Original Article

Multi-omics integration and interactomics reveals molecular networks and regulators of the beneficial effect of yoga and exercise

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Abstract

Background: Yoga is a multifaceted spiritual tool that helps in maintaining health, peace of mind, and positive thoughts. In the context of asana, yoga is similar to physical exercise. This study aims to construct a molecular network to find hub genes that play important roles in physical exercise and yoga. **Methodology:** We combined differentially expressed genes (DEGs) in yoga and exercise using computational bioinformatics from publicly available gene expression omnibus (GEO) datasets and identified the codifferentially expressed mRNAs with GEO2R. The co-DEGs were divided into four different groups and each group was subjected to protein–protein interaction (PPI) network, pathways analysis, and gene ontology. **Results:** Our study identified immunological modulation as a dominant target of differential expression in yoga and exercise. Yoga predominantly modulated genes affecting the Th1 and NK cells, whereas Cytokines, Macrophage activation, and oxidative stress were affected by exercise. We also observed that while yoga regulated genes for two main physiological functions of the body, namely Circadian Rhythm (BHLHE40) and immunity (LBP, T-box transcription factor 21, CEACAM1), exercise-regulated genes involved in apoptosis (BAG3, protein kinase C alpha), angiogenesis, and cellular adhesion (EPH receptor A1). **Conclusion:** The dissimilarity in the genetic expression patterns in Yoga and exercise highlights the discrete effect of each in biological systems. The integration and convergences of multi-omics signals can provide deeper and comprehensive insights into the various biological mechanisms through which yoga and exercise exert their beneficial effects and opens up potential newer research areas.

Keywords: *Exercise, integrative genomics, protein-protein interaction, yoga*

Introduction

Yoga envisages a balance between physical, psychological, mental, and spiritual domains in life. National Institutes of Health Groups Yoga under complementary and alternative medicine.[1] The focus on breath control, mindfulness, and maintenance of posture differentiates it from other physical exercises.[2] Various yoga practices have been explored in a wide range of diseases for their efficacy in mitigating symptoms.

Multiple studies have analyzed the effect of yoga in improving the clinical symptoms in various illnesses. Yoga-based lifestyle intervention has been shown to impact remission in patients with major depressive disorder, irrespective of their response to the antidepressant treatment.[3] In rheumatoid arthritis patients, the practice of yoga decreased the levels of inflammatory cytokines and improved the clinical symptoms.[2] Yoga has also been shown to bring about a modest reduction in blood pressure in hypertensive individuals.[4] The evidence from different randomized controlled trials (RCTs) demonstrates yoga to have beneficial effects on diastolic blood pressure, HDL cholesterol, and triglycerides.[5] Further, sustained yoga practice had a beneficial impact in adults with metabolic syndrome by decreasing waist circumference. It also improved physical functions, central obesity, and alterations in the ghrelin axis.[6]

Recently, multiple studies have explored the molecular alterations and changes in the plasma levels of various biomarkers in Yoga. Yoga has been shown to downregulate pro-inflammatory genes.[7] The pro-inflammatory transcription factor NF-κB was downregulated in individuals practicing yoga.[8] A 12-week practice of yoga in breast cancer survivors reduced the expression of inflammation-related genes,

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including nuclear factor kappa B (NF-κB) and cAMP response element-binding protein family transcription factors.[9] In a study conducted among women with chronic stress, women practicing yoga had reduced methylation of the tumor necrosis factor gene when compared with controls.[10] The decrease in the systemic inflammation observed in yoga-practicing rheumatoid arthritis patients was attributed to its effect on the psycho-neuro-immune axis.[11] Recently, Qu *et al*. have demonstrated that yoga and related practices lead to changes in gene expression profiles in peripheral blood mononuclear cells (PBMCs).[12]

Yoga has also been postulated to have a role in halting cellular aging in healthy populations. A significant decrease in various biomarkers of aging, including 8-hydroxy-2′-deoxyguanosine and total antioxidant capacity, was observed as an effect of yoga and meditation-based lifestyle intervention.[12] Furthermore, yoga in infertile individuals had been shown to bring about epigenetic changes in spermatozoa. Hypomethylation at the promoter sites of genes having a crucial role in male fertility and embryo implantation was identified after yoga-based lifestyle intervention. Further, the practice of yoga also leads to a reduction in DNA damage and a decrease in seminal oxidative stress in spermatozoa.[13,14]

Many of the effects attributed to yoga has also been observed in people who undergo physical exercise. Physical exercise has been shown to positively impact the quality of life and cardiopulmonary fitness.[15] It reduces the incidence of hypertension in the community. Both yoga and physical exercise reduced the odds of developing diabetes.[16] In addition, the exercise was found to be noninferior to pharmacologic prophylactic interventions in the prevention of migraine.[17] Further, aerobic exercise was demonstrated to be effective in alleviating cancer-related fatigue in breast cancer patients.[18]

Different studies have compared the efficacy of yoga to exercise. In an RCT among patients with unipolar depression, yoga has been shown to have comparable efficacy to aerobic exercise in alleviating negative thinking.[19] In a recent meta-analysis by So *et al*., yoga was more effective in reducing anxiety than nonmindful exercise.[20] Guo *et al*. had demonstrated yoga to be more effective than other physical activities in alleviating depression symptoms in college students.[21] Contrastingly, in patients with chronic low back pain, the effectiveness of yoga was limited to short-term gains, whereas physical exercises brought about intermediate-term gain in pain relief.[22] Interestingly, yoga was found to have more effective when compared with physical exercise in improving glycemic control, anxiety, and depression.[23]

Methodology

Data collection

We have searched in the gene expression omnibus (GEO) database by several keywords including "Yoga," "Exercise," "Blood," "Homo sapiens," "Expression profiling by array," "PBMC" from January 01, 2012 to December 17, 2020. Selected Two gene series expressions (GSEs) data were for further study. GSE44777 contains PBMCs and lymphocytes of 10 samples before yoga and 10 samples after yoga, while GSE6053 contains PBMCs and lymphocytes three samples before exercise and three samples after exercise [Figure 1].

Identification of codifferentially expressed mRNAs

GEO2R is an online interactive web tool used to compare two or more groups of samples in a GEO Series to identify genes that are differentially expressed across experimental conditions. We obtain differentially expressed genes (DEGs) from two datasets (GSE44777 and GSE6053) of yoga and exercise with the help of GEO2R with the cutoff criteria of $P < 0.05$. Common genes in both datasets were identified and isolated with the use of the Venn diagram.

The assortment of codifferentially expressed mRNAs in the four groups

All the assorted differential expressions of genes were divided into four groups. Group 1: Upregulated DEGs in both yoga and exercise, Group 2: Down-regulated DEGs in both yoga and exercise, Group 3: Upregulated DEGs in exercise and downregulated DEGs in yoga, Group 4: Downregulated DEGs in exercise and upregulated DEGs in yoga. A heat map was generated for DEGs in all four groups based on the gene expression level of each group and was compared with a whole-body gene expression heat map [Table 1].

Protein–protein interaction network analysis and hub gene identification

STRING, a biological-Interactomic database and web resource of known and predicted protein-protein interactions (PPIs), was used for the Retrieval of Interacting Genes or Proteins. We separated the genes of the four groups and uploaded the gene list of each group in the STRING software. Thereafter, STRING (http://string-db.org/)[24] was used to construct a PPI network using only common DEGs with other interacting genes and more significant than 0.4 confidence score cutoffs. Cytoscape built the interaction networks for each group.[25]

Functional enrichment and Reactome pathway analysis

Functional enrichment analysis is a specific method to identify the various classes of over-represented genes in a large set of genes and may be associated with particular disease phenotypes. The functional gene enrichment analysis of all codifferential genes of four groups was

Figure 1: Workflow of methodology

performed by string database and the functional features of each group were divided into three categories of gene ontology (GO) (1) biological process (BP), (2) molecular function (MF), (3) cellular components (CC). Reactome,[26] an online biological database for pathways analysis, has been used to identify the role of all genes in all four categories.

Gene disease relationship analysis

Gene Disease relationship has been used to understand complex diseases, multiple composite interactions between different phenotype-genotype relationships and gene-disease mechanisms. We have identified the Gene Disease relationship of all four groups by OMIM Disease, Jensen Disease, DisGeNET,[27,28] the database related to human gene-disease associations, and variant-disease associations.

Results

Identification of differential expression of genes in both yoga and exercise

The two human PBMC and Lymphocytes mRNA expression profiles datasets included in this study were GSE44777, which included 10 samples before yoga and 10 samples after yoga, and GSE6053 having three samples before exercise and three samples after exercise. Using $P < 0.05$ as a cutoff criterion, we extracted 1443 and 1122 DEGs from the expression profile datasets GSE44777 and GSE6053, respectively. We used the Venn diagram tool to overlap identified and found 97 overlapping DEGs of two profile datasets, GSE44777, and GSE6053.

Classification of differentially expressed genes in four groups

We have classified common DEGs of yoga and exercise into four groups based on fold change expressions. Group 1: Upregulated DEGs in both yoga and exercise (33 DEGs); Group 2: Downregulated DEGs in both yoga and exercise (37 DEGs); Group 3: Upregulated DEGs in Exercise and downregulated DEGs in yoga (13 DEGs); Group 4: Downregulated DEGs in exercise and upregulated DEGs in yoga (16 DEGs) [Table 1].

Identification of hub genes through protein–protein interaction network

PPI complex networks are formed as a result of biochemical or electrostatic forces.[25] PPI network is crucial for the molecular mechanism of the metabolic process. Using STRING human gene or protein database[29] and Cytoscape software, DEGs for all four groups were used to establish the PPIs network.

In Group 1, 33 common DEGs of GSE44777 and GSE6053 and 10 other interacting genes were used to

Table 1: Classification of four different types of differential gene expressions in yoga and exercise

Gene	Exercise↓ FCE	Yoga↓ FCE	Gene	Exercise↑ FCE	Yoga↑ FCE	Gene	Exercise↑ FCE	Yoga↓ FCE	Gene	Exercise↓ FCE	Yoga↑ FCE
BCL2	0.59	0.95	ABHD5	1.43	1.25	BAG3	1.48	0.85	ABCC2	0.28	1.06
CA12	0.47	0.96	AQP9	1.61	1.25	CBR3	2.05	0.86	AGTPBP1	0.76	1.11
CACNA1I	0.56	0.74	BASP1	1.58	1.18	EPHA1	1.61	0.87	ATP4B	0.52	1.05
CAPN5	0.71	0.91	BTC	2.91	1.06	GABRB3	5.62	0.94	BHLHE40	0.69	1.14
CD160	0.32	0.77	CASP9	1.5	1.09	GAMT	4.75	0.91	CEACAM1	0.61	1.29
CD69	0.73	0.81	CRISPLD2	1.53	1.31	GRM5	2.35	0.94	CLDN18	0.59	1.05
COL5A2	0.58	0.92	DNAJB6	1.71	1.13	MBNL2	1.95	0.93	DAAM2	0.32	1.14
DBP	0.52	0.9	ECT2	1.85	1.14	PRKCA	4.65	0.84	DBT	0.53	1.04
DDIT4	0.6	0.72	EYA3	2.07	1.06	SCNN1G	2.26	0.96	IGF2R	0.69	1.22
DRD2	0.25	0.95	IL1R1	4.36	1.11	SLC17A7	2	0.96	JAKMIP2	0.62	1.06
ESR1	0.28	0.94	KIAA0513	1.46	1.14	ZBED2	3.23	0.96	LBP	0.47	1.06
FARSA	0.75	0.95	KYNU	1.81	1.16				PGPEP1	0.72	1.05
FEZ1	0.38	0.81	LILRB3	1.43	1.19				SLC35A2	0.65	1.07
FKBP5	0.47	0.8	MLF2	1.34	1.09				SLC5A4	0.24	1.04
GADD45GIP1	0.2	0.94	NCF4	1.48	1.23				TAF5L	0.69	1.06
GPM6B	0.32	0.96	NFE2	1.47	1.26				TBX21	0.41	1.07
GRIP2	0.54	0.94	PADI4	1.81	1.26						
HOPX	0.51	0.95	PAPSS2	2.04	1.12						
HSD17B8	0.68	0.9	PDE4DIP	4.76	1.09						
ICA1	0.55	0.91	PLOD1	1.44	1.17						
IDH2	0.72	0.87	RNF24	2.01	1.19						
IQCK	0.62	0.9	S100A11	1.55	1.19						
KLHL3	0.71	0.87	SLC11A1	1.51	1.16						
KLK12	0.43	0.95	SNX27	1.5	1.1						
LDLR	0.3	0.82	SPAG11A	1.91	1.06						
MCF2	0.22	0.94	TEAD4	1.71	1.05						
NOVA2	0.56	0.94	TMEM70	1.9	1.07						
NUP107	0.75	0.92	TREM1	2.48	1.21						
PRDM1	0.72	0.85	TREML2	2.45	1.19						
RAB17	0.44	0.95	TRIB1	1.79	1.35						
RSG1	0.64	0.93	VDR	3.25	1.09						
SIRT3	0.75	0.94	VNN2	1.58	1.18						
SLC1A4	0.35	0.91	VNN3	1.58	1.27						
SLC25A15	0.7	0.9									
SOCS1	0.27	0.86									
TSEN2	0.7	0.91									
TXK	0.64	0.85									

*FCE=Fold change expression, ↑=Up-regulation, ↓=Down regulation. ESR1=Estrogen receptor 1, LDLR=Low density lipoprotein receptor, IDH2=Isocitrate dehydrogenase (NADP[+]) 2, DDIT4=DNA damage inducible transcript 4, FARSA=Phenylalanyl-tRNA synthetase subunit alpha, FKBP5=FKBP prolyl isomerase 5, KLHL3=Kelch like family member 3, PRDM1=PR/SET domain 1, SIRT3=Sirtuin 3, SOCS1=Suppressor of cytokine signaling 1, TSEN2=tRNA splicing endonuclease subunit 2, CASP9=Caspase 9, IL1R1=Interleukin 1 receptor type 1, KYNU=Kynureninase, NCF4=Neutrophil cytosolic factor 4, PDE4DIP=Phosphodiesterase 4D interacting protein, SLC11A1=Solute carrier family 11 member 1, TEAD4=TEA domain transcription factor 4, TREM1=Triggering receptor expressed on myeloid cells 1, TREML2=Triggering receptor expressed on myeloid cells like 2, VDR=Vitamin D receptor, VNN2=Vanin 2, VNN3=Vanin 3, ABCC2=ATP binding cassette subfamily C member 2, TBX21=T-box transcription factor 21, IGF2R=Insulin-like growth factor 2 receptor, SLC35A2=Solute carrier family 35 member A2, PRKCA=Protein kinase C alpha, SLC17A7=Solute carrier family 17 member 7, EPHA1=EPH receptor A1, GABRB3=Gamma-aminobutyric acid type A receptor subunit beta 3, GRM5=Glutamate metabotropic receptor 5, DBT=Dihydrolipoamide branched chain transacylase E2, TAF5L=TATA-box binding protein associated factor 5 like

establish the PPI network by STRING which constituted of 43 nodes, 32 edges and PPI enrichment $P = 0.001$ at medium confidence (0.400). 15 Hub genes aquaporin 9 (AQP9); aquaporin 7; caspase 9 (CASP9); epithelial cell transforming 2 (ECT2); interleukin 1 receptor type 1 (IL1R1); kynureninase (KYNU); neutrophil cytosolic factor 4 (NCF4); phosphodiesterase 4D interacting protein (PDE4DIP); solute carrier family 11 member 1 (SLC11A1); TEA domain transcription factor 4 (TEAD4); triggering receptor expressed on

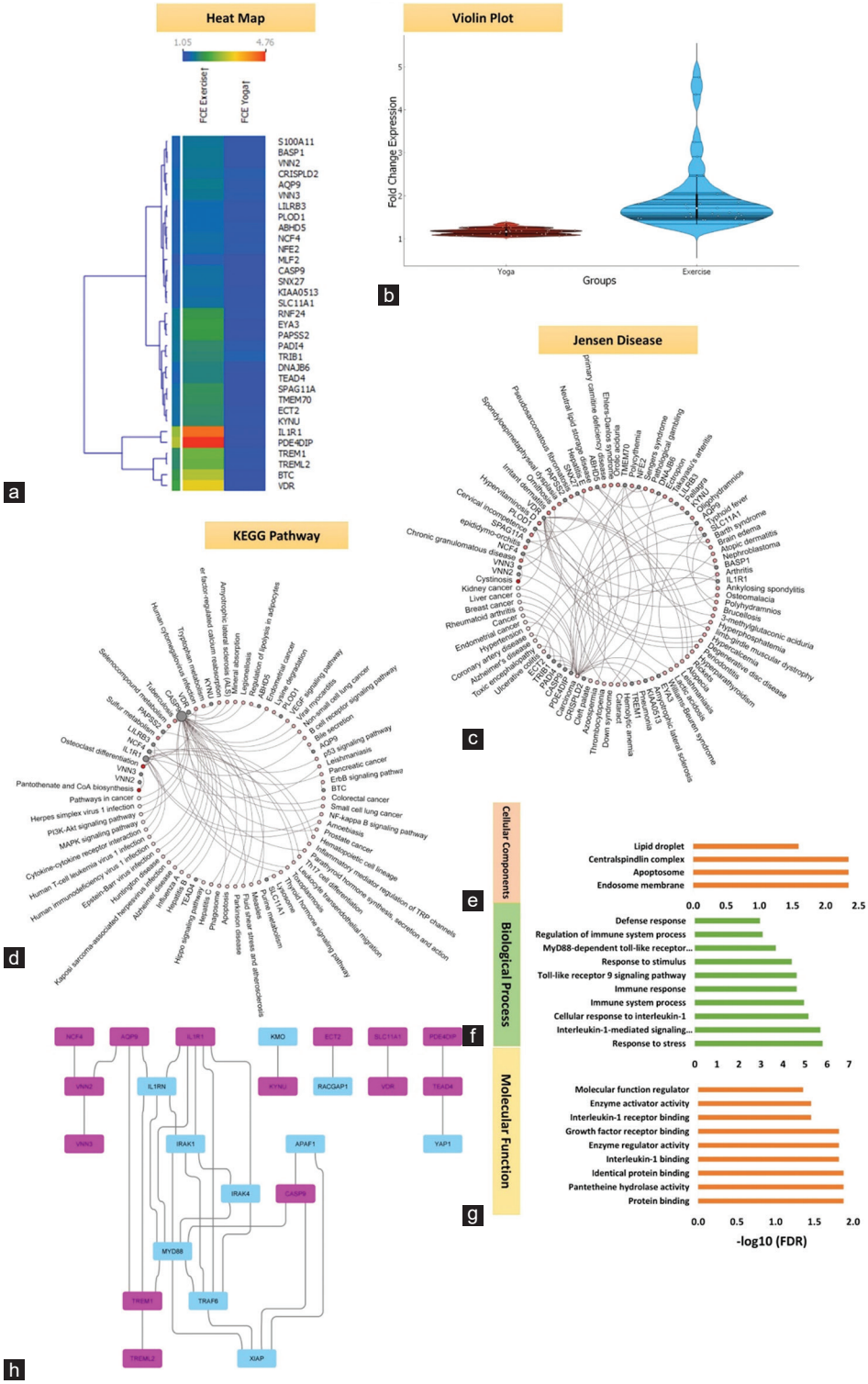

Figure 2: Up-regulated common DEGs of two datasets GSE44777, GSE6053 (Group 1). (a) Heat map up-regulated common DEGs; (the fold change expression of genes are displayed in ascending order from blue to red colour) (b) Violin plot shown the entire FCE distribution of up-regulated common DEGs (Yoga: Red colour, Exercise: Blue colour); (c) Jensen disease (represent the multiple composite interactions between phenotype-genotype relationships and gene-disease mechanisms Gene-Disease Interaction of Group 1); (d) KEGG pathway (This representing the molecular interaction, reaction and relation networks of gene) (e) CC; (f) BP; (g) MF; (h) PPI network.(43 nodes, 32 edges and PPI enrichment *P* = 0.001 at medium confidence [0.400]). 15 Hub genes (Pink Colour) AQP9, AQP7, CASP9, ECT2, IL1R1, KYNU, NCF4, PDE4DIP, SLC11A1, TEAD4, TREM1, TREML2, VDR, VNN2, and VNN3 were identified in the PPI network. DEGs = Differentially expressed genes, BP = Biological process, CC = Cellular components, MF = Molecular function, PPI = Protein-protein interaction, AQP9 = Aquaporin 9, AQP7 = Aquaporin 7, CASP9 = Caspase 9, ECT2 = Epithelial cell transforming 2, IL1R1 = Interleukin 1 receptor type 1, KYNU = Kynureninase, NCF4 = Neutrophil cytosolic factor 4, PDE4DIP = Phosphodiesterase 4D interacting protein, SLC11A1 = Solute carrier family 11 member 1, TEAD4 = TEA domain transcription factor 4, TREM1 = Triggering receptor expressed on myeloid cells 1, TREML2 = Triggering receptor expressed on myeloid cells like 2, VDR = Vitamin D receptor, VNN2 = Vanin 2, VNN3 = Vanin 3

myeloid cells 1 (TREM1); triggering receptor expressed on myeloid cells like 2 (TREML2); Vitamin D receptor (VDR); VNN2 (vanin 2); VNN3 (vanin 3) were identified in the PPI network [Figure 2].

In Group 2, 37 common DEGs of GSE44777, GSE6053 and 10 other interacting genes were used to establish the PPI network by STRING, which constituted 47 nodes, 37 edges, and PPI enrichment $P = 0.0317$ at medium confidence (0.400). Identified 16 Hub genes BCL2 (BCL2 apoptosis regulator), CD160 (CD160 molecule), CD69 (CD69 molecule), DNA damage inducible transcript 4 (DDIT4), estrogen receptor 1 (ESR1), phenylalanyl-tRNA synthetase subunit alpha (FARSA), FKBP prolyl isomerase 5 (FKBP5), isocitrate dehydrogenase (NADP[+]) 2 (IDH2), kelch like family member 3 (KLHL3), low density lipoprotein receptor (LDLR), nucleoporin 107 (NUP107), PR/SET domain 1 (PRDM1), sirtuin 3 (SIRT3), suppressor of cytokine signaling 1 (SOCS1), tRNA splicing endonuclease subunit 2 (TSEN2) in the PPI network [Figure 3].

In Group 3, 11 common DEGs of GSE44777, GSE6053, and five other interacting genes were used to establish the PPI network by STRING, which constituted 16 nodes, 19 edges, and PPI enrichment $P = 0.000$ at medium confidence (0.400). Identified 5 Hub genes gamma-aminobutyric acid type A receptor subunit beta 3 (GABRB3); glutamate metabotropic receptor 5 (GRM5); protein kinase C alpha (PRKCA); solute carrier family 17 member 7 (SLC17A7); EPH receptor A1 (EPHA1) in the PPI network [Figure 4].

In Group 4, 16 common DEGs of GSE44777, GSE6053, and ten other interacting genes were used to establish the PPI network by STRING which constituted 26 nodes, 24 edges, and PPI enrichment $P = 0.003$ at medium confidence (0.400). 06 Hub genes dihydrolipoamide branched chain transacylase E2 (DBT); ATP binding cassette subfamily C member 2 (ABCC2); solute carrier family 35 member A2 (SLC35A2); TATA-box binding protein associated factor 5 like (TAF5 L); insulin-like growth factor 2 receptor (IGF2R); T-box transcription factor 21 (TBX21) were identified in the PPI network [Figure 5].

Gene ontology and reactome pathway analysis

Analyzed GO and reactome pathway enrichment through DAVID, WebGestalt, FunRich, and STRING database with a $P < 0.05$ as significantly enriched and top lowest false discovery rate. GO analysis of DEGs classified them into three functional classes: CC, BP, and MF. Pathway analysis through Reactome Pathways.

Human gene and disease associations

We also identified changes of expression of hub genes and its relation with various types of metabolic and genomic disorders of all four groups.

Group 1: The dysregulation of expression of VDR (hyperparathyroidism, rickets, alopecia, periodontitis), NCF4 (orthosis and atopic dermatitis), IL1R1 (ulcerative colitis, carcinoma), ABHD5 (Ectropion, cataracts).

Group 2: COL5A2 (ehlers-danlos), ESR1 (migraine, myocardial infarction, breast cancer), DRD2 (dystonia), BCL2 (lymphoma and leukemia).

Group 3: GRM5 (toxic encephalopathy, attention deficit hyperactive disorder, alcohol dependence, major depressive disorder, acquired immunodeficiency syndrome), EPHA1 (placenta praevia, craniofrontonasal syndrome, Alzheimer's disease, and cancer), BAG3 (cardiomyopathy, cancer).

Group 4: SLC35A2, ABCC2, AGTPBP1, DAAM2, TBX21, BHLHE40, CLDN18, LBP, IGF2R, SLC5A4, TAF5 L, JAKMIP2 (Carcinoma), SLC35A2, ABCC2 (Bilirubin metabolic disorder) [Figures 2c, 3c, 4c and 5c].

Discussion

Low- and moderate-intensity exercises such as walking and yoga enhance immune function and prevent infections.[30] Yoga and rhythmic breathing (Sudarshan Kriya) have been put forward as a practical and effective tool to improve health, alleviate stress, and increase wellness.[31] In the present study, we observed the T-box transcription factor (Tbx21) and IGF2R to be upregulated in yoga, while a downregulation is followed in exercise. Tbx21 encodes T-bet, which is an immune cell-specific member of the T-box family of transcription factors and has a significant role in cells of both adaptive and innate immune systems.[32] Further, Tbx21 expression in B cells has been demonstrated to have major roles in both protective and pathogenic immune responses.[33] In addition, T-box transcription factors also control neuronal development in the brain.[34] IGF2R hub plays a significant role in growth, development, and energy homeostasis.[35] Apart from the above mentioned two genes, important genes like DBT E2, ABCC2, SLC35A2, and TAF5 L have also been observed to be upregulated in yoga and downregulated in the exercise group.

In contrast, GABRB3, GRM5, PRKCA, SLC17A7, and EPHA1 were observed to be upregulated in exercise while they were downregulated in Yoga. GABRB3, encoding the β3 subunit of GABAA receptor, has a significant role in neurodevelopmental gene and is regulated by non-Mendelian processes and epigenetic modulation.[36] After exhaustive exercise, an increase of 2.66 fold was observed in GABRB3 expression in peripheral blood.[37] Deep RNA-seq analysis has demonstrated GABRB3 to be one of the important genes involved in Neuromuscular-junction development, maintenance, and maturation.[38] GABRB3 genes have also been associated with a wide spectrum of seizure syndromes.[39] Interestingly, Yoga has been demonstrated to have beneficial effects among people with epilepsy.[40]

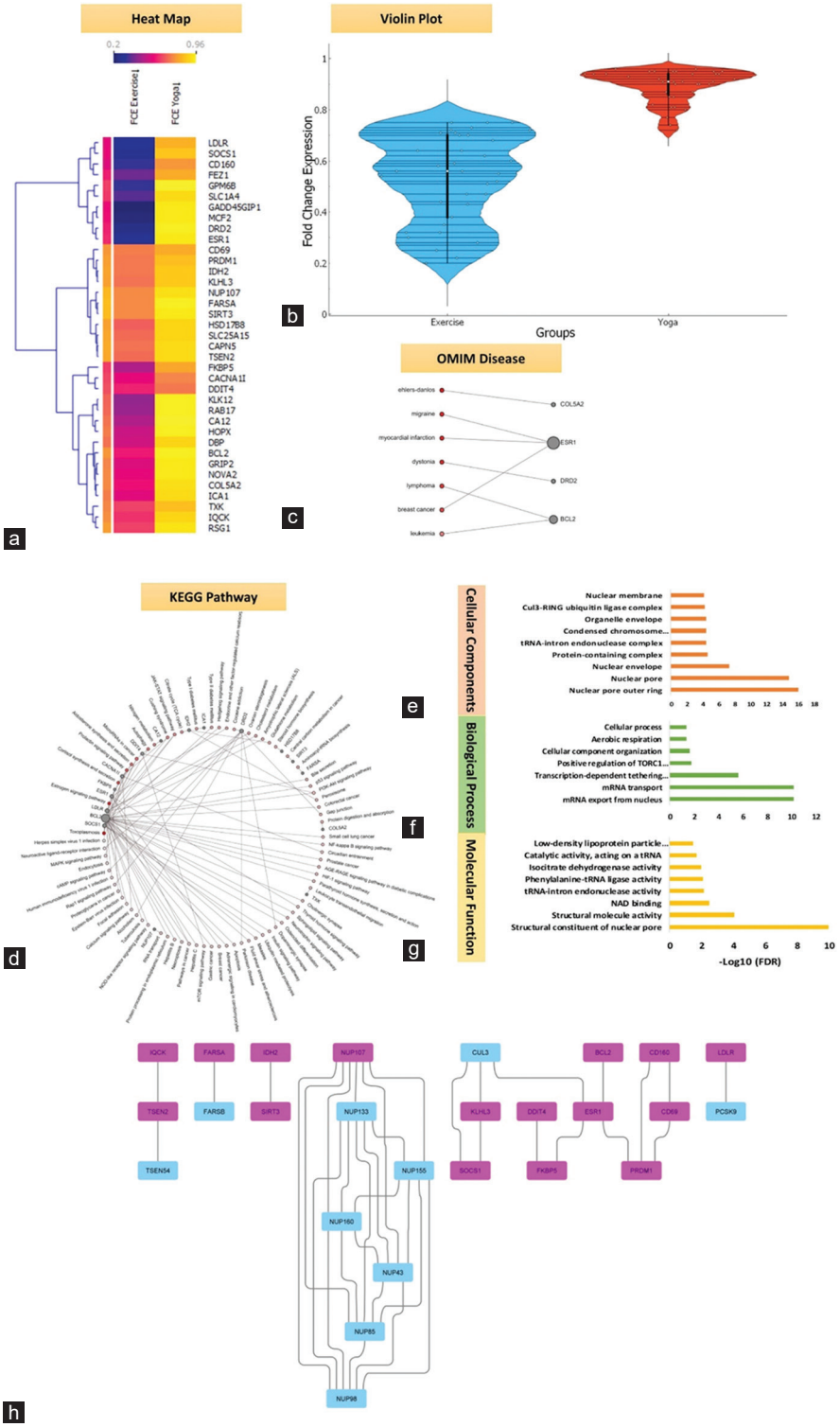

Figure 3: Down-regulated common DEGs of two datasets GSE44777, GSE6053 (Group 2). (a) Heat map (The fold change expression of genes are displayed in ascending order from blue to red colour) of common dDown-regulated common DEGs; (b) Violin plot shown the distribution of common dDown-regulated common DEGs (Yoga: Red colour, Exercise: Blue colour); (c) OMIM Disease (Gene-Disease Interaction of Group 2); (d) KEGG pathway (e) CC; (f) BP; (g) MF; (h) PPI network, (0.47 nodes, 37 edges, and PPI enrichment *P* = 0.0317 at medium confidence [0.400]). Identified 16 Hub genes (Pink Colour) BCL2, CD160, CD69, DDIT4, ESR1, FARSA, FKBP5, IDH2, KLHL3, LDLR, NUP107, PRDM1, SIRT3, SOCS1, and TSEN2 in the PPI network. CD160 = CD160 molecule, CD69 = CD69 molecule, DEGs = Differentially expressed genes, BP = Biological process, CC = Cellular components, MF = Molecular function, PPI = Protein-protein interaction, Bcl-2 = Bcl-2 apoptosis regulator, DDIT4 = DNA damage inducible transcript 4, ESR1 = Estrogen receptor 1, FARSA = Phenylalanyl-tRNA synthetase subunit alpha, FKBP5 = FKBP prolyl isomerase 5, IDH2 = Isocitrate dehydrogenase (NADP[+]) 2, KLHL3 = Kelch like family member 3, LDLR = Low density lipoprotein receptor, NUP107 = Nucleoporin 107, PRDM1 = PR/SET domain 1, SIRT3 = Sirtuin 3, SOCS1 = Suppressor of cytokine signaling 1, TSEN2 = tRNA splicing endonuclease subunit 2

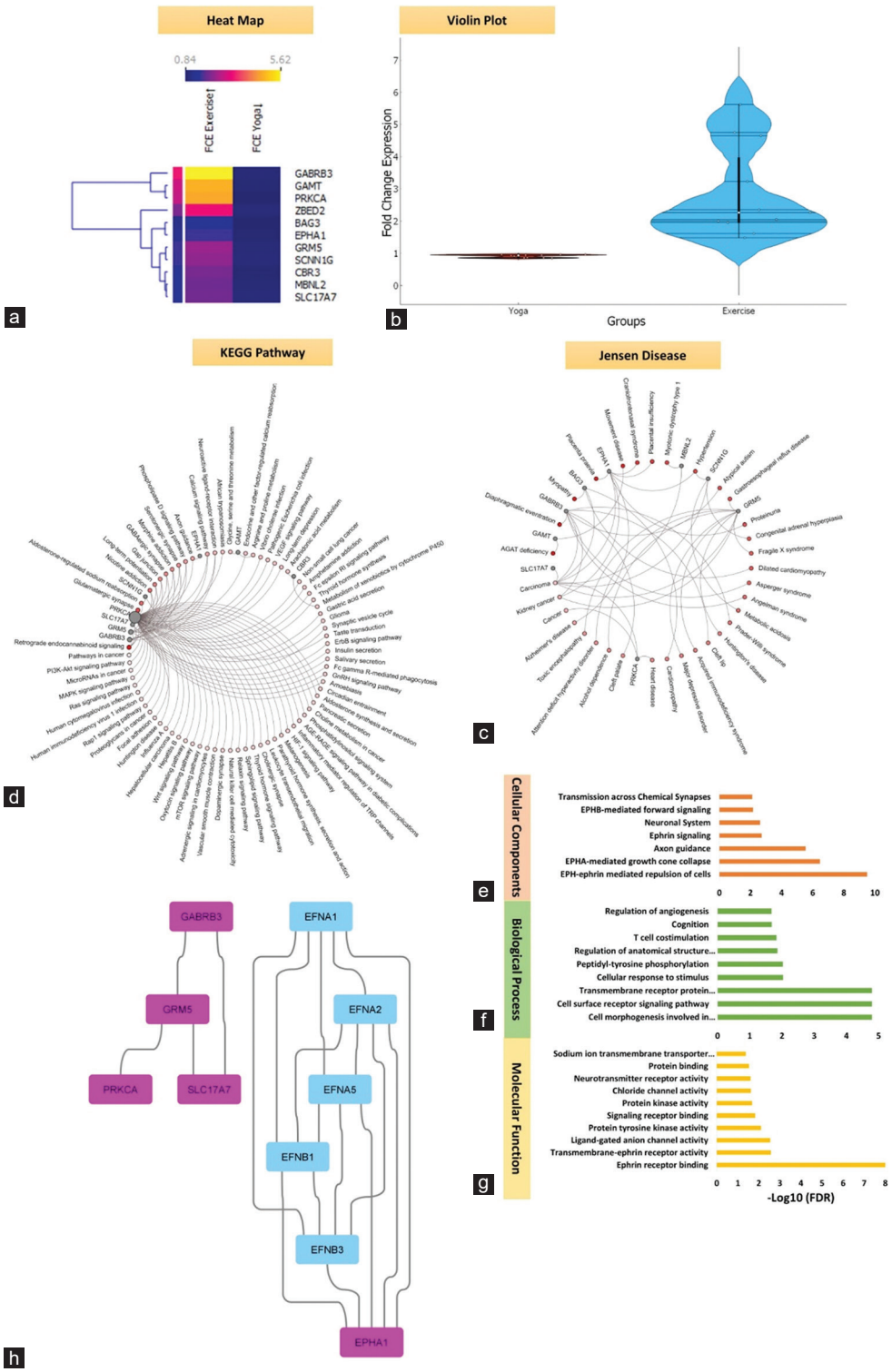

Figure 4: Exercise up-regulated and yoga down-regulated common DEGs of two datasets GSE44777, GSE6053 (Group 3). (a) Heat map (The fold change expression of genes are displayed in ascending order from blue to red colour) of Exercise up-regulated and yoga down-regulated common DEGs; (b) Violin plot shown the entire FCE distribution violin plot of exercise up-regulated and Yoga down-regulated of common DEGs (Yoga: Red colour, Exercise: Blue colour); (c) OMIM disease (gene-disease interaction of group 2); (d) KEGG pathway (e) CC; (f) BP; (g) MF; (h) PPI network (The 16 nodes, 19 edges, and PPI enrichment *P* = 0.000 at medium confidence [0.400]) identified 5 hub genes (Pink colour) GABRB3, GRM5, PRKCA, SLC17A7, in the PPI network. DEGs = Differentially expressed genes, BP = Biological process, CC = Cellular components, MF = Molecular function, PPI = Protein-protein interaction, GRM5 = Glutamate metabotropic receptor 5, PRKCA = Protein kinase C alpha, SLC17A7 = Solute carrier family 17 member 7, EPHA1 = EPH receptor A1, GABRB3 = Gamma-aminobutyric acid type A receptor subunit beta 3

GRM 5 is an excitatory G protein-coupled receptor[41] predominantly expressed on the postsynaptic sites of neurons[42] demonstrated to have a role in psychological disorders, addiction,[43] and anxiety.[44] GRM5

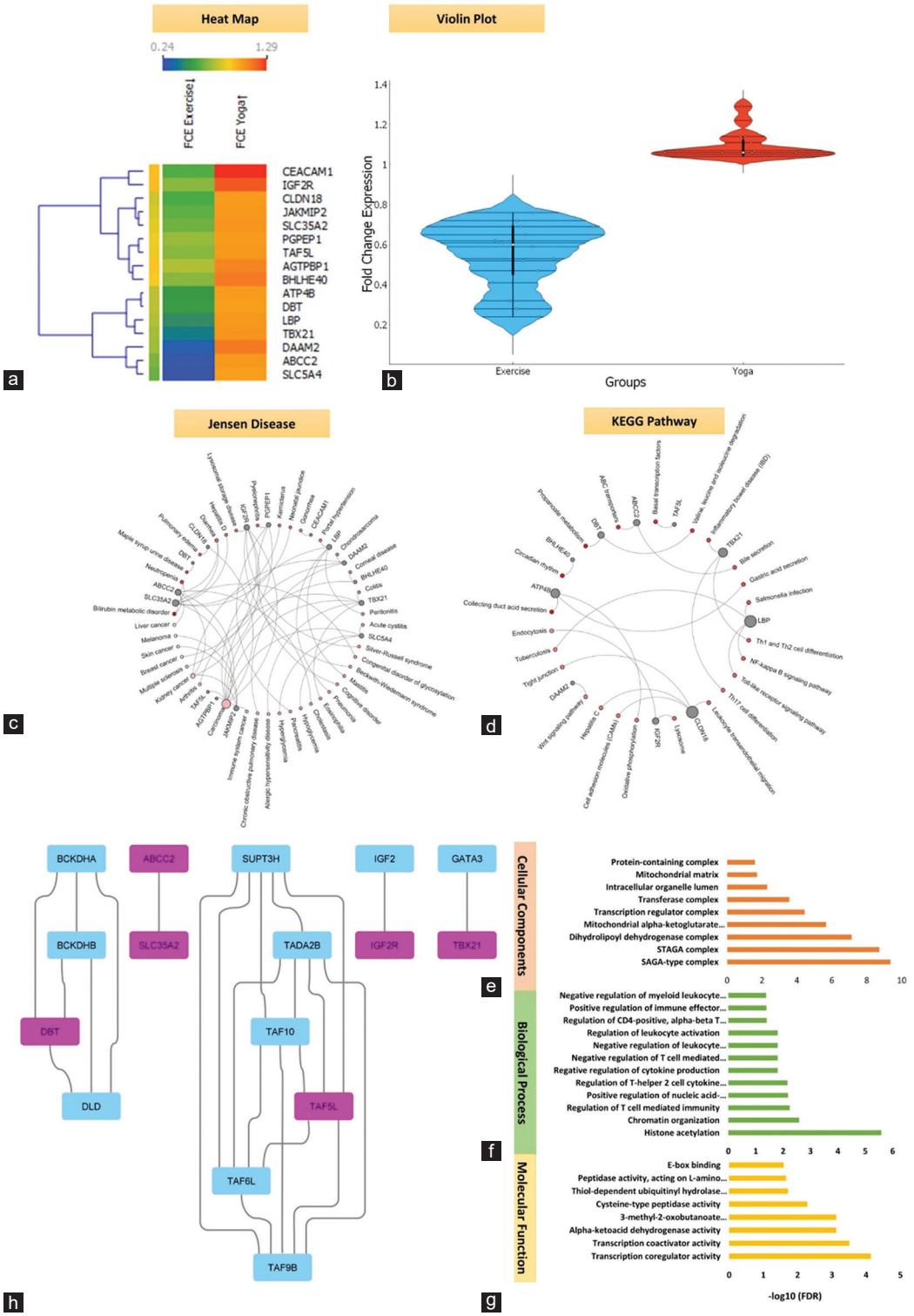

Figure 5: Yoga up-regulated and exercise down-regulated common DEGs of two datasets GSE44777, GSE6053 (Group 3). (a) Heat map (the fold change expression of DEGs are displayed in ascending order from blue to red colour) of yoga up-regulated and exercise down-regulated common DEGs; (b) Violin plot of shown the entire FCE distribution of yoga up-regulated and exercise down-regulated common DEGs (Yoga: Red colour, Exercise: Blue colour); Yoga up-regulated and exercise down-regulated common DEGs; (c) OMIM disease (gene-disease interaction of group 2); (d) KEGG pathway (e) CC; (f) BP; (g) MF; (h) PPI (PPI) network (26 nodes, 24 edges and PPI enrichment *P* = 0.003 at medium confidence [0.400]), 06 Hub genes (Pink colour) DBT, ABCC2, SLC35A2, TAF5 L, IGF2R, TBX21 were identified in the PPI network. DEGs = Differentially expressed genes, BP = Biological process, CC = Cellular components, MF = Molecular function, PPI = Protein-protein interaction, ABCC2 = ATP binding cassette subfamily C member 2, SLC35A2 = Solute carrier family 35 member A2, TAF5 L = TATA-box binding protein associated factor 5 like, IGF2R = Insulin-like growth factor 2 receptor, TBX21 = T-box transcription factor 21, DBT = Dihydrolipoamide branched chain transacylase E2

overactivation plays an important role in the inhibition of autophagy and can result in impaired clearance of neurotoxic aggregates in various neurodegenerative diseases such as Alzheimer's disease and Huntington's disease.[45] Further, the suppression of GRM5 and downstream signaling pathways culminated in neuroprotective effects in Parkinson's disease animal models.[46] The multitude of beneficial effects of GRM5 suppression is attributed to the activation of the mTOR pathway.[47] The activation of the mTOR pathway has been demonstrated to have a crucial role in neurodevelopment and synaptic plasticity.[48] Intriguingly, the beneficial effect of Yoga on neurodevelopment has been demonstrated by Chantal *et al*. by changes in the gray matter using magnetic resonance imaging.[49] The cumulative suppressive effect of Yoga on genes such as GABRB3 and GRM5 highlights the possible neuroprotective effects of Yoga when compared with exercise, as evidenced from the positive outcomes with respect to neurodevelopment and epilepsy management.

The paradoxical nature of the differential expression of these genes in yoga, when compared with exercise, opens up potential areas of future research and will help in better understanding the differing effects of Yoga and exercise in humans.

Apart from the above-mentioned genes, the genes that were upregulated in both yoga and exercise included NCF4, VNN2, VNN3, AQP9, IL1R1, TREM1, TREML2, IL1R1, CASP9, KYNU, ECT2, SLC11A1, VDR, PDE4DIP, and TEAD4. The NCF4 forms NADPH oxidase essential for immune regulating cells, phagocytes for combating bacteria and fungi.[50] VNN2 (vascular noninflammatory molecule 2) participates in hematopoietic cell trafficking and oxidative stress while[51] AQP9 stimulates urea transport and osmotic water permeability.[52] IL1R1 (interleukin-1 alpha receptor alfa-1) an important mediator involved in many cytokine-induced immune and inflammatory responses, binds to the agonist ligands IL-1 and is inhibited by the antagonist IL-1Ra. Natural resistance-associated macrophage protein 1, encoded by the SLC11A1 gene, regulates macrophage activation and has been associated with infectious, autoimmune diseases and tuberculosis susceptibility.[53] Several of the aforementioned genes have been associated with various diseases in their suppressed state. The inverse relation of PBMC VDR expression with disease activity in systemic lupus erythematosus (SLE) patients highlights the possible beneficial role of Yoga and exercise in combating inflammation in SLE patients.[54]

Similarly, the possible positive outcome of Yoga and exercise in cancer may be attributed to the increased expression of IL1R1, which has been demonstrated to have a tumor-suppressive role in breast cancer models, as well as caspase-9, which has a dominant role in the prognosis of colorectal cancer.[55,56] In addition, the de-repression of AQP9 by Yoga and exercise may lead to various neuroprotective effects as the suppressed AQP9 is associated with beta-amyloid-induced neurotoxicity in Alzheimer's disease models.[57]

The following genes were observed to be downregulated in exercise and Yoga: BCL2, CA12, CACNA1I, CAPN5, CD160, CD69, COL5A2, DBP, DDIT4, DRD2, ESR1, FARSA, FEZ1, FKBP5, GADD45GIP1, GPM6B, GRIP2, HOPX, HSD17B8, ICA1, IDH2, IQCK, KLHL3, KLK12, LDLR, MCF2, NOVA2, NUP107, PRDM1, RAB17, RSG1, SIRT3, SLC1A4, SLC25A15, SOCS1, TSEN2, and TXK. B-cell lymphoma 2 (Bcl-2), located on the outer membrane of mitochondria, plays an important role in promoting cell survival and inhibiting the actions of pro-apoptotic proteins. Bcl-2 and Beclin 1 exist as heterodimer complexes in the cytosol, and the dissociation of beclin 1 from Bcl-2 during cellular stress permits autophagy induction.[58,59] The dissociation, triggered by the phosphorylation of Bcl-2, subsequently leads to the formation of the autophagosome.[60] Exercise induces autophagy, via regulation of Bcl-2, culminating in beneficial metabolic effects, especially in carbohydrate metabolism.[60] Our study demonstrates Yoga to be superior to exercise in downregulating Bcl-2. This may translate to Yoga having better beneficial metabolic effects when compared with exercise. Mitogen-activated protein kinase 8 activation by AMPK has been associated with Bcl-2 phosphorylation in cardiomyocytes.[61] Further, c-Jun N-terminal kinase 1 also was observed to induce Bcl-2 phosphorylation and is linked to autophagy induction under starvation conditions in noncardiac cells.[62] However, neither JNK nor MAPK was associated with exercise-induced Bcl2-phosphorylation.[60] Although protein kinase C has been suggested to phosphorylate Bcl-2 and promote cell survival by suppressing apoptosis[63,64] it role in EICA is yet not clear.

Mutations in genes encoding T-type, low-voltage activated, calcium channels (Cav3) channels (CACNA1G, CACNA1H, and CACNA1I) have been linked to a variety of neurodevelopmental, neurological, and psychiatric diseases commonly known as neuronal Cav3 channelopathies.[65] CD160, a marker of lymphocyte populations, has been demonstrated to decrease after 2 h postexercise and correlated with the decrease in lymphocyte count after exercise.[66] The suppression of various tumor-promoting genes such as Bcl-2, NOVA2, and MCF2 again highlights the possible beneficial role of yoga and exercise in various cancers.

Drd1/Drd2 expression in different brain regions had been associated with the stress response. A negative correlation has been demonstrated with elevated levels of Drd1/Drd2 gene expression and the ability to adapt to stress.[67] The decrease in Drd1/Drd2 gene highlights the possible role of Yoga and exercise in better adaptation to stress. The FK506-binding protein 51 (FKBP5), a co-chaperone of the Hsp90 and component of the chaperone-receptor heterocomplex, reduces ligand sensitivity to the glucocorticoid receptor. The

decreased expression of FKBP5 in Yoga and exercise points to its probable usefulness in chronic stress by rectifying the resultant alterations of the HPA axis.[68]

Our study demonstrates that there is an overlap between Yoga and exercise with respect to the differential expression of genes. This leads to the presence of multiple comparable physiological effects for Yoga and exercise. Major physiological functions such as ion transport (ATP4B, ABCC2, SLC5A4, ATP4B, SCNN1G, SLC17A7), neural development (JAKMIP2, AGTPBP1, DAAM2, SCNN1G, SLC17A7), metabolic regulation (IGF2R, DBT, PGPEP1, ATP4B, SCNN1G, SLC17A7), epilepsy management (SLC35A2, GABRB3) were observed to be affected by both yoga and exercise. However, our analysis also throws light onto certain physiological functions whose alterations can be specifically attributed to either yoga or exercise [Figure 6].

We observed that yoga regulated genes for two main physiological functions of the body, namely Circadian Rhythm (BHLHE40) and immunity (LBP, TBX21, CEACAM1). The circadian rhythm creates a sense of harmony between the daily functions of the body and mind and is crucial in the overall wellbeing of an individual. BHLHE40 is a transcriptional repressor involved in the regulation of the circadian rhythm by negatively regulating the activity of the clock genes and clock-controlled genes.[69,70] Our study observed a higher expression of the BHLHE40 gene in yoga when compared with exercise highlighting the beneficial effect of yoga in maintaining the circadian rhythm.

Yoga had been found to reverse the expression of inflammatory mediators and help in maintaining homeostasis. Yoga practices have been shown to down-regulate the expression of various regulators of inflammation and influence the production of pro-inflammatory cytokines

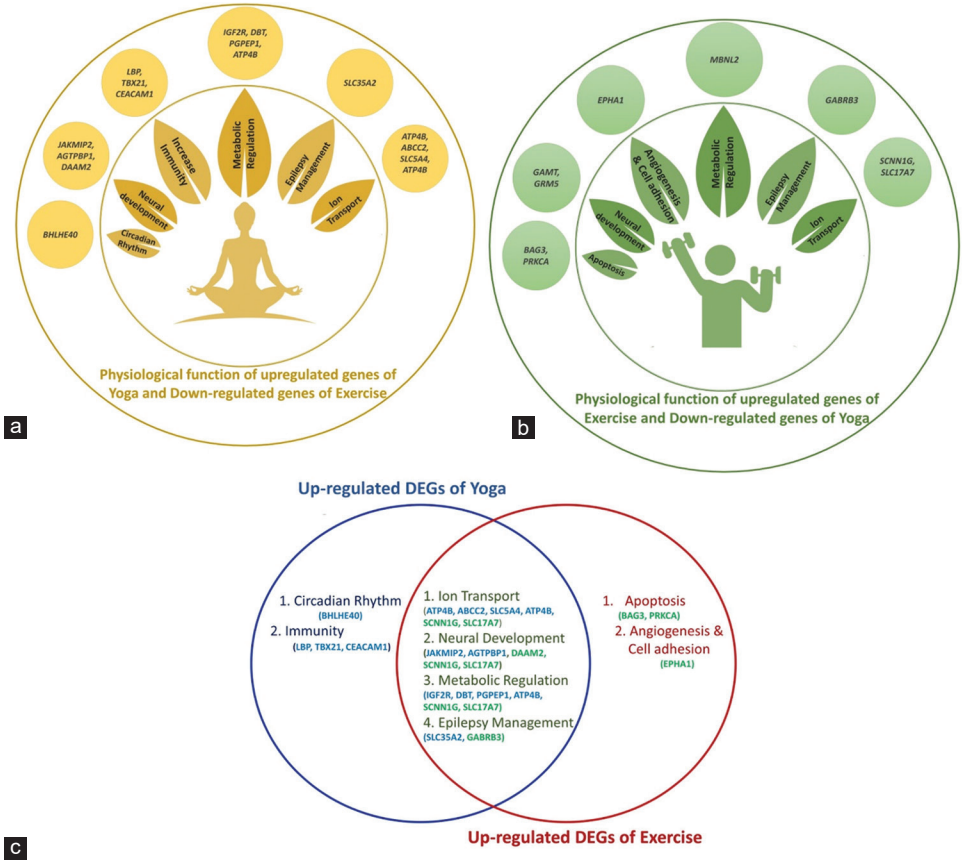

Figure 6: Physiological consequences of yoga or exercise, (a) physiological function of upregulated genes of yoga and down-regulated genes of exercise, all physiological function divided into six classes Circadian rhythm (BHLHE40); Neural development (JAKMIP2, AGTPBP1, DAAM2); Increase Immunity (LBP, TBX21, CEACAM1); Metabolic regulation (IGF2R, DBT, PGPEP1, ATP4B); Epilepsy Management (SLC35A2); Ion Transport (ATP4B, ABCC2, SLC5A4, ATP4B); (b) Physiological function of upregulated genes of exercise and down-regulated genes of yoga, all physiological function divided into seven classes; Apoptosis (BAG3, PRKCA); Neural development (GAMT, GRMS); Angiogenesis and cell adhesion (EPHA1); Metabolic regulation (MBNL2); Epilepsy management (GABRB3); Ion transport (SCNN1G, SLC17A7). (c) Venn-diagram between Upregulated differentially expressed genes (DEGs) of yoga and upregulated DEGs of exercise based on physiological consequences. TBX21 = T-box transcription factor 21, IGF2R = Insulin-like growth factor 2 receptor, SLC35A2 = Solute carrier family 35 member A2, ABCC2 = ATP binding cassette subfamily C member 2, PRKCA = Protein kinase C alpha, SLC17A7 = Solute carrier family 17 member 7, EPHA1 = EPH receptor A1, GABRB3 = Gamma-aminobutyric acid type A receptor subunit beta 3, DBT = Dihydrolipoamide branched chain transacylase E2

in various chronic stress-induced diseases.[71] Our study identified three genes (LBP, TBX21, and CEACAM1), involved in maintaining immune homeostasis, that is upregulated as a result of yoga. LBP binds to the lipid A moiety of bacterial lipopolysaccharide (LPS) present in the outer membrane of all Gram-negative bacteria, plays a crucial role in the innate immune response.[72] It acts as an affinity enhancer for CD14, facilitating its association with LPS and promoting the release of cytokines in response to bacterial LPS.[72] Tbx21 protein is a Th1 cell-specific transcription factor that controls the expression of the hallmark Th1 cytokine, interferon-gamma, and initiates Th1 lineage development from naive Th precursor cells.[73] The protein encoded by CEACAM1 have been attributed has been attributed with multiple functions including roles in the differentiation and arrangement of tissue three-dimensional structure, angiogenesis, apoptosis, tumor suppression, and the modulation of innate and adaptive immune responses.[74]

Contrary to the yoga-regulated physiological processes, the exercise was observed to regulate genes involved in apoptosis (BAG3, PRKCA), angiogenesis, and cellular adhesion (EPHA1).

Exercise-induced apoptosis has been shown to remove damaged cells without pronounced inflammatory responses.[75] The gene BAG3 is involved in chaperone-assisted selective autophagy and stimulates the expression of cytoskeleton proteins in response to mechanical tension via activation of the transcription regulators YAP1 and WWTR1.[76] BAG3 enables the balancing of protein synthesis and degradation under mechanical stress.

The gene EPHA1 belongs to the subfamily ephrin receptors of the protein-tyrosine kinase family. The ephrin receptors are divided into two groups based on the similarity of their extracellular domain sequences and their affinities for binding ephrin-A and ephrin-B ligands. EPH and EPH-related receptors have been implicated in mediating developmental events, particularly in the nervous system, and have roles in angiogenesis and cell adhesion.[77]

Conclusion

The differential expression of multiple genes in Yoga and exercise reveals the unique effect that each has on the genetic expression patterns in individuals. Both Yoga and exercise demonstrated immunomodulation capacity based on the data obtained from the DEGs. However, the modulation of the immune system happens at different levels in Yoga and exercise. The genes modulated in Yoga predominantly affect the Th1 and NK cells, whereas Exercise regulated the expression of cytokines, macrophages activation, and oxidative stress. Our study also demonstrated the significant effect of Yoga on genes encoding and regulating transporter channels. Interestingly, Exercise was found to regulate the genes involved in neural regulation and development. In addition, our analysis also shed light on certain physiological functions whose alterations can be specifically attributed to either Yoga or Exercise. We observed that yoga regulated genes for two main physiological functions of the body, namely circadian rhythm (BHLHE40) and immunity (LBP, TBX21, CEACAM1). In contrast, exercise-regulated genes are involved in apoptosis (BAG3, PRKCA), angiogenesis, and cellular adhesion (EPHA1). The contrast in the effect of Yoga and Exercise on certain gene expressions brings forth the specific beneficial effect of one over the other. Future research in these emerging areas will help us to better understand the unique effect of Yoga and exercise on human physiology.

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Ethical clearance

The institutional ethics committee of All India Institute of Medical Sciences, Jodhpur approved the study "AIIMS/IEC/2021/3564".

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Conflicts of interest

There are no conflicts of interest.

Data Availability Statement

All Supplementary data were deposited in an appropriate public repository (https://doi.org/10.6084/m9.figshare.19170218).

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