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RESEARCH ARTICLE

Yoga: unraveling the internal pharmacy – Impact on genome and epigenome

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ABSTRACT

Complex and chronic lifestyle disorders have become the leading cause of death and disability worldwide. They involve multiple morbidities necessitating the attention of numerous healthcare facilities as well as community-based care too. Stress and anxiety brought on by the fast-paced life, unhealthy eating habits, sedentary lifestyle, poor quality of life, polypharmacy, and high medical costs have significantly influenced the development of such multimorbid conditions. Most chronic complex diseases share a similar underlying pathology including high levels of stress, inflammatory immune response, persistent activation of the hypothalamo-pituitary-adrenal axis, oxidative stress, accelerated immune-aging, dysregulated blood flow, enhanced apoptosis and accelerated aging with shorter telomeres and DNA damage. These are modifiable factors which can impact disease progression and no single treatment modality in modern medicine can alone impact all these factors. As a result, the treatment must involve an integrated approach that targets both mind and body and each of these factors which form an architectural framework which supports the onset of these complex lifestyle disease and thus though we may enjoy longer lifespan, but it is accompanied by shorter health span. Yoga, a mind-body intervention with Indian roots, strives to bring about the synchronization of physical and mental health by unraveling and switching on the internal pharmacy and maintenance of homeostasis at cellular and molecular level.

Keywords: Yoga, meditation, gene expression, epigenome, inflammation, healthy aging, health, complex

Introduction

Yoga is mind-body energy medicine with Indian roots that dates back thousands of years. Being a non-pharmacological mind-body intervention, yoga plays a key role in prevention of diseases and promotion of health and wellness[1].Yoga is a profound science of wellbeing which has tremendous rehabilitative potential and dynamically alters gene expression patterns, which is how it unravels the pharmacy within[2]. It seeks to alleviate pain and promote the best possible mental and physical health to bring about optimism. Yoga rejuvenates the mind by reducing stress, restoring endocrine health, and calming the body by preserving flexibility and increasing joint mobility through a well-defined psycho-neuro-immune system[3]. Most complex diseases, such as cancers, autoimmune diseases, depression, and heart disease, are brought on by the interaction of multiple genes, environmental factors, and our unhealthy social habits[4]. Our biology is determined by our genes, but our epigenome is influenced by our attitudes, dietary habits, and way of life. These complex lifestyle disorders have common underlying etiologies including oxidative stress (OS), depression, anxiety, stress, shorter telomeres, chronic inflammation, dysbiosis of the gut microbiome, and dysregulated immune system[5–7]. Yoga addresses each of these elements by restoring homeostasis and reestablishing balance in the dysregulated systems. Achieving mental peace and cultivating a sense of well-being, relaxation, enhanced self-esteem, higher productivity, enhanced attentiveness, less irritation, and a positive view on life are some of the key objectives of yoga[1]. Numerous yogic studies and literature highlight the benefits of yoga activities for obtaining a holistic health[1,2,8,9].

Yoga combines physical exercise with an inwardly focused, attentive concentration on awareness of the breath, energy, and self. The benefits of yoga practices include increased muscular strength, flexibility, neuromuscular coordination, range of motion, improved respiratory and cardiovascular health, aid in addiction treatment and recovery, less stress, anxiety, and depression, better sleep patterns through regulation of circadian rhythm, and an overall improvement in one's quality of life and general well-being. Yoga possesses the ability to enhance general wellbeing and productivity at work, as well as provide therapeutic advantages to individuals with chronic illnesses brought on by stressful life events. In Yoga Sutras term "eight limbs," or "*ashtanga*," refers to Patanjali's eightfold route to enlightenment and awareness. The eight limbs are *yama* (abstinence), *niyama* (observances), *asana* (yoga posture), *pranayama* (breath control), *pratyahara* (withdrawal of the senses), *dharana* (concentration of the mind), *dhyana* (meditation) and *samadhi* (absorption)[10]. The eight limbs consist of moral guidelines for leading a meaningful and purposeful life. They act as a guide for moral behavior and self-control, emphasizing the spiritual parts of human nature while focusing on one's physical well-being.

Gene expression regulation by yoga

It is known that environmental factors, including psychological, social, and lifestyle factors, can cause different variations in gene expression. Adoption of a simple lifestyle-based intervention like yoga helps to normalize the levels of dysregulated transcripts, especially

of genes regulating free radical levels and maintaining DNA integrity[11–17]. Yoga aids in the regression of inflammatory processes by downregulating the pro-inflammatory genes and upregulating the anti-inflammatory and antioxidant genes[11,13,18]. Yoga positively affects the transcriptome and epigenome through the normalization of several inflammatory gene expression patterns, and epigenetic modifications[11,19]. An account of existing literature consisting of various clinical trials on the effect of yoga on gene expression, epigenetic alterations and gene polymorphisms is shown in Table 1. Studies show that these behaviors are linked to a downregulation of nuclear factor kappa B (NF-κB), which is involved in the translation of stress into inflammation and is created when stress stimulates the sympathetic nervous system[20,21]. In a study by Li et al., 2005, there was a downregulation in the genes associated with the ubiquitin degradation pathway and cellular stress response in Qigong practitioners[22]. The Qigong group also exhibited higher expression of several immunity-related genes, including interferon gamma (IFN-γ), IFN-related, and IFN-regulated genes. Through apoptosis, or programmed cell death, the lifespan of inflammatory neutrophils was lowered whilst that of normal neutrophils was extended. These findings suggested that through modifying gene expression, Qigong practice may have positive impacts on immunity, metabolic rate, and apoptosis[22]. Dusek et al., 2008, studied the gene expression changes related to oxidative phosphorylation, ubiquitin-dependent protein catabolism, nuclear mRNA splicing, ribosome, metabolic processes, NF-kB signaling, and regulation of apoptosis triggered by the relaxation response and these changes might indicate a greater capacity to respond to OS and associated detrimental effects[23]. Gene expression profiling can also be useful in comparing various practices, such as different forms of meditation, and in identifying the various effects that these practices may have from a molecular to a systemic level[19]. There are studies which have focused on the rapid and long-term effects of yoga on gene expression changes. Qu et al., 2013 reported rapid changes in the gene expression in PBMCs of yoga practitioners within 2 hours of the start of practice during the comprehensive yoga program[24]. They found the significant changes in the expression of genes (*CCR7, AVIL, PFKFB3, CEACAM1, MMP28, NFE2, RAB24,* and *EXT1*) related to immune cell differentiation, platelet production, megakaryocyte maturation, and NK cell cytotoxicity. Bhasin et al., 2013, showed that immune response and telomere maintenance related pathways are affected among long-term relaxation response practitioners[25]. A study by Dhawan et al., 2018 highlighted the beneficial effects of yoga in optimizing the dysregulated sperm transcripts (*OXG1, SOX3, OGG1, PARP1, RPS6, RBM9, RPS17* and *RPL29*) associated with the embryonic development[14]. A notable decrease in OS parameters in this study served as evidence of yoga's influence. The most crucial indicator of potential fertility, sperm progressive motility, significantly improved when reactive oxygen species (ROS) levels were lowered. According to earlier research conducted in our lab, sperm DNA mutagenic load, OS, and ODD significantly decrease after six months of yoga intervention[26]. OS may have a major effect on the sperm epigenome due to its changed methylation levels, which affect the epigenome[27].

Another study showed a significant decrease in intraocular pressure in individuals with primary open angle glaucoma, along with activation of genes related to cellular repair and downregulation of pro-apoptotic and pro-inflammatory genes[16]. Integrative medicine approaches have the potential to change the transcription of genes and result in changes to DNA methylation and histones.

Yoga also helps to slow down the rate of cellular aging by upregulating the activity of the telomerase enzyme and genes involved in DNA repair and cell cycle regulation[28,29]. Previous studies from our lab showed that there was an improvement in the symptoms of a chronic inflammatory immune arthritis which was estimated with the help of disease activity scores, disability index and pain acuity after eight weeks of yoga-based lifestyle intervention (YBLI) in RA patients[13,30,31]. This could be explained by the reduction of pro-inflammatory markers and elevation of immune-modulatory molecules like soluble HLA-G and various anti-inflammatory and antioxidant markers[30,32]. Following yoga practice, there was a notable improvement in mitochondrial integrity as evidenced by increase in the mitochondrial membrane potential, nicotinamide adenine dinucleotide (NAD+), cytochrome c oxidase (COX-II), mitochondrial copy number, and expression of genes (*AMPK, IGF1R, PRC-1, TFAM, SIRT-1, TIMP-1,* and *KLOTHO*) that support mitochondrial biogenesis and preserve mitochondrial integrity[12]. This helps to maintain optimal levels of free radicals, enhances insulin and energy metabolism, and consequently lowers the rate of telomere attrition by producing supra-physiological ROS levels[12,33]. Previous studies from our lab also documented the normalization of the dysregulated transcripts (*IL-6, TNF-α, NFKB1, TGF-β*, and *CTLA4*) associated with the inflammation, stress pathway and immune system in RA patients after 8-weeks of yoga-based lifestyle intervention[13].

Yoga is a mind-body activity that dates back thousands of years. It improves health, reduces the onset of disease, and can be used as an adjuvant therapy for complex illnesses. Yoga is a fundamental science that operates on a clearly defined psycho-neuro-immune axis that impacts many processes, including stress response, aging, immune-response, blood pressure, organ system maintenance, reproductive health, basic metabolism, epigenetics, DNA repair, and oxidative bioprocesses[3,13].Through the control of stress on a physical, emotional, and psychological level via both high-level and low-level brain networks, yoga enhances self-regulation mechanisms[34,35]. Through various *asanas* (physical postures), *pranayama* (breathing exercises), *dhyana* (meditation), and *savasana* (relaxation methods), yoga improves focused attention, cognition, and memory. Yoga is also known to enhance neuroplasticity by improving brain-derived neurotrophic factor (BDNF), serotonin, neuregulins, and neurotrophins, lowering the Beck Depression Inventory-II (BDI-II) depression measurement scale, increasing thickness of cerebral cortex, neural connectivity, and positive changes in electroencephalogram (EEG)[35,36]. It functions via a variety of pathways and has been linked to numerous beneficial changes in a person, such as lowering stress and anxiety, preventing depression, enhancing sleep, lessening sympathetic distress, lowering inflammation, reducing symptoms of hypertension, and enhancing quality of life. Yoga induces a relaxation response that

improves mind-body communicative markers, lowers sympathetic overactivity, increases β-endorphins, and improves cardio-vagal tone[16,37,38].Yoga combines a series of physical postures/asanas with an awareness of regulated breathing practices to gain emotional control and resilience to promote mental peace and general relaxation. In addition, several genes which maintain integrity of mitochondrial and nuclear genome show enhanced expression like *MTHFR, PARP* and genes of 1carbon metabolism.

Epigenetic effects of yoga

Numerous studies have shown that external factors have an epigenetic influence on both physiological and cognitive responses. Through real-time regulation of gene activity without altering the DNA sequence, epigenetic mechanisms enable the genome to adjust its activities to shifting environmental settings[39].It has been demonstrated that inner silence can alleviate symptoms associated with stress, it might be viewed as a potent instrument to counterbalance the harmful consequences of poor lifestyle factors and environmental detriments. However, there is a dearth of studies on the epigenetic profiles that arise from mindful movement techniques. Gene promoter regions that are known to experience alterations with aging are the primary places where DNA methylation takes place[40]. A study by Ren et al., 2012 examined the epigenetic effects of Tai Chi on the methylation of 66 sites using saliva samples from experienced practitioners. They found that there were notable variations between the trainees and controls at six CpG sites on several chromosomes. Interestingly, they found that the age-related methylation trends at those CpGs was slower in the Tai Chi group compared to the controls[41].Tai chi practice may be protective against age-related epigenome degradation, according to the scientists, since the age-related decline in DNA methylation reflects the slow decline of key regulatory activities of the genome. Another study focused on the CpG methylation levels of immune system genes like, *TNF, IL-6* and *CRP* in chronically stressed women post yoga therapy. They found out that yoga was linked to the hypomethylation of the *TNF* gene, whereas *IL-6* and *CRP* did not seem to be impacted [42]. Chaix et al., 2017 conducted an epigenetic clock analysis in long-term meditators, which is a reliable and consistent indicator of biological aging, which is elevated by chronic disorders associated with aging and lifetime stress[43]. Researchers found that the longer a person meditates, the more substantial the reduction in epigenetic aging occurs in those who practice mindfulness and compassion meditation. The same authors conducted a follow-up study in which they demonstrated that brief meditation sessions might quickly alter the methylome of experienced meditators at genes linked to aging and immune metabolism[44]. Another study by Kaliman et al., 2014 explored the impact of rapid mindfulness meditation on the in the experienced meditators and observed the lower expression of pro-inflammatory genes (*RIPK2* and COX2), changes in global histone modifications (H4ac; H3K4me3), and reduced expression of histone deacetylase genes (*HDAC*2, 3 and 9).This study's findings imply that practicing mindfulness meditation affects pathways that are comparable to those that are the focus of several anti-inflammatory medications, including cyclooxygenase inhibitors and HDAC

inhibitors[45]. Bishop and colleagues focused on the CpG methylation of two specific genes (*SLC6A4* or *FKBP5)* whose expression influence the risk for developing post-traumatic stress disorder. *FKBP5* methylation increased in responders following MBSR intervention compared to decreases in non-responders implies that a successful meditation intervention may be connected to molecular pathways related to stress. *FKBP5* DNA methylation profiles may be useful as markers of how well meditation treatments work for post-traumatic stress disorder patients[46].A previous study from our lab showed sperm methylome changes followed by a yoga-based lifestyle intervention in primary infertile male patients[27]. OS may have a major effect on the sperm epigenome due to its changed methylation levels. Yoga enhances the integrity of nuclear and mitochondrial DNA and has a beneficial effect on the sperm epigenome[27,47]. This impacts the health trajectory of the offspring. Yoga, an integrative health technique, helps to lower disease activity and ameliorate symptoms associated with RA, by regressing inflammatory pathways through the normalization of many inflammatory indicators, gene expression patterns, and epigenetic modifications[30].Global DNA hypomethylation causes abnormal gene expression and is linked to several autoimmune and inflammatory diseases. After eight weeks of yoga intervention, there was an overall rise in the percentage of global 5-methyl cytosine DNA and reduction in percentage of global 5-hydroxymethyl cytosine in the yoga group compared to the non-yoga group, which may have resulted in the downregulation of pro-inflammatory genes[11]. Yoga group also showed a decline in the levels of histone deacetylase 1 (HDAC1) inhibitors which act via altering the gene expression to generate immune-modulatory effects. Yoga addresses the psychological as well as the physical components of the disease and supports immunological homeostasis across different populations of T cells, particularly Tregs and Th17. Yoga acts via psycho-neuro-immune axis to normalize relapses and achieve remission in RA by establishing a homeostatic balance between the sympathetic and parasympathetic limbs of the autonomic nervous system during the aggressive symptomatic phase[13].

Response of genetic polymorphisms and individual variations to yoga

Genetic differences can affect an individual's response to specific interventions, such as mind-body therapies. It is imperative to acknowledge that individuals may exhibit distinct genetic predispositions and reactions to yoga practices. Comprehending the relationship between genetics and yoga could assist in customizing strategies for the best possible health results. In 2018, Tolahunase M et al. examined the impact of yoga on major depressive disorder (MDD) remission in patients with *MTHFR 677C>T* and *5-HTTLPR* polymorphisms who are resistant to selective serotonin reuptake inhibitors (SSRIs) treatment[48]. Yoga therapy might be an adjunct treatment for MDD regardless of the diversity in the disorder's etiopathogenesis[35].It is important to understand that there is no single remission gene can be influenced by a particular pharmacological intervention, hence a wholesome approach like yoga has become the need of an hour which can normalize the altered dynamic physiological functions. Another study from our lab highlighted the effectiveness of yoga in RA patients having disease susceptibility

genotypes (*HLA-G +3142GG* and *HLA-G 14 bp ins/ins*)[32,49]. This study demonstrated the improvement in clinical outcome and reduction in disease severity after 8-weeks of yoga intervention in HLA-G 14 bp ins/del and +3142 G>C polymorphism irrespective of their genotypes. By decreasing disease activity and upregulating sHLA-G levels, yoga may be utilized as an adjuvant therapy for this chronic, severe autoimmune inflammatory arthritis, regardless of genotype by reducing disease activity and upregulation of levels of sHLA-G[18].

Although there is still much to learn about the relationship between yoga and genetics, the research indicates that yoga practices may have an impact on gene expression and improve health outcomes. Yoga may improve our mind-body connections, lower stress, reduce inflammation, and improve our epigenetic makeup by switching on gene programs beneficial for human health. Nonetheless, yoga can enhance general wellbeing and encourage a healthier genetic profile when combined with a holistic lifestyle.

Effect of yoga on telomeres and cellular aging

It has been demonstrated that yoga practices lower stress levels and enhance the body's stress response. Prolonged stress can hasten cellular aging and cause adverse alterations in gene expression. Stress is associated with high levels of cortisol and lower total antioxidant capacity and reduced expression of genes promoting neuroplasticity. Cellular aging is associated with telomeres, the protective caps on the ends of chromosomes. Research indicates that mind-body techniques, such as yoga and meditation, may contribute to the maintenance of cellular health and telomere length[28,29,50,51]. To sustain a healthy life, cellular integrity must be maintained. Yoga contributes to the preservation of cellular health and longevity via maintenance of redox homeostasis, genomic damage, and maintenance of telomere length via telomerase upregulation. Stress and inflammation cause hypothalamo-pituitary-adrenal axis hyperactivity which in turn raises the risk of oxidative DNA damage by altering the methylation of DNA repair genes, modulating base-excision repair activity, and producing more free radicals, all of which contribute to OS[52]. An OS condition leads to the excessive generation of ROS by mitochondria, low levels of antioxidants, impaired mitochondrial dynamics, electron transport chain defects, bioenergetics imbalance, activation of p53/p21 and p16/pRb pathways resulting in cellular senescence[53]. Nuclear DNA, cell membranes, and even mitochondrial DNA are all severely affected by this metabolic and redox imbalance, which also damages cellular integrity. ROS can indirectly regulate the activity of the epigenetic machinery. This suggests that epigenetic modifications are closely related to the cell's energy levels and overall metabolism. Previous research conducted in our lab has shown that yoga lowers OS, increases overall antioxidant capacity, upregulates the telomerase enzyme, and preserves mitochondrial integrity by upregulation of transcripts associated with mitochondrial biogenesis and architecture, increasing the activity of COX, elevation of NAD+ levels and maintenance of mitochondrial membrane potential[12,33]. Yoga helps to preserve genomic stability, telomere length maintenance and chromosomal integrity by slowing down the rate of cellular aging which lowers the risk of emergence of age-related

chronic diseases and complex lifestyle problems[29,30,50]. In addition, yoga increases expression levels of sirtuins independent of intake of red wine or resveratrol or caloric restriction and increase in levels of NAD+ which maintains cross talk between mitochondrial and nuclear DNA. Gautam et al., 2023 also noted a significant decrease in the aged T cell subset population especially the aged Th17 and aged Treg cells in RA patients after 8-weeks oof yoga therapy along with disease modifying anti-rheumatic drugs[11]. Thus, by maintaining cellular health and lifespan, yoga not only prevents the immune system from aging too quickly in RA patients but also lessens the disease's activity, severity, and co-morbid functional impairment[30].Additionally, yoga raises melatonin levels, which are a powerful antioxidant and a master regulator that control the sleep-wake cycle. Melatonin is most concentrated in mitochondria, which are both the source and the target of damage caused by free radicals. As a result, melatonin levels increase and help reduce oxidative damage to mitochondrial DNA, which in turn lowers the frequency of mitochondrial mutations[12,53]. Research on several complicated lifestyle disorders, including glaucoma, depression, idiopathic recurrent pregnancy losses, and unexplained male factor infertility, has revealed that yoga may play a significant role in extending cellular longevity and slowing down the pace of cellular aging, hence enhancing health and lifespan[14,15,27,30,37,47,54].

Our lab's research on infertility with unknown cause has revealed that yoga can minimize testicular inflammation by enhancing OS indicators, which lowers oxidative DNA damage and, in turn, lowers the likelihood of infertility and its aftereffects in subsequent generations[27,55]. Yoga may improve sperm DNA integrity by reducing oxidative DNA damage, OS, and improving the effectiveness of DNA repair processes[14,26]. Overall health benefits are demonstrated by the development of genetically sound sperm that will carry on this genetic material to future generations, hence reducing the incidence of genetic-epigenetic illnesses. Yoga also upregulates the MTHFR expression, a key enzyme of the interlinked folate- homocysteine-methionine metabolism pathway, whose mutation results in a rare autosomal recessive inborn error of metabolism[17]. *MTHFR* polymorphisms are reported to increase the vulnerability to neural tube defects, congenital heart disease, atypical hemolytic uremic syndrome, various neuropsychiatric disorders like autism spectrum diseases and attention deficit hyperactivity disease, cleft palate, acute leukemia, cardiovascular diseases, occlusive vascular disease in children[56,57]. Yoga has the potential to decrease the oxidative damage brought on by increased free radicals and upregulates *MTHFR* expression, which increases the enzyme's capacity to mitigate OS-induced aberrant sperm DNA methylation that would have had a greater impact on the sperm epigenome[17].

Conclusion

Yoga is an all-encompassing philosophical system that aims to balance the body, mind, and spirit. The three main components of yoga are *pranayama* (regulated breathing practices), *asanas* (postures) and *dhyana* (meditation). Yoga enhances bodily functions and increases the mind's ability to overcome illness through several downstream regulatory pathways. Yoga switches on the internal pharmacy by optimizing gene expression patterns,

maintaining immune-homeostasis (Th17/Treg), balancing pro- and anti-inflammatory markers, OS eustress, regulating psychological stress, regulating epigenetic markers, synchronizing sleep-wake cycles and circadian rhythms, promoting neuroplasticity and stimulating neurogenesis, slowing down the rate of cellular aging through regulation of telomere metabolism, achieving mitochondrial and nuclear genomic stability, and upregulating immune regulatory molecules. Yoga helps to slow down the rate of cellular aging and psychological stress by gradually lowering blood levels of free radicals, increasing telomerase activity, lowering cortisol and inflammatory cytokines, and increasing the expression of several anti-inflammatory and cell cycle control genes, as well as by enhancing mitochondrial integrity and upregulating the expression levels of multiple genes that code for antioxidants and so increasing the total antioxidant capacity. Hence, yoga not only promotes health, prevents onset of diseases, and has rehabilitative potential but can also act as a powerful adjunct to modern medicine in management of diseases especially complex lifestyle diseases.

Conflict of Interest Statement:

None

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Table 1. Description of the clinical trials on the effect of yoga on gene expression, epigenetic alterations and response to genetic polymorphisms

Study Design; participants	Number of participants	Duration	Intervention Description	Control Description	Genetic/epigenetic/Systemic Biomarkers	Results	References
RCT; RA patients	n=64; Yoga group=32; Non-yoga group=32	8-weeks	Yoga group: yoga-based mind-body intervention based on Patanjali's Raja yoga: 120 min per day and 5 sessions per week for 8 weeks by yoga instructors + prescribed DMARDs	Non-yoga control group: to follow normal day to day physical activities + prescribed DMARDs	Assessment of T cell subsets [Th17 cells and Treg cells], markers of T cell aging [aged Th17 cells and aged Treg cells], pro-inflammatory markers [IL-6, and IL-17], anti-inflammatory markers [TGF-β, and IL-10], epigenetic alterations [5-methyl cytosine, 5-hydroxymethyl cytosine, and HDAC1] and gene expression patterns [*RORγt*, *FoxP3*, *IL-17*, *IL-6*, *TGF-β*, *CXCL2*, *CXCR2*, and *JUN*]. Disease activity assessment: DAS28-ESR	IL-6, and IL-17 showed a significant ($p < 0.05$) decline, whereas TGF-beta and IL-10 ($p < 0.05$) showed a significant increase in yoga group as compared to control. A significant increase in % of global 5-mC ($p < 0.05$) and reduction in % of global 5-hmC ($p < 0.05$) and decrease in HDAC1 levels ($p < 0.05$); Upregulation of anti-inflammatory genes (*FoxP3* and *TGF-β*), downregulation of pro-inflammatory genes (*RORγt*, *IL-17*, *IL-6*, *CXCL2*, *CXCR2*), and no change in *JUN*. A significant decline in DAS28ESR scores of yoga group as compared to the control group ($p < 0.05$)	Gautam S *et al.*,2023[11]
Prospective Clinical Trial; Infertile men	n=30	3 weeks	Supervised yoga session based on asanas, pranayama and dhyana (1 hour/day) for 3 weeks	None	*MTHFR* gene expression	More than fivefold up-regulation in the expression of *MTHFR* gene. A significantly higher *MTHFR* polymorphic variants in infertile male patients was found as compared to healthy fertile controls.	Borthakur D et al., 2023[17]
RCT; RA patients	n=140; Yoga group=70; Usual care control group=70	8-weeks	Yoga group: yoga-based lifestyle intervention based on Patanjali's Raja yoga: 120 min per day and 5 sessions per week for 8 weeks by yoga instructors + prescribed DMARDs	Usual care control group: followed normal day to day physical activities + prescribed DMARDs	Assessment of soluble HLA-G levels and *HLA-G* 3'UTR +3142G>C and 14 bp ins/del polymorphisms Assessment of disease activity score	Low-producing sHLA-G genotypes, *i.e.*, +3142GG and 14 bp ins/ins, showed a significant increase in sHLA-G levels after yoga intervention.	Gautam S *et al.*,2022[32]

RCT; Breast cancer survivors	n=30; High dose of vitamin D (HVD) group (n=10); Yoga with a low dose of Vitamin D (Y-LVD) group (n=10); Yoga with a high dose of Vitamin D (Y-HVD) group (n=10)	12 weeks	Y-HVD group: yoga with 4000 IU of Vit D; Y-LVD group: yoga with 2000 IU of Vit D. Yoga description for Y-LVD & Y-HVD: 12 weeks yoga regimen (twice a week), based on Hatha yoga style and included physical postures, breath control, and meditation. Each class lasted around 60–90 min; the yoga class started with 60 min and progressively increased 15 min each month to reach 90 min.	HVD group: a high dose (4000 IU) of Vit D supplementation	Physical assessments, handgrip strength tests, quality of life Cytokine level assessment (IL-10, TNF-α, and IL-6), cytokine gene expression levels (*IL-10*, *TNF-α*, and *IL-6*).	Body fat percentage, handgrip strength and QoL indicators include global health, functional scales, and symptoms scales were significantly improved in both YHD and YLD groups compared to the HD group ($p<0.05$). The anti-inflammatory index (IL-10/TNF-α expression) was significantly increased in both the yoga groups ($P<0.05$).	Naderi M *et al.*, 2022[58]
RCT; RA patients	n=70; Yoga group=35; Non-yoga group=35	8-weeks	Yoga group: yoga-based mind-body intervention based on Patanjali's Raja yoga: 120 min per day and 5 sessions per week for 8 weeks by yoga instructors + prescribed DMARDs	Non-yoga control group: to follow normal day to day physical activities + prescribed DMARDs	Mitochondrial health assessment: mitochondrial DNA copy number (mtDNA-CN), OS markers, mitochondrial activity, mitochondrial membrane potential, circadian rhythm markers and transcripts associated with mitochondrial integrity: *AMPK*, *TIMP-1*, *KLOTHO*, *SIRT-1*, and *TFAM*. Disease activity and disability quotient assessment	Yoga significantly improves mitochondrial health by upregulation of mtDNA-CN, NAD+ levels, improvement in COX-II activity, optimization of OS markers, and alteration of circadian rhythm markers. A significant upregulation of genes (*AMPK*, *TIMP-1*, *KLOTHO*, *SIRT-1*, and *TFAM*) associated with maintenance of mitochondrial integrity with improvement in disease activity score and disability index in yoga group.	Gautam S *et al.*,2021[12]
A pre-post pilot study; Idiopathic primary male infertility patients	n=10	21 days	Yoga-based lifestyle intervention (YBLI) group: 2hours/day; included a series of physical postures (*asanas*), breathing exercises, meditation and ended with relaxation via *Shavasana*.	None	Next-generation sequencing-based methylome analysis	Yoga practice was found to be associated with DNA methylation changes at nearly 400 genes, 147 of which were hypermethylated while 229 were hypomethylated, which included promoters of several genes linked to maintenance of fertility and genomic integrity.	Bisht S *et al.*,2020[27]

Pilot RCT; HTN and/or type 2 Diabetes	n=48; Brain education-based meditation (BEM) intervention group (n=24); Health education intervention group (n=24)	8-weeks	BEM group: applies 5 steps of brain education, also known as brain wave vibration meditation, with features of both yoga and meditation. (2 classes/week)	Health education intervention group	Assessment of serum glutamic-oxaloacetic transaminase, serum glutamic pyruvic transaminase, gamma glutamyl transpeptidase, creatinine, high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol. Inflammatory gene expression levels: *NFKB2*, *RELA*, and *IL1B*. Self-report assessment of mental/physical health	LDL cholesterol level was significantly decreased in the BEM group after the intervention. Expression of inflammatory genes was significantly reduced after 8 weeks of the BEM training. Mental/physical health self-reports showed a significant improvement (all $p<0.05$).	Lee SH *et al.* 2019[59]
RCT; Major depressive disorder patients	n=178 Yoga group; n=89 Drug group; n=89	12-weeks	Yoga group: Yoga-based lifestyle intervention 5days/week along with routine drug therapy with suitable selective serotonin reuptake inhibitors (SSRI's)	Drug group: Suitable SSRIs as per the prescription of psychiatrists.	Assessment of 5-HTTLPR and *MTHFR* 677C>T polymorphisms in MDD treatment with either YBLI or routine drug therapy	Yoga provides MDD remission irrespective of the presence of 5-HTTLPR and *MTHFR* 677C>T polymorphisms.	Tolahunase MR *et al.*, 2018[48]
Prospective exploratory study; Male partners of Recurrent pregnancy loss couples	n=42	21 days	Yoga-based lifestyle intervention (YBLI) based on physical postures (*asanas*), breathing exercises, meditation	None	Assessment of gene expression analysis on spermatozoal *FOXG1*, *SOX3*, *OGG1*, *PARP1*, *RPS6*, *RBM9*, *RPS17* and *RPL29*. Levels of seminal reactive oxygen species (ROS) and sperm DNA damage	*SOX3*, *OGG1* and *PARP1* were upregulated, while *FOXG1*, *RPS6*, *RBM9*, *RPS17* and *RPL29* showed downregulation after YBLI program. A significant reduction in ROS levels, an increase in sperm motility, sperm count and a decrease in sperm DNA damage was seen after YBLI.	Dhawan v *et al.*, 2018[14]
Longitudinal RCT; Breast cancer survivors	n =128; Mindfulness -based cancer recovery intervention (MBCR group); n=53 Supportive expressive group therapy (SET group); n=49 Stress management seminar (Control group); n=26	8-12 weeks	MBCR group: MBCR program consists of mindfulness, awareness of the present moment for 8 weeks of 90 min duration. SET group: SET program encourages openness and emotional expression for 90 min weekly for 12 weeks	Control group: Control group participated in 1-day (6 hour) didactic seminar management seminar	Assessment of Profile of Mood States (POMS) Assessment of Symptoms of Stress Inventory (SOSI), the Calgary SOSI (C-SOSI) Measurement of relative telomere length (TL) using quantitative real-time polymerase chain reaction (qPCR)	Both MBCR & SET groups-maintained TL over 3-month intervention period, whereas control group demonstrated a trend towards decrease in relative TL. No associations noted between changes in TL and changes in mood or stress scores over time.	Carlson LE *et al.*, 2015[51]
RCT; Breast cancer survivors	n=31; Iyenger yoga group, (n==16); Health education group (n==15)	12-weeks	Iyengar yoga group: twice a week for 90 min duration	Control group: Health education control condition	Genome-wide transcriptional profiling on blood Assessment of circulating inflammatory markers: soluble TNF receptor type II, IL-1 receptor antagonist, IL-6, CRP	Yoga group showed reduced activity of the pro-inflammatory transcription factor NF-κB, increased activity of the anti-inflammatory glucocorticoid receptor, and reduced activity of cAMP response element-binding protein (CREB)	Bower JE *et al.*, 2014[60]

					Assessment of Salivary cortisol	family transcription factors relative to controls (all *ps* < .05). Yoga resulted in a significantly decreased soluble TNF receptor type II. No significant change in IL-1 receptor antagonist, IL-6, CRP and diurnal cortisol in yoga group	
Rapid response study; Healthy people	n=10	2 days for 2 hours; 1.5 months to 5 years of experience	Comprehensive yoga program group: Sudarshan kriya, yoga and related practices	Control regimen group: (within-subject controls) Relaxation with nature walk and listening to relaxing music	Rapid global gene expression profile changes in the peripheral blood mononuclear cells (PBMCs)	Comprehensive yoga program has a rapid and significantly greater effect on gene expression in PBMCs compared with the control regimen.	Qu S*et al.*, 2013[24]
RCT; Family dementia caregivers	n=45 Kirtan Kriya Meditation (KKM) group (n=23) Relaxing Music (RM) group (n=16)	8 weeks; 12 minutes daily	Kirtan Kriya Meditation (KKM) group: yogic meditation chanting practice	Relaxing Music (RM) group: Relaxation practice in a quiet place with closed eyes while listening to relaxing instrumental music	Genome-wide transcriptional profiling from peripheral blood leukocytes	Yogic meditation reverses NF-κB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers.	Black DS et al., 2013[61]

Abbreviations: RCT: Randomized controlled trial; RA: Rheumatoid arthritis; DMARDs: Disease modifying anti-rheumatic drugs; Th17: T helper 17; Treg: T regulatory; IL: Interleukin; *TGF*-beta: Transforming growth factor beta; 5-mC: 5-methyl cytosine; 5-hmC: 5-hydroxymethyl cytosine; HDAC1: Histone deacetylase 1; RORγt: RAR-related orphan receptor gamma, FoxP3: forkhead box P3; CXCL2: Chemokine (C-X-C motif) ligand 2, CXCR2: CXC- receptor 2; JUN: C-jun; MTHFR: 5, 10 methylenetetrahydrofolate reductase; HLA-G: Human leukocyte antigen-G; YHD: Yoga with high dose of Vit D; YLD: Yoga with low dose of Vit D; HD: High dose of vitamin D; TNF-alpha: Tumor necrosis factor- alpha; mtDNA-CN: mitochondrial DNA copy number; OS: oxidative stress; NAD+: Nicotinamide adenine dinucleotide; AMPK: 5′ adenosine monophosphate-activated protein kinase; TIMP-1: tissue inhibitor of matrix metalloproteinases 1; TFAM: transcription factor A mitochondrial precursor; KLOTHO: a Greek word for the gene that regulates lifespan; SIRT1: sirtuin 1; COX-II: cytochrome c oxidase; YBLI: Yoga-based lifestyle intervention; HTN: hypertension; NFKB2: nuclear factor kappa B subunit 2, RELA: REL-associated protein involved in NF-KB; SSRIs: selective serotonin reuptake inhibitors; MDD: major depressive disorder; 5-HTTLPR (serotonin transporter-linked polymorphic region); ROS: reactive oxygen species; FOXG1: forkhead box G1; SOX3: SRY-related HMG-box 3, OGG1: 8-oxoguanine DNA glycosylase; PARP1: Poly (ADP-ribose) polymerase 1; RPS6: Ribosomal Protein S6; RBM9: RNA binding motif protein 9, RPS17: ribosomal protein S17 and RPL29 ribosomal protein L29; CRP: C- reactive protein.