly within three distinct sub-telomeric regions that include the GPR31 (G protein-coupled receptor 31) and SERPINB9 (Serpin family B member 9) genes. Length of telomeres in meditators showed no correlation with their age, indicating a diminished rate of telomere attrition as individuals aged [63]. GPR31 is responsible for coding a cell membrane receptor with a strong affinity for 12-S-HETE, an arachidonic acid metabolite that is produced by both platelets and tumor cells. It can induce the retraction of endothelial cells, thereby facilitating processes such as extravasation and metastasis [64]. GPR31 emerges as a promising target for oncology treatments due to its role in KRAS (Kirsten rat sarcoma viral oncogene homolog) membrane association, a significant mechanism in the development of tumors. Thus, differential methylation observed at sub-telomeric regions in GPR13-associated telomeres of those who practice meditation may serve as an indication of a reduced risk of cancer and metastasis [63].

SERPINB9 is responsible for coding a protein belonging to the serine protease inhibitor family, serpins, and protects cytotoxic T-lymphocytes from apoptosis [65]. SERPINB9 plays an important role in inflammation. Reduced stress and inflammation are frequently observed in meditation practices, and that may be potentially due to the differential methylation of this SERPINB9 gene among other epigenetic mechanisms. Short telomeres cause genomic instability and disease states. Therefore, telomere length directly influences health and well-being. Improved telomere health via greater genomic stability, lower telomere attrition, and sub-telomeric methylation can be observed among mindfulness mediators and it can lead to lower potential tumorigenesis [63]. Moreover, other studies also found that increased telomerase activity was associated with the practice of mindfulness meditation [66,67], and also, as the meditation time increased, both mindfulness and plasma telomerase exhibited improvement, suggesting that engaging in meditation may have the potential to positively influence plasma telomerase levels, thereby contributing to increased longevity, delaying cellular aging, and enhanced mental and physical well-being [67]. Another study also reports on significantly longer telomere length following Zen meditation practice [68].

Some studies revealed that individuals practicing mindfulness and compassion meditation exhibited a notable reduction in their epigenetic aging rate, which was correlated with the duration of their meditation practice [69]. The study conducted by García-Campayo and his colleagues compared the methylation profiles in circulating lymphocytes between experienced meditators, with a history of over 10 years of practice and meditation-naïve subjects and found 64 differentially methylated regions, corresponding to 43 genes that play vital roles in neurotransmission, glucose homeostasis, protein folding, lipid metabolism, and the modulation of inflammatory pathways, and those genes are associated with immune diseases such as Inflammatory Bowel Disorder, atopic dermatitis, Multiple Sclerosis and psychiatric diseases such as bipolar disorder, schizophrenia,

autism, and major depressive disorder. In this study, hypomethylation of the NR4A2 (Nuclear Receptor Subfamily 4 Group A Member 2) gene was observed, and this gene encodes a nuclear receptor protein that is involved in the maintenance of the dopaminergic system [4].

Another study on Transcendental meditation exhibits a differential expression of 200 genes that are related to different diseases such as Hematologic Diseases, Coronary Artery Disease, Diabetes Complications, Inflammation, and Cardiovascular Disease. In the study, in comparison to the control group, 49 inflammation-related genes in the meditators were found to be downregulated, whereas genes associated with antiviral mechanisms and antibody components of the defense response exhibited upregulation. As well as six genes associated with erythrocyte function exhibited the most significant variations in expression. the study showed an upregulation of 5 genes (*CXCL10*, *MICA*, *FPR2*, *CASP5*, and *CASP7)* predominantly linked to anti-cancer activity, 3 genes (OAS1, ATF3, and IFIT3) that demonstrate dual roles in both anti-cancer and anti-microbial activities, and 4 genes (CCL4L1, IL1B, ANKRD22, TLR4) that are associated with the defense response to viruses and bacteria indicating that meditators exhibited a notable improvement in the antibacterial, antiviral, and anti-cancer activities [70].

VII. EFFECTS OF MOVING MEDITATIONS

Practicing Yoga, Tai Chi, and Qigong is associated with improved attention, self-control, and mindfulness, as these activities promote inner silence through intentional and mindful movements [9]. Several research investigations have delved into the molecular-level physiological impacts of these practices. The study conducted by Bower et al. showed significant downregulation of proinflammatory gene expression and reduction in proinflammatory transcription factor NF-κB activity in young breast cancer survivors experiencing persistent fatigue after 12-week mindfulness-based yoga practice. The study also revealed increased activity of anti-inflammatory glucocorticoid receptors and reduction in the activity of cyclic AMP responsive element binding protein (CREB) family transcription factor compared to the control group [71]. Another study by Chen et al. identified a substantial decrease in plasma cholesterol, LDL-cholesterol, insulin levels, and several endothelial microparticles (EMPs) following yoga practice. In addition, there was a decline in the release of pro-inflammatory cytokines. The study pointed towards the potential positive impact of yoga practice on metabolic and inflammatory markers [72].

Harkess and collaborators focus was on analyzing the CpG methylation levels of specific genes associated with immune function (TNF, IL-6, and CRP) in the blood samples of chronically stressed women who practiced Yoga. The primary finding indicated that engagement in Yoga correlated with decreased methylation of the TNF gene and elevated levels of IL-6. However, no significant variations were evident for the other genes, and the researchers suggested the necessity of conducting more comprehensive studies to unravel the epigenetic processes of these practices [53]. Another study by Twal et al. investigated the effect of yoga on salivary cytokines and identified that the levels of IL-1 β, IL-8, and monocyte chemotactic protein-1 show significant decreases in yoga practitioners [73]. As well as another study by Rajbhoj et al. also demonstrated a significant decrease in soluble IL-2 receptor (sIL-2 R) levels, signifying a reduction in inflammation [74]. These results indicate that Yoga practices may have the potential to exert anti-inflammatory effects.

A study was conducted by Nair and colleagues with 61 individuals diagnosed with type 2 diabetes (T2D), and it demonstrated a significant reduction in DNA damage indicators and oxidative DNA damage markers after 10 weeks of yoga intervention. Furthermore, the study revealed substantial improvements in fasting blood sugar levels compared to individuals participating in routine exercises. Additionally, the investigation found an upregulation in the expression of oxo guanine glycosylase 1 (OGG1) protein that promotes DNA repair. These results suggested that yoga enhances DNA repair efficiency exerting positive influences on DNA damage in individuals with Type 2 Diabetes [75]. Khedmati Zare and colleagues studied the combined influence of Yoga and Vitamin D supplementation on gene expression and the psycho-physical state in breast cancer survivors who had finished chemotherapy and radiotherapy five years before the study. They investigated the expression patterns of anti-apoptotic genes such as p53 and Bcl2 that enhance cell survival, apoptotic Bax gene, and NF-κB that regulate key biological processes, including immunity, inflammation, and apoptosis in leukocytes. Results showed an increased expression of p53 and Bcl2 genes in yoga and vitamin D groups and a trend of down-regulation in apoptosis genes (NF-κB & Bax), which was not statistically significant. The authors concluded that a combination of yoga and a substantial vitamin D dose may offer potential advantages for the health and recovery of breast cancer survivors [76].

Another study investigated the influence of a 12-week yoga-based lifestyle intervention (YBLI) on the expression of genes related to oxidative stress, inflammation, and aging in a group of obese adults. The study did not reveal significant alterations in the fold change of TERT, IL-6, and NF-kappa B between the groups after 12 weeks. However, both YBLI and standard groups exhibited a significantly higher relative fold change in TERT at 2 weeks, though the change was greater in the YBLI group. In the Standard group, TNF α gene

expression significantly decreased at weeks 2 and 4 compared to baseline, but it showed an increase at week 12. However, these findings should be interpreted carefully and in conjunction with other research outcomes. Further comprehensive studies are essential to understand the positive effects of YBLI on oxidative stress, inflammation, and aging-related gene expression in obesity [77].

Kumari and colleagues conducted a study on the impact of yoga in women with Polycystic Ovary Syndrome (PCOS) and identified the genes Peroxisome Proliferator-Activated Receptor Gamma (PPARG), insulin receptor (INSR), Insulin Receptor Substrate 2 (IRS2) and Calpain-10 (CAPN10), are upregulated following engagement in Yoga. Those gene expression changes have potential benefits for insulin sensitivity, metabolic rate, and BMI of PCOS individuals. Furthermore, the study found a reduction in the expression of microRNA- 21, a key player in triggering inflammation associated with PCOS, and microRNA-128, a suppressor of INSR. Apart from that, Yoga practitioners displayed significantly longer telomere length, along with heightened telomerase activity and levels, indicating a positive effect on telomere metabolism and cellular longevity. Thereby, the study showed that Yoga emerges as a potent solution in the effective management of complex lifestyle diseases like PCOS and its related systemic disorders [78].

Another study by Gautam et al. investigated the impact of 8-week yoga practice on gene expression in rheumatoid arthritis patients. Studies suggested that the practice of yoga brings about positive epigenetic changes, influencing global methylation levels, global hydroxyl methylation levels, and HDAC1 levels, which may influence the regulation of gene expression patterns. Additionally, downregulation of RORγt, IL-17, IL-6, CXCL2, and CXCR2, and upregulation of FoxP3 and TGF-β, which are epigenetic and inflammatory markers, following yoga, were observed [79]. The practice of Tai Chi has been proven to boost immune system activity through a reduction in plasma inflammatory cytokines such as IL-6, IL-12, TNF-α, IL-10, and IL-4 [80]. In addition, several other studies have uncovered alterations in transcription profiles of different inflammatory markers after practicing Tai Chi, affecting the pathways related to inflammation, antiviral responses, energy regulation, and adrenergic activation [81,82,83].

VIII. EFFECTS OF COMBINATION THERAPIES

Mindful practice combinations have been developed and introduced in numerous clinical contexts. In a study conducted by Kaliman et al., a downregulated expression of histone deacetylase genes HDAC 2, 3, and 9 and the suppression of pro-inflammatory genes (RIPK2 and COX2) were observed following eight hours of mindfulness-based practice. These changes were associated with accelerated physical recovery from stressful situations, ultimately leading to improved health and well-being [84].

Bishop and his colleagues conducted a study to examine the peripheral blood mononuclear cell DNA of veterans who had post-traumatic stress disorder (PTSD) after mindfulness meditation training. The study focused on the CpG methylation of two specific genes (SLC6A4 and FKBP5) which are potential biomarkers for depression. They reported a differential methylation in the FKBP5 gene encoding the FK505 binding protein 5, which regulates the glucocorticoid receptor. FKBP5 plays a role in modulating glucocorticoid activity and the acute stress response through its involvement in a negative feedback loop. Increased transcription of genes related to stress and long-term dysregulation of stress are often associated with demethylation of the gene. Elevated FKBP5 methylation following treatment was observed among meditators, while non-meditators displayed a decrease. This implied a potential beneficial association between effective meditation and the HPA axis stress-related pathway. However, the study did not observe a significant change in the methylation pattern of the SLC6A4 gene to the treatment [85].

As well as another study reported elevated levels of microRNA-29c (miR-29c) in exosomes derived from neurons (NDEs) within the bloodstream and a significant decrease in the expression of DNA methyltransferase 3 alpha (DNMT3A) and DNMT3B in the neuron-16 derived extracellular vesicles of elderly individuals after a Mindfulness-Based Stress Reduction program. The findings indicate a potential role for MBSR in preventing neuronal loss and cognitive decline in the elderly, possibly through the enhancement of miR-29c expression in neurons [86].

Table 1: Summary of the different studies discussed

Author	Type of MBT	Key results	References
Chaix et al. (2020)	Mindfulness meditation	Reduced methylation at CpG sites of TBKBP1, TNFSF13B, PRF1, PHF21A, and SAP18 genes, Reduced expression of COX2 protein	[60]
Dutcher et al.	Mindfulness	Reduced expression of pro-	

(2022)	meditation	inflammatory genes of NF-κB pathway	[61]
Álvarez-López et al. (2022)	Mindfulness meditation	Increased methylation of TBKBP1 and TNFSF13B genes, Inflammatory gene expression changes	[62]
Mendioroz et al. (2020)	Mindfulness meditation	Differential methylation of GPR31, SERPINB9 genes, Reduced rate of telomere attrition	[63]
Le Nguyen et al. (2019) Dasanayaka et al. (2022)	Mindfulness meditation	Increased telomerase activity	[66], [67]
Alda et al. (2016)	Zen meditation	Longer telomere length	[68]
Chaix et al. (2017)	Mindfulness And compassion meditation	Reduction in their epigenetic aging rate	[69]
García-Campayo et al. (2018)	Mindfulness meditation	Differential methylation of 43 genes related to inflammatory pathway, glucose homeostasis, protein folding, and lipid metabolism. hypomethylation of the NR4A2 gene	[4]
Wenuganen et al. (2021)	Transcendental meditation	Downregulation of 49 inflammation-related genes, Upregulation of genes related to antiviral mechanisms and antibody components	[70]
Bower et al. (2015)	Yoga	Downregulation of proinflammatory genes, upregulation of anti-inflammatory genes	[71]
Chen et al. (2016)	Yoga	Differentiation expression of genes in the inflammatory pathway	[72]
Harkess et al. (2016)	Yoga	Reduced DNA methylation at CpGs of TNF gene	[53]
Twal et al. (2016) Rajbhoj et al. (2023)	Yoga	Differentiation expression of inflammatory markers	[73], [74]
Nair et al. (2022)	Yoga	Upregulation of OGG1, reduced expression of DNA damage markers.	[75]
Khedmati Zare et al. (2021)	Yoga	Increased expression of p53 and Bcl2 genes, decreased expression of NF-κB & Bax genes	[76]
Sharma et al. (2022)	Yoga	Differentiation expression of genes related to the inflammatory pathway, oxidative stress	[77]

Kumari et al. (2023)	Yoga	Upregulation of PPARG, INSR, IRS2 genes, Reduced expression of microRNA-21 and microRNA-128	[78]
Gautam et al. (2023)	Yoga	Differentiation expression of genes related to the inflammatory pathway	[79]
Campo et al. (2015) Irwin et al. (2015) Kinney et al. (2019) Hamasak et al. (2024)	Tai chi	Differentiation expression of genes related to the inflammatory pathway	[80], [81], [82], [83],
Kaliman et al. (2014)	Combination therapies	Downregulation of HDAC 2,3,9 genes, suppression of pro-inflammatory genes (RIPK2 and COX2)	[84]
Bishop et al. (2018)	Combination therapies	Increased methylation of FKBP5 gene	[85]
Hashizume et al. (2021)	Combination therapies	Increased expression of microRNA-29c, decreased expression of DNMT3A and DNMT3B genes	[86]

GPR31= G protein-coupled receptor 31, SERPINB9 = Serpin family B member 9, NR4A2 = Nuclear Receptor Subfamily 4 Group A Member 2, OGG1= Oxo Guanine Glycosylase 1, PPARG = Proliferator-Activated Receptor Gamma, INSR= Insulin Receptor, IRS2= Insulin Receptor Substrate 2, CAPN10 = Calpain-10, HDAC = Histone deacetylase, COX2 = cyclooxygenase-2, DNMT3A= DNA methyltransferase 3 Alpha, DNMT3B= DNA methyltransferase 3 Beta.

IX. CONCLUSION

Growing evidence indicates that the influence of a stressful environment on the genome is facilitated through epigenetic alterations, inducing stable modifications in gene expression and in behavior mediating maladaptive responses. It's fascinating that meditation practices appear to share common gene targets with epigenetic deregulations that occur in response to stress. However, the relationship between stress and meditation and their impact on shared epigenetic processes is not yet fully understood. Findings from these various studies have shown that MBT, including meditation, yoga, and tai chi, can bring about changes at the epigenetic level that may help prevent diseases and promote health and well-being. However, there is a lack of comprehensive molecular and epigenetic evidence to firmly establish a cause-and-effect connection for the effects of mindful activities due to the novelty of the field. Unlocking the mechanistic details of mindfulness practices demands more extensive research, particularly with a focus on epigenetics. An increased and comprehensive knowledge of these techniques will bring us toward the potential incorporation of these strategies as non-pharmacological interventions for stress-related diseases, psychological disorders, and many other diseases.

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Corresponding Author: I. U. Kumarage
[1]Department of Molecular Biology & Biotechnology, Faculty of Science, University of Peradeniya, Sri Lanka