COFFEE BOOK
on
TRADITIONAL SCIENCES
Volume- II

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Foreword

I am deeply honoured to be granted the chance to write the foreword for this book entitled "Traditional Sciences." This book serves as a scholarly investigation into the scientific underpinnings of traditional medicine with a special emphasis on the profound impact of Yoga on human health. This book provides insights offered by the practice of yoga in maintaining holistic well-being, in today's dynamic world.

The significance of Yoga and traditional medicine has resurged with remarkable vitality. And within the pages of the book, the readers will embark on an illuminating journey that navigates the rich tapestry of Yoga interwoven with the latest scientific research. This book serves as a synergy between Yoga as an ancient science and modern scientific methodologies serving to provide holistic health in a fast-paced world. This book provides a comprehensive manual offering guidance to delve into the field of Yogic sciences. It encourages the expansion of existing knowledge concerning the role of Yoga and urges the aspiring educators, students, and emerging scientists to explore the uncharted territories within the domain of Yoga.

The present book is a testament to the dedication and guidance provided by Prof. Akshay Anand. Distinguished alumni and ongoing research scholars from Neuroscience Research Lab and CCMB CCRYN centre, PGIMER have contributed to the production of data concerning Yoga and Meditation.

The present book substantiates through scientific validation of the role of Yoga in maintenance of healthy lifestyle. This book offers valuable insights into the utilization of Yoga as a lifestyle strategy for managing chronic low back pain and enhancing the psychological well-being and quality of life for pregnant women and hematopoietic stem cell recipients. Additionally, at the molecular level this book reveals the enhancement of the stem cell population among practitioners of Yoga. In addition to its scientific contributions, the book delves into the current challenges confronting the traditional healthcare system and provides valuable suggestions for overcoming these obstacles.

This book serves as a valuable resource for scientists, students, and the general public, offering a comprehensive array of information on traditional medicine, with a specific focus on the efficacy of Yoga at molecular and psychological levels.

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RESEARCH ARTICLE

Effectiveness of integrated approach of yoga therapy versus usual care in management on chronic low back pain patients: A randomized controlled pilot study

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Abstract

Background: Chronic low back pain is associated with both psychological and functional limitation. Yoga therapy has been shown to improve both the aspects. The present study was planned to evaluate integrated approach of yoga therapy with usaul care.

Aims: This controlled randomized trial was done to evaluate the clinical and molecular changes resulting from integrated approach of yoga therapy (IAYT) as an adjunct regimen and compared it with usual care for the management of chronic low back pain patients.

Material and methods: We enrolled 29 adult patients with non-specific chronic low back pain (CLBP). Patients were randomly divided into two groups. The control group received the usual care of treatment as per institutional protocol. The yoga group received IAYT as an adjunct to usual care. Primary outcomes were pain intensity assessed by verbal numerical rating scale (VNRS) and functional ability assessed by Modified Oswestry Disability Index (MODI). Secondary outcomes were pain catastrophizing, quality of life, fear of movement related to CLBP, type of pain, levels of β-endorphin and TNF-α, and salivary CGRP. All parameters were measured at baseline, 1 and 3 months.

Results: A Significant decrease in VNRS score at 1 and 3 months was observed in both the groups with the yoga group showing a more significant reduction in pain over time than the control group ($p=0.036$). MODI improved significantly only in the yoga group at 1 and 3 months. Intergroup comparison revealed significantly better MODI over time in the yoga group ($p<0.001$). DN4, PDQ, PCS, HADS (anxiety), and Euro QOL had a statistically significant improvement at 1 and 3 months in the yoga group compared with the control group. The HADS (depression) had a statistically significant reduction scores in the yoga group at 3 months compared with the control group ($p=0.012$). There was a significant reduction in TNF-α values in the yoga group compared with baseline ($p=0.004$).

Conclusion: IAYT therapy helped in addressing the psychological components of pain and improved quality of life patients with chronic low back pain compared with usual care.

KEYWORDS
chronic low back pain, integrated yoga therapy, Modified Oswestry Disability Index, salivary CGRP, TNF-α, verbal numeric rating score, β-endorphins

INTRODUCTION

Low back pain (LBP) is the most common and potentially disabling public health problem worldwide.[1,2] Globally, it is among the top four leading causes of years lived with disability (YLDs) as determined by the Global Burden of Disease 2017 study for 354 diseases across 195 countries.[3] Also the prevalence of LBP in India is alarming and nearly 60 percent of individuals suffer from it at some point during their lives.[3] The estimated lifetime, point and 1 year prevalence (95% CI) of LBP in India is reported to be 57% (54%–59%), 32% (28%–30%), 48% (46%–51%), and 59% (56%–62%), respectively in a recent community-based study. In this community study of women, increasing age and lifting activities were the most significant positive predictors of LBP.[4]

Chronic low back pain (CLBP) is a much more complex problem affecting various aspects of an individual's life, including biological, psychological, social, functional, and financial. LBP is reported to result in significant disability, which critically affects the quality of life of the patients.[5] A quarter of patients reported depression.[5] Despite various modalities options available for CLBP, management is usually suboptimal or inadequate.[5] Most of these modalities seem to mainly focus on the biomedical aspect of pain and overlook the mind–body component.[6] Yoga, as an adjunct treatment for CLBP, has emerged as a potential intervention, supported by various randomized controlled trials,[7,8] systematic reviews,[9] meta-analysis, and clinical guidelines.[10] As CLBP patients are more susceptible to psychological and psychosocial factors, Mind–Body Stress Release (MBSR) offers a beneficial technique for back pain and has also been adopted by more than 18,000 Americans.[11,12] Based on a similar approach of the MBSR technique, the integrated approach of yoga therapy (IAYT) can offer a perspective and synergistic culmination for effective management in CLBP.[13–15]

There is a dearth of data on evaluating IAYT in the Indian CLBP population despite the Indian origin of yoga. Also, very few studies have examined the role of pain biomarkers like brain-derived neurotrophic factor (BDNF), C-reactive protein (CRP), and tumor necrosis factor alpha (TNF α) in evaluating the effects of yoga on CLBP patients.[16–18] To the best of our knowledge, no prior research has investigated the mechanistic role of yoga in pain biomarkers with CLBP patients in the Indian population.

We therefore, conducted a pilot study to evaluate the clinical and molecular changes resulting from IAYT administration as an adjunct regimen to the usual care for the management of CLBP patients.

MATERIALS AND METHODS

Study design

This is a randomized controlled trial employing a 2×3 repeated measure design with two groups and three assessment periods (pre-intervention, 1 and 3 months follow-up) conducted in the pain clinic of the Department of Anesthesia and Intensive care of a tertiary care institute. The study period was from May 15, 2020 to August 15, 2020.

Ethics approval and trial registration

The study was approved by the Institute Ethics Committee. The study was registered with the Clinical Trial Registry of India dated 30/04/2020 and has adopted the CONSORT standard guidelines for clinical trial reporting.

Enrolment

All consecutive patients with non-specific CLBP attending the pain clinic were screened for the inclusion criteria. Inclusion criteria were patients with non-specific axial lumbosacral chronic low back pain of more than 3 months duration not responding to conservative management with a verbal numerical rating scale of ≥5 at the time of enrolment. Patients with vertebral fracture, organic pathology, such as compressive mass, malignancy, bony deformities, such as kyphosis, scoliosis, coccidynia, lumbar canal stenosis, patients with diagnosed psychiatric illness were excluded from the study. The eligible adult with non-specific CLBP patients were shortlisted at the pain clinic outpatient department (OPD). Based on the initial evaluation of physician for symptoms and radiodiagnostic methods, the selected patients were further approached by the researcher confirming on their diagnosis and pain status. The patients were given a detailed explanation regarding the study (potential risks/benefits, voluntary participation, procedures) and were provided with adequate time to reflect on the information. The enrolled patients were called in four batches, taking care of all the social distancing measures and COVID appropriate behavior.

Diagnosis

The assessment of patients was based on comprehensive clinical evaluation and assessing their symptoms, the degree of functional limitation, and psychological well-being. Radio-diagnostic methods involved MRI scans of the lumbosacral spine.

During the pretreatment assessment, written informed consent was obtained from the patients. An initial pain history interview was conducted along with the administration of the baseline questionnaires.

Randomization

The patients were randomly divided into the two groups. The control group received the usual care of treatment

as per institutional protocol. The yoga group received IAYT as an adjunct to usual care.

The study used a block randomization design. A random allocation sequence was generated by the statistician. For each participant, an opaque envelope was opened, in consecutive order, by an external research assistant not involved in the inclusion process. The participants did not know the content of the different intervention arms. The yoga leader was not blinded. However, the research group assessing the study's outcome was blinded during the data collection and data analysis.

After randomization, the participants received information about the offered intervention from a research assistant not involved in the offered interventions. Yoga, strength training, and evidence-based advice were all presented as well-established interventions, to equalize the participants' expectations.

Participants then completed the 3-month treatment program that they were allotted into, while both the groups continued with their routine medical care. These patients were allowed to interact and communicate with the physician, the study investigator, and the therapist via telecommunication method whenever the need arise. Follow-up assessments were conducted in-person in four batches at 1 and 3 months intervals post-treatment.

STUDY INTERVENTION

Yoga group

The chosen IAYT protocol was designed for CLBP patients based on extensive research and contribution toward the promotion of health and efficiently treating pathologies for more than 30 years now. The protocol was planned with the inputs from the previous studies, yoga experts, expert medical professionals, physiotherapists, and was further streamlined with the help of literature review, yoga investigators, physiotherapists, and expert medical professionals.

IAYT is a treatment protocol with a combination of modern scientific approaches blended with ancient wisdom, based on the basic principle of *Panchkoshas*, that is, five layers of existence to human beings. These practices were aimed at body level (*Annamaya Kosa*) include loosening stretches, asanas (postures); at subtle energy level (*Pranamaya Kosa*) including pranamaya (breathing practices), and the mind level (*Manomaya Kosa*) including meditation and relaxation techniques.[12]

The series of 60 min IAYT classes using all of the components of yoga (body, subtle energy, and mind level), was conducted for 2 weeks (6 sessions/week, 12 sessions total). The sessions were designed for participants to gradually progress from simple poses to more challenging poses adjusting to the patient's development. No props were used. Before the session, the participants were advised to keep their bowel and bladder empty. During the practice, care was taken regarding individual body limitations, and was advised not to strain too much to attain the correct posture with advice to suggest that.

It was followed by yoga practice at home and follow-ups at the set intervals for a total span of 3 months. Home practice for at least 45 min was strongly encouraged throughout the intervention period after sessions ended. We provided the participants with a four-page all-inclusive colored IAYT pamphlet with pictorial presentations depicting practices (Appendix S1) as well as the audio recordings of the complete protocol to be used at home.

Control group

Patients in the control group were provided with usual care as per institutional protocol involving education about disease process and role of self-care, ergonomic, and posture advice, advice to stay physically active, lifestyle modification, provision of a back care booklet which is developed and validated at the part taking site (Appendix S2),[19] medications as per the decision of treating physician, etc. They adhered to the treatment protocol for the same duration, under the guidance of a pain physician and physiotherapist.

Participant adherence

Adherence to the yoga protocol was defined as attending at least 9 of the 12 yoga classes. For the usual care group, adherence was defined as reading at least three-fourths of the book by self-report.

The participants were assessed to adherence to home sessions by keeping a logbook of record the time spent on practicing and surprise video callings. A WhatsApp group was created for encouragement and motivation at regular intervals.

Clinical assessment and follow-up

Baseline assessments included pain intensity using verbal numerical rating scale (VNRS)[20] functional ability using Modified Oswestry Disability Questionnaire (MODQ),[21] types of pain using Douleur neuropathic-4 questionnaire (DN4)[22] and Pain Disability Questionnaire (PDQ),[23] pain catastrophizing using pain catastrophizing scale (PCS),[24] Quality of life using EuroQol (EQ-5D-5L)[25] patients mental and emotional state using Hospital Anxiety and Depression Scale (HADS)[26] and fear of movement related to CLBP using Tampa Scale of Kinesiophobia (TSK).[27] Patients were followed up at 1 and 3 months and the above-mentioned assessment were recorded. Medications prescribed by pain physician for

CLBP were also assessed at all the three-time points. These drug therapies were reported as "mono therapy" for 1 medication and "dual therapy" for two medications. Further, medicine dosages were also evaluated to assess the changes in the overall dosage requirement. The patients rated their change on this 7-point scale that ranged from "very much improved" to "very much worse," with "no change" as the mid-point.[28,29] The investigators recording data at baseline and follow-up were blinded to the treatment group.

Data collection on any unfavorable outcomes or serious health events was also collected.

Biomarker assessment

We measured β-endorphin and TNF-α from the blood samples; and CGRP from the saliva of the CLBP patients to study the mechanistic role of yoga at baseline, 1 and 3 months. β-endorphin is involved in pain management and is a chief natural suppressor of hyperexcitability.[30,31] TNF-α is an inflammatory marker that can interact with other neurotrophic factors and modify pain sensation.[32] CGRP is involved in the transmission of pain and pain perception.[33,34]

A known quantity of 5 mL of blood was collected early morning (empty stomach) at baseline, 1 and 3 months. The samples were collected in a serum separator vacutainer kept at room temperature for half an hour followed by centrifugation at 2500 rpm for 30 min. The serum was then separated, aliquoted, coded, and subsequently stored at −80°C until use.

For the saliva collection, the participants were instructed to rinse their mouth with distilled deionized water to remove debris and moisture, before the collection. Post 10 min of rest, the salivary collection process was commenced. During the collection, the participants were asked to keep their eyes open during salivation and not to speak or mentally stimulate salivary flow. The participants were instructed to sit upright and with their head slightly titled forward, non-stimulated whole saliva pooling at the floor of the mouth was gathered in a collection tube.

The expression level of β-endorphin, and TNF-α in the serum and CGRP in the saliva was analyzed using commercially available ELISA kits (Qayee Bio). The OD was observed at 450 nm on the ELISA reader.

SAMPLE SIZE AND STATISTICAL ANALYSIS

In the absence of available published data comparing IAYT with usual care in Indian CLBP patients for management as well as assessing the mechanistic molecular role of IAYT, we performed this pilot feasibility study. We performed post hoc power analysis to calculate the power of study. We conducted both intentions to treat (ITT) and per-protocol analysis with ITT being primary. Data of all patients having one follow-up at 1 month was included with the last observation carried forward imputation for missing data.

Descriptive statistics, including means, medians, and standard deviations for continuous variables, and the number and proportions for categorical variables are reported. Data are presented as mean ± SD and median (IQR) and were analyzed for normality using Kolmogorov–Smirnov Z test. Between-group (yoga group vs control group) comparisons of normally distributed variables were performed using an independent t-test; while the Wilcoxon-Mann–Whitney test was used for non-normally distributed variables. Categorical data were analyzed by χ^2-test or Fischer exact test where appropriate. Generalized estimating equations (GEE) was used for the analysis of repeatedly measured data at a various time interval (VNRS, MODI, DN4, PDQ, PCS, EuroQOL, HADS, and TSK) using linear regression to estimate mean change from baseline. GEE was used to include all available data, and account for intra-subject correlations on repeated measurements, and explore the overall average effect. For GEE, all observed data were used without imputation for missing values. The analysis was considered to be unbiased under a missing at-random (MAR) assumption. To account for correlation among repeated measures for the same individual, an unstructured covariance for the initial model was assumed. A simpler model was used for the covariance if appropriate. Results are presented as between-group differences in adjusted mean with 95% confidence intervals (CI) of the differences and effect sizes (ES; adjusted mean difference/pooled baseline SD). The analysis was carried at a 5% level of significance level ($\alpha = 0.05$). SPSS software version 22 (SPSS Inc.) was used for data analysis.

RESULTS

Of the 87 patients screened for eligibility, 65 were found eligible. A total of 35 patients were approached for enrolment after fulfilling the inclusion criteria. Out of these 35 patients, four patients did not turn up for the initial assessment. The final sample consisted of 31enrolled participants ($n = 14$ yoga group and $n = 17$ control group). And 29 patients completed the assessment at the three time points (preintervention, 1 and 3 months) and 2 patients were lost to follow-up from the control group at 1 month ($n = 15$). The flow of participants is presented in the CONSORT flow diagram (Figure 1).

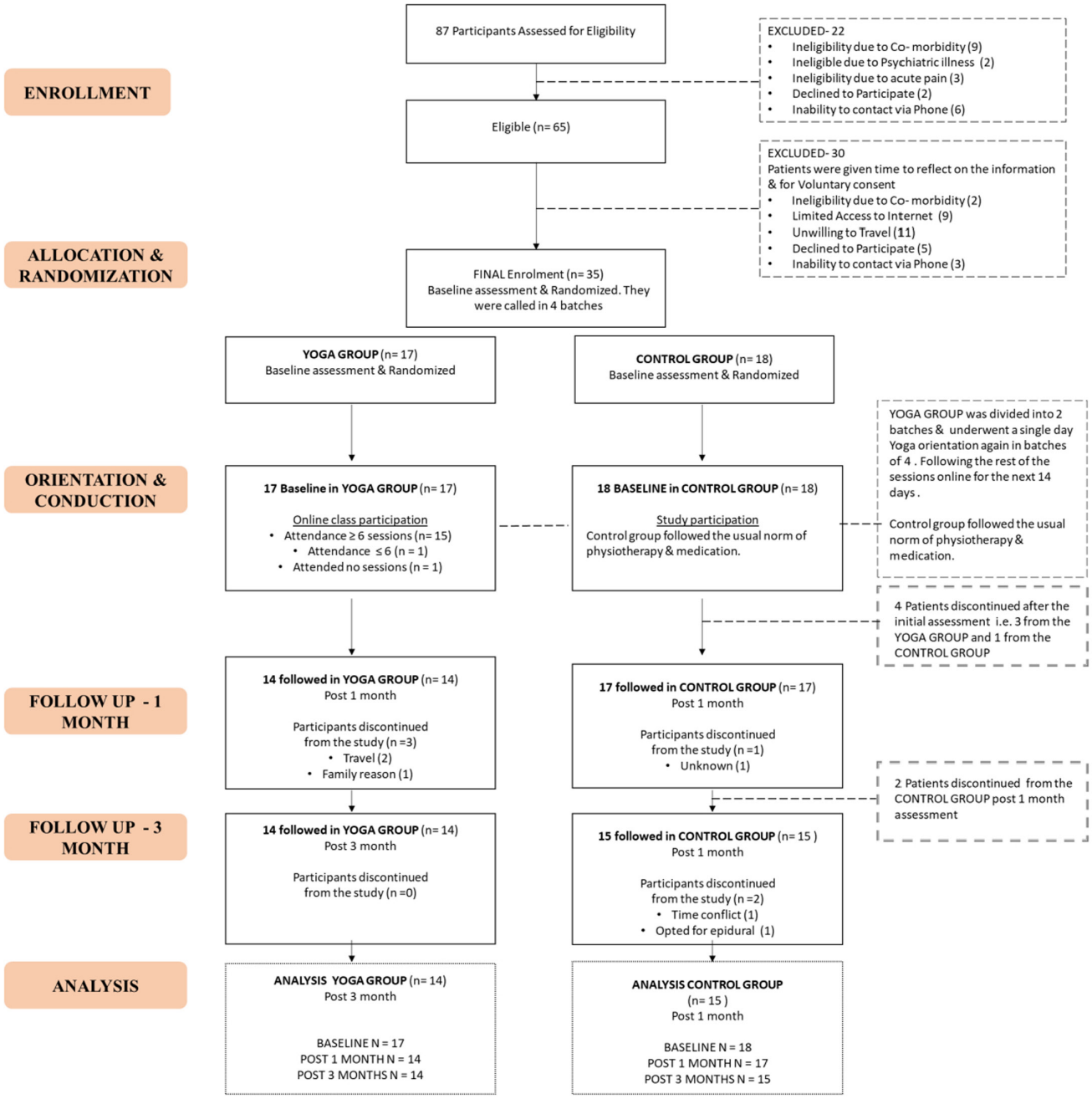

FIGURE 1 Consort flow diagram.

Baseline demographic data

The baseline sociodemographic characteristics (age, sex, weight, height, and occupation) were comparable in both control and yoga groups (Table 1).

Baseline clinical variables

The baseline clinical variables (duration of symptoms, diagnosis, drug therapy, drug dosage, VNRS, MODQ, PDQ, DN4, EuroQOL, PCS, HADS, TSK, and biomarkers) were comparable in both the control and yoga groups (Table 2).

Primary outcome

Primary outcomes of the study were VNRS and MODQ at 3 months. The VNRS improved significantly over time in both the groups compared with baseline (yoga group $p < 0.001$, control group $p < 0.001$). The reduction in VNRS in the yoga group was significantly more in comparison with the control group over time ($p = 0.036$; using

TABLE 1 Baseline sociodemographic data.

Parameters	Group		
	Yoga ($n=14$)	Control ($n=15$)	p Value
Age (years)	36.93 ± 10.34	34.27 ± 8.86	0.346[a]
Age group			
18–30 years	3 (21.4%)	5 (33.3%)	0.837[b]
31–40 years	6 (42.9%)	7 (46.7%)	
41–50 years	4 (28.6%)	3 (20.0%)	
51–60 years	1 (7.1%)	0 (0.0%)	
Gender			
Male	5 (35.7%)	6 (40.0%)	0.812[c]
Female	9 (64.3%)	9 (60.0%)	
Weight (kg)	66.50 ± 14.63	65.73 ± 9.89	0.878[a]
Height (cm)	160.68 ± 13.50	166.13 ± 5.28	0.093[a]
Occupation			
Housewife	5 (35.7%)	8 (53.3%)	0.271[b]
Others	8 (57.1%)	4 (26.7%)	
Farmer	0 (0.0%)	2 (13.3%)	
Student	1 (7.1%)	1 (6.7%)	

Note: Values are represented as mean ± SD and number (percentage).
[a]Wilcoxon-Mann–Whitney U test.
[b]Fisher's exact test.
[c]Chi-squared test.

GEE). At 1 month, the mean difference between the two groups was 1.35 (95% CI: 0.15–2.55) and the effect size was 0.83 ($p=0.04$). At 3 months, the mean difference was 1.13 (95% CI: 0.61–2.87) and the effect size was 0.48 ($p=0.21$; Figure 2).

MODI improved significantly in the yoga group over time ($p=0.049$); however, no significant improvement was observed in the control group ($p=0.949$). Between-group comparison revealed significantly better MODI over time in the yoga group compared with the control group (GEE; $p<0.001$). At 1 month, the mean difference between the two groups was 13.81 (95% CI: 6.04–21.58) and the effect size was 1.33 ($p=0.002$). At 3 months the mean difference was 17.62 (95% CI: 7.83–27.41) and the effect size was 1.35 ($p=0.002$; Figure 3).

Secondary outcomes

DN4, PDQ, PCS, and HADS (anxiety) had a statistically significant reduction at 1 month and 3 months in the yoga group compared with the control group (Table 3). The HADS (depression) had a statistically significant reduction in scores in the yoga group at 3 months. The Euro-QOL scores increased significantly in the yoga group at both 1 month and 3-month time points, indicating that

TABLE 2 Baseline clinical variables.

Parameter	Yoga group ($n=14$)	Control group ($n=15$)	p Value
Duration of symptoms (months)	41.86 ± 76.62	41.13 ± 42.52	0.208[a]
Diagnosis			
B/L legs pain	6 (42.9%)	6 (40.0%)	0.890[b]
Right/left leg pain	5 (35.7%)	7 (46.7%)	
LBA	3 (21.4%)	2 (13.3%)	
Drug therapy (baseline)			
Monotherapy	6 (42.9%)	9 (60.0%)	0.356[c]
Dual therapy	8 (57.1%)	6 (40.0%)	
Pregabalin dose (mg/day) (baseline)	78.57 ± 67.12	85.00 ± 66.68	0.836[a]
Amitriptyline dose (mg/day) (baseline)	9.29 ± 2.67	8.33 ± 6.45	0.403[a]
Pregabalin + amitriptyline dose (mg/day) (baseline)	87.86 ± 66.35	93.33 ± 64.13	0.875[a]
VNRS (baseline)	7.57 ± 0.58	7.47 ± 1.13	0.77[a]
MODQ (baseline)	49.86 ± 16.33	50.93 ± 10.14	0.913[a]
PDQ (baseline)	9.79 ± 5.95	10.40 ± 5.37	0.930[a]
DN4 (baseline)	2.79 ± 1.93	3.33 ± 1.91	0.536[a]
EuroQOL (baseline)	0.22 ± 0.27	0.35 ± 0.19	0.162[a]
PCS (baseline)	34.43 ± 10.26	29.60 ± 7.76	0.143[a]
HAS (depression) (baseline)	8.64 ± 4.40	7.47 ± 2.77	0.234[a]
HADS (anxiety) (baseline)	11.07 ± 4.43	10.60 ± 3.70	0.709[a]
TSK (baseline)	42.64 ± 5.20	45.8 ± 4.81	0.090[a]

Note: Values represented as mean ± SD, number (percentages).
[a]Wilcoxon-Mann–Whitney U test.
[b]Fisher's exact test.
[c]Chi-squared test.

QOL improved more in patients receiving IAYT. The GEE was used to find the overall change in *p*-value over time between the groups. All parameters had a significant *p*-value (<0.001) except for PDQ ($p=0.195$). The adjusted mean differences (95% CI) with effect size between yoga and control groups at 1 month and 3 months for the above-mentioned secondary outcomes are provided in Table 3.

Drug therapy

Patients in both the groups were either on pregabalin or amitriptyline as monotherapy or a combination of both the drugs as per treatment protocol. Baseline drug therapies were comparable in both groups. The baseline mean dosage of pregabalin in the yoga group was 78.57±67.12 mg/day a significant reduction in dosage of pregabalin was noted over time, at 3 months the dosage reduced to 30.57±13.36 mg/day ($p=0.001$). The baseline pregabalin dosage in the control group was 85.00±66.68 mg/day with dosage at 3 months 95.00±87.73 ($p=0.819$). Intergroup comparison revealed a significant dose reduction in the yoga group compared with the control group overtimes ($p=0.001$). For the doses of amitriptyline, a significant reduction ($p=0.008$) from baseline (9.29±2.67) to 3 months (5.71±7.03) was noted only in the yoga group. No significant dose reduction of amitriptyline was observed in the control group. On intergroup comparison, no significant difference in the dose of amitriptyline was seen in both the groups over time. For the combined pregabalin plus amitriptyline, a significant dose reduction was reported from baseline (87.86±50.44) both at 1 (49.64±50.44) and 3 months (10.00±15.93) in the yoga group ($p=0.001$). No significant reduction was observed in the control group. The yoga group had a significant reduction in comparison to the control group ($p=0.001$).

A total of 6 out of 14 (42.9%) patients in the yoga group stopped medication at 3 months due to improvement. Four patients were switched from dual to monotherapy at 1 month in the yoga group. In the control group, none of the patients stopped medication at 3 months. Only two patients in the control group switched from dual therapy to monotherapy at 3 months. On comparative analysis, a significant number of patients stopped medication at 3 months in the yoga group in comparison with the control group ($p=0.008$).

Biomarker's analysis

We analyzed 21 samples for the assessment of TNF-α in the serum of CLBP patients. The values of biomarkers obtained were normalized against each patient's total serum protein values, to reduce and adjust for the interpatient variability. Eight cases were excluded due to errors while processing samples. The within the group analysis of subsequent follow-up samples (1 and 3 months) showed significant reduction in TNF-α levels of the yoga group ($p=0.004$) as compared with the control group ($p=0.002$) GEE analysis revealed comparable TNF-α levels compared over time ($p=0.77$). A total of 24 participants samples were processed for levels of beta-endorphins. Five cases were excluded due to sample processing errors. We found that the beta-endorphins levels were comparable at the base line (0.02±0.01) pg/mL and showed non-significant increase in the yoga group to (0.03±0.01) pg/mL at 1 and 3 months as compared with the control group (0.02±0.01) pg/mL.

A total of 22 samples were processed for the estimation of salivary CGRP. Seven patients were excluded due to sample processing error. We found that the CGRP levels differed significantly at the baseline ($p=0.001$) and also at 1 month follow-up ($p=0.006$) between yoga (5.92±2.74) pg/mL and control groups (8.42±1.67) pg/mL.

DISCUSSION

The result of our study revealed significant reduction in VNRS in the yoga group in comparison with the control group over time with medium to large effect. Also, significant improvement in MODI was observed in the yoga group. A moderate-to-large effect was seen both at 1 and 3 months (effect size = 1.33 and 1.35 respectively) with an overall *p*-value = 0.001. Additionally, we observed significant improvement in all secondary outcomes both at 1 and 3 months in the yoga group compared with the control group.

Few studies have evaluated the role of yoga therapy for management of CLBP patients. Saper et al.[35] revealed a significant reduction in pain after the 12 weeks of yoga intervention, irrespective of the number of yoga classes attended. A systemic review by Chang et al.[36] reported that yoga reduces pain in CLBP patients. Another comprehensive review reported an analysis of eight randomized controlled trials.[37] The results indicated that the overall post-treatment effect size of yoga on pain was 0.623 (95% CI: 0.377–0.868) indicating a medium to large effect which reduced with time. We observed comparable results in the present study. At 1 month, the effect size was 0.83 (95% CI: 0.15–2.55) indicating medium to large effect. On following at 3 months, the reported effect size was reduced to 0.48 (95% CI: 0.61–2.87).

Two of the meta-analysis and a systematic review, recommending yoga as a beneficial adjuvant approach for CLBP reported moderate effect sizes on disability.[10,36–39] Holtzman and Beggs[37] noted that the post-yoga effect for functional disability was in the moderate-to-large range, $d=0.645$. We noted similar moderate-to-large effect at 1 and 3 months (effect size = 1.33 and 1.35 respectively) in our study yoga group. Our results are also in strong approval with the existing guideline recommendation on nonpharmacological therapies, as the first-line treatment method for CLBP patients.[36–39]

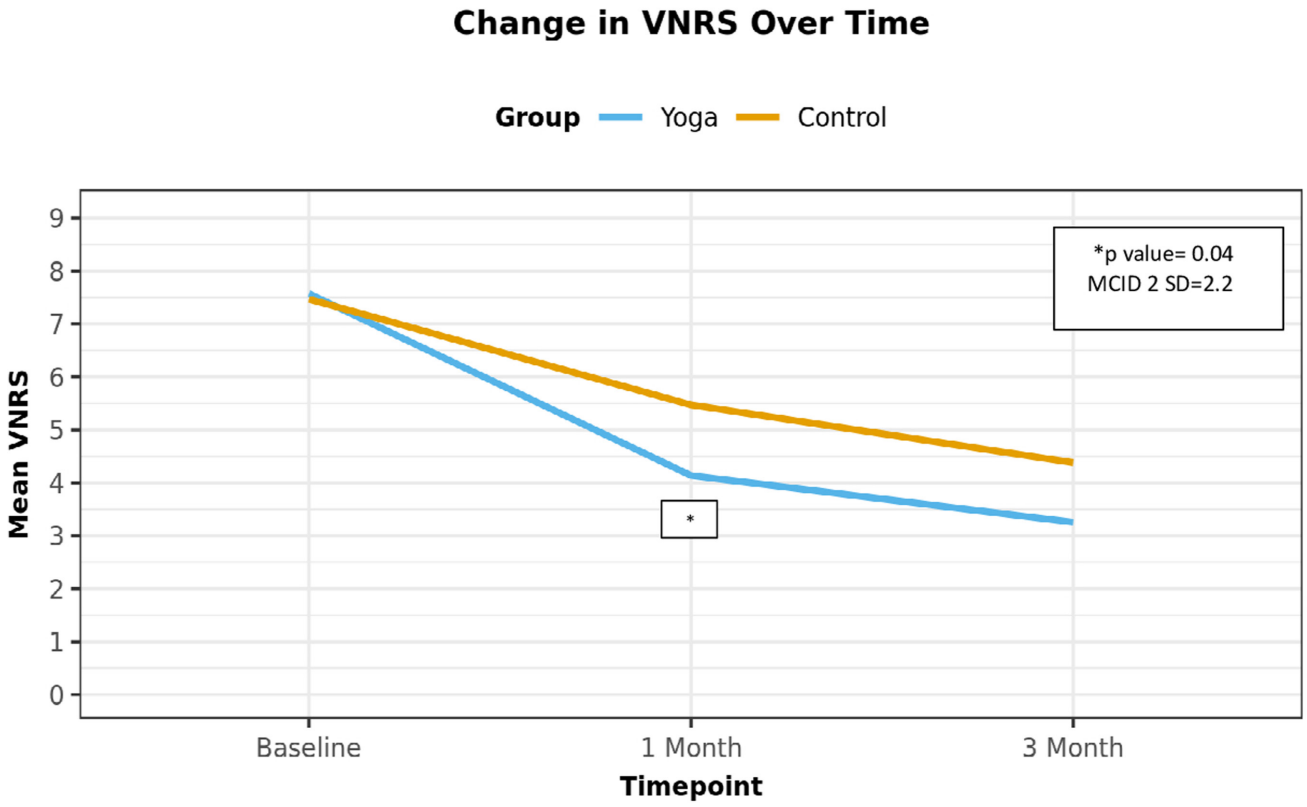

FIGURE 2 Line diagram showing change in verbal numerical rating scale (VNRS) over time and significant difference in the mean VNRS value between of yoga and control at 1 month timepoint (Wilcox-Mann–Whitney test). *$p<0.05$.

Neuropathic pain was found to be considerably reduced with yoga in our trial. The present study thus provides evidence that yoga therapy reduces pain even of neuropathic origin. Comparative data with other studies in respect to PDQ and DN4 is not available at present, but a recent study validates that yoga is a cost-effective approach for the management of neuropathic pain.[40,41]

CLBP is a complex condition that affects all aspects of life. This results in economic burden, reduced work productivity and affects the quality of life (QOL).[42] Yoga studies for CLBP patients conducted so far have limited data on the measures of QOL, mental health conditions (depression, anxiety, etc.), and other psychological impacts.[10,43–45] Tekur et al.[15] demonstrated the usefulness of IAYT in improving QOL within the CLBP nursing populations. They observed a significant improvement in all the four domains of WHOQOL-BREF in the yoga-based lifestyle module as compared with the physical exercise-based lifestyle module.[15] The present study reciprocates similar results. A significant increase in the EuroQol score over time was noted in the yoga group compared with the control group.

We found depression score using HADS was lower in the yoga group at both time points with significant reduction at 3 months. This is consistent with the past research, where in yoga, CBT, and MBSR have reported to be substantially effective in reducing depression and anxiety in CLBP patients.[39,43–45] Anxiety was significantly reduced in the yoga group, both at 1 ($p=0.02$) and 3 months ($p=0.005$) compared with the control group. The additional benefits of yoga therapy like social connectedness and spirituality as highlighted in recent reports, enhanced its primary effects of decreasing disability and promoting mental well-being.[46]

We studied both kinesiophobia and the catastrophic effects of pain by TSK and PCS.[47] Our study reported a significant reduction for both parameters in the yoga group compared with the control group at all time points. This was in contrast to the study of William et al.[48] who did not report a significant reduction in kinesiophobia after Iyenger yoga therapy up to 16 weeks. William et al.[48] explained the lack of treatment effect on the psychological and behavioral subscales by the following facts. Firstly, the study was not adequately powered. Secondly, more time may be required to change long-held negative cognitions and beliefs about CLBP such as movement-related pain. The Iyengar technique of yoga involves a large number of difficult standing postures that require repeated practice to obtain correct pelvic alignment thus diminished the efficacy of the intervention. Lastly, that the impact of the yoga intervention would have been greater with a more experienced instructor. In contrast, the present study used the IAYT and not the IYENGER yoga technique and ensured a more experienced instructor which helped patients in easily understanding the techniques.

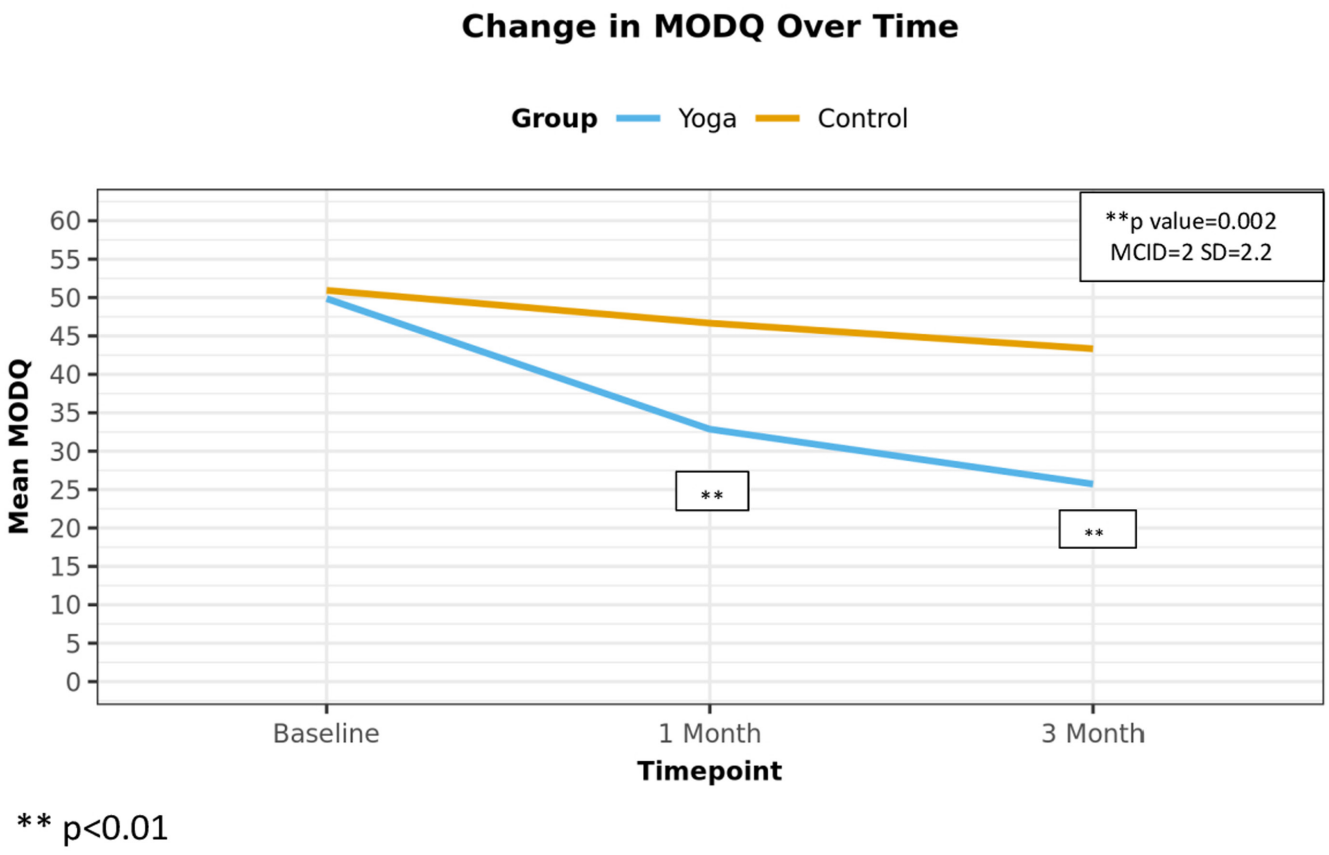

FIGURE 3 Line diagram showing change in Modified Oswestry Disability Questionnaire (MODQ) over time and significant difference in MODQ values between in yoga and control at 1 and 3 month timepoints (independent *t*-test).

TABLE 3 Adjusted mean difference (95% CI) between yoga and control and at 3 months with an effect size.

Variable	Yoga ($n=14$) Mean±SD	Control ($n=15$) Mean±SD	Adjusted mean difference (95% CI)	Effect size	*p* Value
Adjusted mean difference at 1 month					
DN4#,**	1.07±1.07	2.93±1.71	1.86	1.32	0.003[1]
PDQ#,*	5.14±3.63	7.93±3.59	2.79	0.79	0.04[1]
PCS#,**	15.93±10.16	27.47±8.37	11.54	1.27	0.003[1]
EuroQOL***	0.65±0.10	0.41±0.23	0.24	1.33	<0.001[1]
HADS (ANXIETY)#,*	6.36±3.71	9.47±3.31	3.11	0.9	0.02[1]
HADS (DEPRESSION)#	5.43±3.32	7.00±3.02	1.57	0.69	0.195
TAMPA#,***	33.71±5.33	44.53±5.25	10.82	2.08	<0.001[1]
Adjusted mean difference at 3 month					
DN4#,**	0.57±0.65	2.20±1.66	1.63	1.3	0.007[1]
PDQ#,*	2.71±3.20	6.40±4.15	3.69	1.01	0.005[1]
PCS#,*	11.86±11.92	24.80±10.07	12.94	1.27	0.003[1]
EuroQOL**	0.76±0.20	0.46±0.23	0.30	1.43	0.001[1]
HADS (ANXIETY)#,**	5.07±3.73	9.13±3.36	4.07	1.17	0.005[1]
HADS (DEPRESSION#,*	3.71±3.12	6.87±3.18	3.16	1.02	0.012[1]
TAMPA#,***	30.64±6.67	42.87±6.09	12.23	1.95	0.001[1]

Note: Values are presented as mean±SD, 1 – significant *p-value <0.05, **p<0.01, ***p<0.001, #reduction in score indicates better outcome, increase in score indicates the improved quality of life. Wilcoxon-Mann–Whitney test was used for DN4, PDQ, EuroQOL, PCS, TAMPA for intergroup comparison at 1 and 3 months. *T*-test was used for HADS (anxiety and depression) for intergroup comparison at 1 and 3 months.

These differences can be attributed to a significant effect in both TSK and PCS.

A noteworthy observation in our study is significant reduction in pain medication dosage with some patients becoming off medications at 3 months. We noted that 42% of patients become off medication in the yoga group and a significant in dosage was observed in comparison with the control group ($p = 0.008$). These findings correlate with the results of randomized controlled trials.[48] William et al.[48] reported 88% of the patients in the yoga group having a reduction in medication with significant reduction in the yoga group compared with the control group. This finding further adds clinical relevance to using yoga as adjuvant therapy in patients with CLBP.

We wanted to see efficacy of yoga as an adjuvant to prescribed medical treatment in CLBP patients at molecular level. For this, we estimated salivary CGRP along with serum TNF-α and beta-endorphin in both the groups. Neuroinflammatory processes affect inflammatory mediators such as TNF-α in the plasma. The elevated levels are linked to elevated pain intensity which plays an important role in CLBP patients.[49,50] In the present study, TNF-alpha, reduced significantly as the pain intensity reduced over time in both groups. But the comparative analysis did not have a statistically significant value. Our results align with a study of overweight people with chronic inflammatory conditions where reduced TNF-α levels were found in those who practiced yoga,[50] but in this study, there was no comparative control group and the study was a short-term follow-up of 12 weeks. The reduction in TNF-alpha cannot be attributed to yoga due to multiple confounders. The TNF-α levels are altered by amitriptyline intake[51] which could act as confounder, hence, we found significant decrease in the TNF-α levels in both the groups.

We also studied levels of beta-endorphins and salivary CGRP. The beta-endorphins are the most extensively researched and beta-endorphin level may serve as a surrogate marker for treatment response of patients with CLBP.[30] In patients with CLBP, beta-endorphin levels have been reported suppressed stably and not affected by a placebo effect.[31,52] We found that beta-endorphins showed an increasing trend in the yoga group as compared with the control group although it was not statistically significant. Research indicates that CGRP might have a pro-inflammatory role in the peripheral nervous system by releasing pro-nociceptive substances, and they also found the relationship between measured CGRP levels and neuropathic pain.[33] CGRP is an abundant neuropeptides in nervous tissue and also present in saliva and plays a significant role in the pathophysiology of chronic pain.[34] Salivary CGRP shows a significant increase in saliva and plasma concentration of CGRP during headache episodes and migraine,[53] especially during active pain periods.

The non-significant change in the beta-endorphins can be attributed to the confounders-like psychological state, pain intensity, and medications. Amitriptyline which being an anti-depressant is known to affect the level of this biomarker.[54] Similarly, Pregabalin is known to modulate CGRP levels which might be implicated for non-significant change in its serum levels in both the groups.[55] Moreover, TNF-α is known to control CGRP expression[56] and as two of these molecules are synergistically lowered in our study suggesting their involvement in some common pain related pathway. TNF-α, beta-endorphins, and CGRP interact with various other genes. In inflammatory conditions like acute pancreatitis, TNF-α, interleukins 3,6 are downregulated, and MAPK, NF-κB, and STAT3 signaling is inhibited in CGRP dependent manner.[57] Hence, we propose that further studies must be carried out after adjusting the confounders like age, gender, comorbidities and life style habits, with larger sample size will also add to the strength of the study.

No adverse events were reported during the yoga intervention.

Limitation

One of the limitations of this study is small sample size with pilot feasibility design and is not powered to detect difference in the biomarkers between the groups. However, for pain score (VNRS), post hoc power analysis revealed the power of 88% with a MICD 2 and SD of 2.2, α-error of 0.05 and sample size of 29. Second limitation is the potential bias of the increased involvement of the participants in the yoga group by virtue of their continued sessions and additional, Whatsapp group, surprise checks, log book, adherence checks, etc. The participants might have felt more motivated and disciplined to continue. It could have been minimized by adding equal number of provider patient interactions in the control group, for example, just calling patients and doing predefined random talk. The effect of these interventions is by themselves are known to affect the studies of primary and secondary outcome. Third limitation is that supervised yoga session could be provided for only 2 weeks followed by self-practice session at home due to logistic pragmatic reasons. This is reflected in a significant change in VNRS score only at 1-month but could not be sustained at 3 months. Supervised sessions for a longer duration could have resulted in more sustained and long-term results. Fourth limitation is the short follow-up of 3 months, this was primarily due to logistic reasons with many patients attending the pain clinic from far of remote places. Fifth, the patients and physician could not be blinded because of the design of study. However, the bias was taken care by keeping the follow-up researcher and statistician blinded to the group allocated and keeping

the study cases in between the routine clinical cases. Future randomized clinical trial including a larger patient population with adequate sample size calculation, longer supervised yoga sessions, having patient provider interaction in the control group to minimize bias and longer follow-up are warranted.

CONCLUSION

In conclusion, IAYT reinforces the possibilities of being a substantial adjunct intervention to reduce pain symptoms and pain-associated disability in adult patients with CLBP. It seems to have a positive effect on depression and anxiety and even benefitting the overall QOL, with maintaining its neutral effect on the Pain biomarkers.

AUTHOR CONTRIBUTIONS

S.P. – main project researchers conducted cases, follow-up and drafting of manuscript, D.D. – Drafting results, data interpretation and manuscript writing, B.G. – corresponding author, initiating research, patient assessment, manuscript drafting and final formatting. D.M. – correcting formatting manuscript, K.M. – formatting study project and manuscript formatting, K.K. – manuscript formatting, sample collection. A.A. – Biomarkers assessment, results, conducting tests and manuscript formatting.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no competing interest.

DATA AVAILABILITY STATEMENT

The data for the above research can be made available on request at ghaibabita1@gmail.com, subject to maintaining the anonymity of the patients.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Appendix S1.

Appendix S2.

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Mind-body practice as a primer to maintain psychological health among pregnant women–YOGESTA–a randomized controlled trial

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Objective: The objective of this study was to investigate the impact of Gestational Yoga-YOGESTA (Gestational Yoga), on the neuropsychology, quality of life, and personality of pregnant women.

Design: Open label, randomized controlled trial, used allocation concealment to allocate the treatment.

Setting: Department of Obstetrics and Gynecology and Neuroscience Research Lab, Department of Neurology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Participants: We recruited a total of 100 pregnant women visiting the Outpatient Department of Obstetrics and Gynecology. Participants were aged between 18 and 35 with uncomplicated pregnancies and they were randomly assigned to either the Yoga group (YG) or the usual care group (UCG). A total of 77 pregnant women completed both the pre- and post-survey, with 34 participants in the Yoga group and 43 in the Usual care group.

Intervention: Pregnant women in their second and third trimesters were provided with a 16-week online Prenatal Yoga intervention. The intervention began after enrollment in the 2nd trimester, specifically between the 16th and 20th week, and was conducted 5 days a week until delivery, with an average intervention period of 47.18 $\pm$ 2.031 (mean $\pm$ SEM) days.

Chief outcome measures: We measured Perceived stress, Depression, Anxiety, Stress, and quality of life by using standard questionnaires.

Results: A total of 77 participants were included in the analysis, with 34 assigned to the Yoga group and 43 assigned to the control group. Most of the measured parameters demonstrated significant changes. The Yoga group exhibited a noteworthy decrease in perceived stress, depression, anxiety, and psychological stress, as well as an improvement in the psychological and environmental domains of QOL-BREF. Conversely, the control group demonstrated a significant increase in perceived stress, depression, anxiety, and psychological stress, along with a reduction in the physical, psychological, and social domains of QOL-BREF at the follow-up stage. Although the two groups were similar at baseline, the Yoga group showed substantial enhancements in perceived stress, depression, anxiety,

physiological stress, and overall quality of life when compared to the control group at follow-up.

Conclusion: The study's findings indicate that stress, anxiety, and depression are more likely to occur as gestational age progresses during pregnancy. Nevertheless, practicing Prenatal Yoga can effectively manage these changes and enhance the quality of life for expectant mothers.

Clinical trial registration: Clinical Trials Registry-India, Identifier CTRI/2021/01/030827.

KEYWORDS

pregnancy, Yoga, mind body intervention, neuropsychologial assessment, stress, prenatal Yoga, YOGESTA

Introduction

Pregnancy is marked by continuous physiological, metabolic, and mental challenges that can be difficult to adapt to. A woman's neuropsychology and ability to manage these challenges effectively can play a crucial role in her adaptation to the physical and physiological demands of pregnancy. Stress, anxiety, and depression are common sources of distress during pregnancy that can have negative impacts on both maternal and fetal health (1). To ensure the smooth progression of pregnancy and fetal development, it is important to consider both biological and psychological factors such as anxiety, and physical and psychological stress, which may contribute to pregnancy-related complications (2). During the prenatal and postpartum periods, women experience significant changes in their psychological health, physiological function, and social interactions, all of which can have a significant impact on their lives. Stress, anxiety, and depression are the most common factors that affect neuropsychology during pregnancy and can contribute to various complications that arise during pregnancy (3). A study conducted in Sweden on a population of 1,734 pregnant women revealed that psychiatric disorders were prevalent in 14.1% of pregnant women, with 3.3% exhibiting signs of major depression, 6.9% showing signs of minor depression, and 6.6% displaying signs of anxiety during pregnancy (4). Studies have shown that women in late pregnancy experience poorer sleep quality, worse physical health, and higher rates of depression compared to women in early pregnancy (4). The physical and psychological changes brought on by pregnancy also impact the different aspects of quality of life (QOL). Additionally, poor quality of life has been linked to an increased risk of pregnancy complications such as premature birth and low birth weight. Therefore, healthcare providers should be aware of the psychological changes that occur during pregnancy and provide additional support to pregnant women (5). The effects of prolonged psychological stress on pregnant women include premature births, abnormal fetal development at birth, and attention disorders or reduced performance of new-born with regard to executive function in later life (6). It is important to manage stress levels in pregnant women and implement interventions that are designed to reduce psychological distress. However, it should be noted that psychopharmacological stress management may not be suitable for pregnant women due to concerns about the adverse effects of some commonly used pharmaceuticals (7). It is crucial to manage psychological distress during pregnancy for the well-being of both the mother and the fetus. Early detection and non-pharmacological management through techniques such as psychological counseling, stress management, lifestyle modifications (including light physical activity and a balanced diet), and social support can significantly improve the psychological health and quality of life of pregnant women (8). Incorporating non-pharmacological interventions, such as exercise and Yoga, has been shown to be effective in managing psychological problems during pregnancy. These interventions provide a proactive approach for pregnant women to promote their wellness during this critical time.

Existing research indicates that psychological distress can have a negative effect on the ability to participate in physical activity (9). Physical inactivity is a prevalent issue during pregnancy, with approximately 60% of pregnant women being sedentary. This is often due to a lack of awareness about the advantages of exercising during pregnancy, which may lead to hesitation among women. However, exercise during pregnancy is of utmost importance in terms of maternal and fetal health, as it effectively reduces common pregnancy issues such as depression, insomnia, anxiety, fatigue, and excessive weight gain in the mother (10, 11). With growing evidence and awareness of their benefits, exercise and Yoga have become more widely embraced and practiced by pregnant women (12). In general, exercise has a significant effect on the improvement of neuropsychology in adults as well as in older adults (13, 14). Given the limited feasibility of engaging in intense physical activities during pregnancy, gentle exercise practices such as Yoga may be a preferred option for pregnant women. Yoga can provide a combination of physical and mental wellness benefits that are well-suited to the needs of pregnant women.

Yoga is usually a mix of physical exercise, mental exercises, meditation, different types of deep breathing, stretching, and relaxation. The meditation component of Yoga promotes deep relaxation, which helps to calm the senses and improve the focus of the mind, thereby enhancing mental health. Practicing Yoga during pregnancy is known to promote a holistic connection between the mind, body, and fetus of expectant mothers (15). Previous research has shown promising results regarding the benefits of Yoga during pregnancy (16). Studies have demonstrated that practicing Yoga can

reduce stress, anxiety, and depression, improve mood, and enhance overall well-being (17, 18). However, there is a need for further research to confirm and extend these findings.

Moreover, it is important to note that there is limited awareness about mental health issues during pregnancy, and routine screening for such problems is not common practice, thereby neglecting their significance as high-risk factors in pregnancy (19). However, it is crucial to acknowledge that psychological imbalances, including stress, anxiety, and psychosocial factors, have been associated with adverse outcomes such as preterm birth, low birth weight, and complications during both antepartum and intrapartum periods (19, 20). The generality ofthe need to carry out a counter-stress randomized controlled trial (RCT) in this region is imperative. It is worth mentioning that the labor room unpublished statistics of the hospital where our study was conducted revealed that out of a total of 5,202 deliveries in 2022, approximately 20.8% were preterm deliveries without a known cause. Psychological distress during pregnancy remains relatively understudied and often goes unnoticed as it is not routinely assessed during prenatal checkups. Hence the rationale of this study owes its origin to the need to investigate the incidence of psychological distress in pregnant women. We aimed to study the potential impact of Yoga on distress and its relationship to quality of life in healthy pregnant women. Our hypothesis is that regular practice of Yoga may enhance psychological resilience and lead to improved quality of life during pregnancy, thereby reducing the incidence of psychological distress. This study provides a rigorous and detailed investigation into the potential benefits of an online Yoga intervention for psychological distress and quality of life among uncomplicated pregnant women, and the randomized controlled design adds to the robustness of the study and the outcomes. By examining these variables in uncomplicated pregnant population, we hope to provide insights into the incidents of psychological distress during pregnancy, its progression throughout the period, and the potential role of Yoga as a preventive intervention for psychological distress during pregnancy. Further, this investigation might provide preliminary data about the incidents of psychological distress among pregnant women which can further be used to identify the mental health problem, its associated risks for maternal and fetal complications, and the need for psychological counseling during antenatal checkups.

Through our examination of these variables in women with uncomplicated pregnancies, our aim is to shed light on the occurrence and progression of psychological distress during pregnancy. Additionally, we seek to explore the potential role of Yoga as a preventive intervention for managing psychological distress during this critical period. Furthermore, this investigation may yield preliminary data regarding the incidence of psychological distress among pregnant women, which can contribute to identifying mental health issues, associated risks for maternal and fetal complications, and the need for psychological counseling during antenatal checkups.

Materials and methods

Study design and setting

The YOGESTA (Gestational Yoga) trial was carried out at the Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India after taking approval from the institutional ethics committee PGIMER.

This was an Open label, Parallel randomized controlled trial of online Yoga intervention among uncomplicated pregnant women. We recruited the participants in the 16th to 20th week of pregnancy and randomized them into Yoga and Usual care groups (UCG). Yoga group participants attended online morning Yoga classes from the time of recruitment until delivery, with daily attendance records and screenshots/videos of Yoga classes taken to ensure compliance with the intervention. UCG participants did not practice any Yoga or exercise during the study period. Assessment was done at two time points, baseline and follow-up. Baseline measurements were collected at the time of recruitment, i.e., between the 16th and the 20th week of pregnancy, and follow-up measurements were taken after 32 gestational weeks, using questionnaires to assess perceived stress (PSS); depression, anxiety, and stress (DASS); and quality of life (WHO-QOL BREF). The study design is both a between-subjects variable (comparing the Yoga group to the usual care group) and a within-subjects variable (comparing pre and post-intervention). The study was registered prospectively in the Clinical Trials Registry-India.

Participants

From November 2021 to January 2023, pregnant women who visited or tele-consulted with the Department of Obstetrics and Gynecology at PGIMER were recruited for the study by the first author, based on defined inclusion criteria, which included uncomplicated normal pregnancy aged between 18 and 35 years in the 16th to 20th week with a BMI < 30 and no associated anomalies such as hypertension or gestational diabetes. Pregnancies with any associated comorbidities like hypertension, gestational diabetes mellitus, small cervical length, low-lying placenta, and high-risk pregnancies were excluded from the study. The sample size was estimated based on the mean and standard deviation from published research which had delivered Yoga interventions to the pregnant population, using the formula $n = t2s2/r2m2$ where t is the value of t statistic for 95% confidence, s is the standard deviation, r is the relative precision, taken as 0.05 in this case and m is the mean. The maximum sample size was then taken to ensure the estimation and testing of the hypothesis for the variable having maximum variance. The participants were invited by telephone or directly approached during antenatal clinic checkups, 100 agreed and provided written consent. The first author then randomly allocated the participants into the Yoga group ($n = 50$) and usual care group ($n = 50$) by using specific codes (A = Yoga group, B = Usual Care Group) concealed in sealed envelopes. The allocation ratio of randomization of the control to the Yoga group was 1:1. Whole process of recruitment and randomization was done by the first author. Blinding was not possible for this study due to the nature of the intervention, which involved participants actively engaging in Yoga sessions. As the participants were aware of their group assignment and actively participated in the Yoga intervention, it was not feasible to blind them or the researchers conducting the study to the treatment allocation. The protocol was reviewed and approved by the institutional ethical committee before the recruitment of participants. The final analysis included 77 participants (34 in the Yoga group and 43 in the usual care group) with a power level of 95% and an effect size of 0.5. The participants' flow from baseline to

follow-up is shown in Supplementary Table S1, as per the CONSORT flow chart. The participants' age, BMI, and height did not differ between the two groups. The socioeconomic status [LIG- Low-Income group (5,000–16,000/month), MIG-1- Middle-Income group-1 (17,000–40,000/month), MIG-II- Middle Income group-II (41,000–85,000/month), HIG- High-Income group (85,000 and above)], demographics, and other parameters are reported as frequency and presented in Table 1.

Prenatal Yoga protocol

To cater to the changing physiological needs of pregnant women, our study aimed to implement gestational Yoga which we abbreviated as YOGESTA among uncomplicated pregnant women. YOGESTA consists of two distinct Yoga protocols for the 2nd and 3rd trimesters. The protocols incorporated a range of practices including stretching, breathing, relaxation, and meditation (details presented in Supplementary Table S2). The Yoga protocol was adapted from the book "Yoga for Pregnancy" by *HR Nagarathna*, with necessary modifications made by the Institute Ethical Committee, in consultation with an obstetrician. The modifications were made keeping in mind the safety and comfort of pregnant women, given the online nature of the intervention. The protocol was designed as 60 min for the second trimester and 40 min for the third trimester. The intervention was delivered by certified Yoga experts via the Google Meet interface 5 days a week from the time of recruitment until delivery. All the sessions were delivered online by instructors who observed and corrected the postures of individual participants. Daily attendance was recorded for every participant throughout the period of intervention. Participants in the Yoga group attended Yoga sessions for an average of 47.18 ± 2.03 (Mean ± SEM) days. The UCG participants were contacted via telephone follow-up to ensure that they were not involved in any physical activity except normal walking.

Briefly, the protocol comprised of asana (physical postures), pranayama (breathing practices), kriya (tratak), meditation, and relaxation practices.

Instrumentation

Multiple scales were used in this research study, including the PSS-10, DASS-42, and WHO-QOL-26, to comprehensively assess psychological distress in pregnant women and evaluate the impact of Yoga on these parameters, ensuring a comprehensive and multi-dimensional assessment of psychological well-being and quality of life.

Perceived stress scale

The Perceived Stress Scale (PSS-10) is a 10-item stress assessment instrument originally, scale was developed in *1983* by *Cohen*, *Kamarck*, *and Mermelstein* (21). (PSS-10) was used to measure the perceived stress levels among pregnant women. It is a widely recognized and validated scale that assesses how various situations and events impact an individual's thoughts and feelings, providing valuable insights into the specific stressors experienced during pregnancy. The scale asks questions related to negative events like how often you have been upset because of something that happened unexpectedly, how you felt you were unable to control important things in your life, and how often your felt nervous and stressed. Some questions are related to positive events which are revered during scoring, these are how often you felt confident about your ability to handle personal problems, how often you were able to control irritation, and how often you felt on top of things. Reliability, Validity, and scalability of PSS-10 during pregnancy have already been established by previous studies (22, 23) which show PSS-10 to be an appropriate scale to measure the perceived stress among pregnant women. The PSS measures an individual's perceived stress, with scores ranging from 0 to 40. A score of 0–13 is considered low, 14–26 is moderate, and 27–40 is high.

Depression anxiety stress scale

The Depression Anxiety Stress Scale (DASS-42) is a self-report measure that assesses the severity of negative emotions. The scale consists of three subscales, namely depression, anxiety, and stress, which are measured separately. Scores on each subscale can range from normal to extremely severe, depending on the severity of the symptoms reported by the individual. The severity levels are categorized as normal, mild, moderate, severe, and extremely severe (24). The scale contains 14 questions related to dysphoric moods such as sadness and unworthiness, measuring depression; 14 questions related to panic attacks and fears, measuring Anxiety, and the remaining 14 questions relate to tensions and irritability, measuring stress. Validation of DASS reliability during pregnancy has been done by previous studies (25, 26). (DASS-42) was employed to evaluate the severity of negative emotions, including depression, anxiety, and stress. By utilizing this comprehensive scale, we were able to capture a broad spectrum of psychological distress symptoms commonly experienced by pregnant women.

Who- quality of life- BREF scale

Quality of life was measured using the WHO-QOL-BREF questionnaire which contains 26 original items, among which 2 items measure overall perception of quality of life and 24 items examines 4 domains (D1- Physical, D2- Psychological, D3- Social, and D4- Environmental) (27). This is also a reliable scale to be used during pregnancy (28). This questionnaire depicts score from 0 to 100 and a higher score signifies better QOL. This questionnaire was used to assess the overall quality of life of pregnant women across multiple domains, including physical, psychological, social, and environmental aspects. This scale provides a holistic understanding of the impact of pregnancy on various aspects of life.

Results

In total, 100 participants gave their consent to participate and were randomized into Yoga ($n = 50$) and control or usual care groups ($n = 50$). During the course of the study, in the Yoga group, 16 participants dropped out for various reasons. Five of these individuals were not willing to participate in the Yoga intervention, eight started but discontinued the intervention, one participant experienced a

miscarriage, and two did not complete the required neuropsychological assessments. In the Usual care group, five discontinued the trial, and two experienced miscarriages. When accounting for miscarriages, the attrition rate was found to be 23%. However, if miscarriages are not included, the attrition rate for the study is 20%. Finally, 77 participants who completed the neuropsychological assessment at both time points were included in the data analysis including 34 and 43 in YG and UCG groups, respectively.

The two groups were found to be similar in terms of age, height, weight, BMI, occupation, education level, parity distribution, diet, socio-economic status, pregnancy method, and complications, indicating no significant differences between them in these demographic and lifestyle factors (Table 1).

All results are reported as Mean ± SEM and frequencies in %. Frequency percentage was reported as low, moderate, and high for PSS and normal, mild, moderate, severe, and extremely severe for DASS as per the standard questionnaire classification using descriptive statistics (Table 3). Within-group changes and between-group changes of Yoga and control groups are reported as Mean ± SEM in Table 2 along with the effect size of each parameter and considering $p \leq 0.05$ as a significant change. The effect size was calculated by dividing the difference of mean value between two groups by pooled standard deviation and is reported as a value of Cohen's d where $d = 0.2$ is small, $d = 0.5$ is medium and $d = 0.8$ is considered as large based on the benchmark suggested by Cohen (29).

Perceived stress

When the average scores were compared, both groups reported the same level of stress at baseline (UCG: 16.79 ± 0.763, Yoga: 17.38 ± 0.943) without any significant differences ($p = 0.623$). However, within-group analysis after follow-up showed a significant increase in perceived stress from 16.79 ± 0.763 to 20.84 ± 0.927 ($p = 0.000$) in the UCG (average change: −4.047) and a significant decrease in perceived stress from 17.38 ± 0.943 to 13.41 ± 0.943 ($p = 0.000$) in the YG (average change: 3.971).

Between-group analysis at follow-up demonstrated a highly significant reduction in perceived stress in the Yoga group, with an average change of −7.425 ($p = 0.000$) compared to the UCG.

At baseline, the UCG reported a low level of perceived stress at 20.9%, while the remaining 79.1% reported a moderate level. These levels changed at follow-up, with only 11.6% reporting low stress, 67.4% reporting moderate stress, and 20.9% reporting high stress. However, the YG reported 26.5% low stress, 70.6% moderate stress, and 2.9% high stress at baseline, which changed to 55.9% low stress and 44.1% moderate stress after the intervention.

Depression, anxiety, and stress

At baseline average score of the two groups did not differ for depression, anxiety, and stress. UCG reported a significant increase in depression from 7.33 ± 0.938 to 10.35 ± 1.191 ($p = 0.016$), anxiety from 7.44 ± 0.818 to 9.93 ± 1.044 ($p = 0.016$), and stress from 11.70 ± 1.090 to 16.93 ± 1.342 ($p = 0.000$) at follow-up. However the opposite trend was seen in YG with a significant decrease in depression from 8.71 ± 1.441 to 4.41 ± 0.998 ($p = 0.000$), anxiety from 9.09 ± 0.946 to 6.35 ± 0.774 ($p = 0.011$) and stress from 12.38 ± 1.346 to 7.35 ± 1.010 ($p = 0.000$) after intervention.

In the UCG group, at baseline, 72.16% were in the normal category of depression which decreased to 48.8% at follow-up. However, in mild, moderate, severe, and extremely severe categories percentages increased from 14.0, 11.6, 0, and 2.9%, to 23.3, 20.9, 4.7, and 2.3%, respectively. Similarly, the percentage of anxiety and stress in the normal range decreased from 58.1 and 81.4% to 48.8 and 41.9%, respectively. However, incidents of anxiety in the mild, moderate, severe, and extremely severe ranges increased from 4.7, 27.9, 9.3, and 0% to 11.6, 14.0, 11.6, and 14.0%, respectively. There were only 16.3% mild and 2.3% moderate incidents of stress while at follow-up only 9.3% were in the mild range, the moderate range increased to 27.9 and 20.9% were in the severe range.

In the YG group, the baseline there were 70.6% in the normal range of depression which increased to 91.2% after intervention, while the mild, moderate, and extremely severe range decreased to 2.9% only from 11.8 and 5.9%. Incidents in the normal range of anxiety and stress also increased after intervention from 47.1 and 70.6% to 70.7 and 88.2%, respectively. However, the mild and extremely severe ranges of anxiety remained the same at 8.8 and 2.9%, while the moderate and severe ranges decreased from 29.4 and 11.8% to 14.7 and 2.9%. Incidents of stress in the mild category decreased from 11.8 to 5.9%, remaining the same (i.e., 5.9%) in the moderate category and there were no incidents in the severe and extremely severe categories of stress after intervention which were 8.8 and 2.9% at baseline.

Quality of life

Initially, no significant differences in the quality of life (QOL) were observed between the two groups. However, during the follow-up period, the group that received usual care (UCG) showed a significant decline in physical, psychological, and social domains, with scores decreasing from 68.21 ± 1.672 to 59.28 ± 2.190 ($p = 0.001$), 69.07 ± 1.924 to 62.07 ± 2.229 ($p = 0.001$), and 76.77 ± 3.140 to 67.5 ± 3.269 ($p = 0.002$), respectively, indicating a reduced quality of life with the progression of gestation. In contrast, the Yoga group reported a significant increase in psychological and environmental domains, with scores increasing from 64.76 ± 2.732 to 74.68 ± 2.789 ($p = 0.001$) and 66.15 ± 2.913 to 75.18 ± 2.358 ($p = 0.002$), respectively, indicating improved quality of life after Yoga.

Comparison of only follow-up data from both groups, the Yoga group demonstrated improved QOL, as evidenced by a significant average change of 8.486 (0.007), 12.607 ($p = 0.001$), 9.277 (0.050), and 11.269 ($p = 0.002$) in the physical, psychological, social and environmental domains, respectively, when compared to the UCG.

Discussion

Our study underscores the impact of advancing gestational age on the neuropsychology of pregnant women, which can increase their vulnerability to symptoms of stress, anxiety, and depression. The findings emphasize the significance of prioritizing the psychological well-being of expectant mothers, particularly through Yoga, which can enhance their psychological resilience, as evidenced by the positive outcomes reported by the Yoga group. While the study findings

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TABLE 1 Characteristics and demographic details of participants.

Variables	Yoga group (n = 34)		Control group (n = 43)		
	n	%	n	%	p-value
Age distribution					
18–25	4	11.8	3	7.0	
26–30	18	52.9	23	53.5	0.752
31–35	12	35.3	17	39.5	
Occupation					
Housewives	26	76.5	26	60.5	0.151
Job	8	23.5	17	39.5	
Education level					
12th	7	20.6	11	23.6	0.248
Graduate	14	41.2	23	53.5	
Post graduate	13	38.2	9	20.9	
Occupation of husband					
Unemployed	0	0	0	0	
Employed	34	100	43	100	
Smoke/alcohol					
No	21	61.8	25	58.1	0.817
Yes	13	38.2	18	41.9	
Parity distribution					
Nulliparous	30	88.2	31	72.1	0.098
Multiparous	4	11.8	12	27.9	
History of miscarriage					
Yes	5	14.7	4	9.3	0.497
No	29	85.3	39	90.7	
Year of marriage					
2010–2014	1	2.9	6	14.0	0.126
2015–2020	33	97.1	37	86.0	
Diet					
Vegetarian	23	67.6	27	62.8	0.810
Non-vegetarian	11	32.4	16	37.2	
Religion					
Hindu	27	79.4	41	95.3	0.159
Sikh	5	14.7	2	4.7	
Jaat	1	2.9	0	0	
Jain	1	2.9	0	0	
Socio-economic status					
LIG	5	14.7	–	–	0.336
MIG-I	10	29.4	14	32.6	
MIG-II	9	26.5	14	32.6	
HIG	10	29.4	15	34.9	
Average Age Mean ± SEM	29.31 ± 3.415		29.71 ± 3.00		0.116
Average Height Mean ± SEM	1.58 ± 0.3293		1.59 ± 0.5269		0.412
BMI Mean ± SEM (in 2nd trimester)	22.32 ± 0.435		22.32 ± 0.378		0.413
BMI Mean ± SEM (in 3rd trimester)	26.09 ± 0.519		25.85 ± 0.401		0.414

Characteristics and demographics of participants in Yoga group (n = 34) and Usual care group (n = 43). Descriptive statistics was done to derive the frequency of variables and chi-square was done to obtain significance level of differences. LIG, Low-income group; MIG, Middle-income group; HIG, High-income group; BMI, Basal metabolic Rate; SEM, Standard Error Mean. Significance was observed at $p \leq 0.05$.

TABLE 2 Neuropsychological scoring within and between two groups.

Scale	Study group	Baseline Mean (SEM)	Follow-up Mean (SEM)	Average change Mean (SEM)	Effect size baseline vs. follow-up	Baseline vs. follow-up (*p* value)	Yoga vs. control *at baseline #at follow-up (*p* value)	95% confidence interval of the difference (* baseline # followup)	
								Lower	Upper
Perceived stress scale	YG	17.38 (0.941)	13.41 (0.943)	3.971 (0.963)	0.658	**0.0001**	0.623*	−1.796	2.979
	UCG	16.79 (0.763)	20.84 (0.927)	−4.047 (0.898)	−0.73	**0.0001**	**0.0001**#	−10.091	−4.76
Depression	YG	8.71 (1.441)	4.41 (0.998)	4.294 (0.992)	0.57	**0.0001**	0.408*	−1.923	4.684
	UCG	7.33 (0.938)	10.35 (1.191)	−3.023 (1.204)	−0.43	**0.016**	**0.0001**#	−9.14	−2.734
Anxiety	YG	9.09 (0.946)	6.35 (0.774)	2.735 (1.011)	0.38	**0.011**	0.191*	−0.837	4.13
	UCG	7.44 (0.818)	9.93 (1.044)	−2.488 (0.992)	−0.41	**0.016**	**0.010**#	−6.29	−0.865
Stress	YG	12.38 (1.346)	7.35 (1.010)	5.029 (0.981)	0.7	**0.0001**	0.691*	−2.728	4.097
	UCG	11.70 (1.090)	16.93 (1.342)	−5.233 (1.339)	−0.66	**0.0001**	**0.0001**#	−13.078	−6.076
Physical domain	YG	64.71 (2.188)	67.76 (2.006)	−3.059(2.634)	0.18	0.254	0.199*	−8.892	1.885
	UCG	68.21 (1.672)	59.28 (2.190)	8.930 (2.393)	0.71	**0.001**	**0.007**#	2.425	14.546
Psychological domain	YG	64.76 (2.732)	74.68 (2.789)	−9.912 (2.787)	0.67	**0.001**	0.19*	−10.784	2.173
	UCG	69.07 (1.924)	62.07 (2.229)	7.000 (1.928)	0.51	**0.001**	**0.001**#	5.584	19.63
Social domain	YG	78.00 (3.336)	76.32 (3.218)	1.676 (2.884)	0.07	0.565	0.79*	−7.955	10.42
	UCG	76.77 (3.140)	67.05 (3.269)	9.721 (2.403)	0.46	**0.002**	**0.050**#	−0.005	18.559
Environmental domain	YG	66.15 (2.913)	75.18 (2.358)	−9.029 (2.640)	0.64	**0.002**	0.597*	−9.252	5.36
	UCG	68.09 (2.310)	63.91 (2.572)	4.186 (2.269)	0.26	0.072	**0.002**#	4.151	18.388

Baseline and follow-up changes in neuropsychology were compared between the Yoga group ($n = 34$) and usual care group ($n = 43$) at baseline and at follow-up using independent *t*-test and with the group using paired *t*-test. Significance was observed at $p \leq 0.05$.

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TABLE 3 Descriptive of PSS and DASS as per the severity.

	Yoga group (*N* = 34)		Usual care group (*N* = 43)	
Variables	Baseline *N* (%)	Followup *N* (%)	Baseline *N* (%)	Followup *N* (%)
PSS				
Low	9 (26.5%)	19 (55.9%)	9 (20.9%)	5 (11.6%)
Moderate	24 (70.6%)	15 (44.1%)	34 (79.1%)	29 (67.4%)
High	1 (2.9%)	–	–	9 (20.9%)
Depression				
Normal	24 (70.6%)	31(91.2%)	31 (72.16%)	21 (48.8%)
Mild	4 (11.8%)	1 (2.9%)	6 (14.0%)	10 (23.3%)
Moderate	4 (11.8%)	1 (2.9%)	5(11.6%)	9 (20.9%)
Severe	–	–	–	2 (4.7%)
Extremely severe	2 (5.9%)	1 (2.9%)	1 (2.9%)	1 (2.3%)
Anxiety				
Normal	16 (47.1%)	24 (70.6%)	25 (58.1%)	21 (48.8%)
Mild	3 (8.8%)	3 (8.8%)	2 (4.7%)	5 (11.6%)
Moderate	10 (29.4%)	5 (14.7%)	12 (27.9%)	6 (14.0%)
Severe	4 (11.8%)	1 (2.9%)	4 (9.3%)	5 (11.6%)
Extremely Severe	1 (2.9%)	1 (2.9%)	–	6 (14.0%)
Stress				
Normal	24 (70.6%)	30 (88.2%)	35 (81.4%)	18 (41.9%)
Mild	4 (11.8%)	2 (5.9%)	7 (16.3%)	4 (9.3%)
Moderate	2 (5.9%)	2 (5.9%)	1 (2.3%)	12 (27.9%)
Severe	3 (8.8%)	–	–	9 (20.9%)
Extremely severe	1 (2.9%)	–	–	–

Percentage of PSS (perceived stress scale) and DASS (depression anxiety stress scale) as per the severity at baseline and at follow-up in Yoga group ($n = 34$) and usual care group ($n = 43$).

suggest that Yoga can enhance psychological resilience in pregnant women, it is crucial to acknowledge the challenges associated with engaging a large population in such interventions. Despite offering the intervention at no cost and making it convenient to attend from home, with flexible scheduling options, a considerable number of eligible participants declined to participate and a few dropouts also occurred. This may indicate a need for healthcare providers to increase awareness among the pregnant population about the potential benefits of such interventions. Nonetheless, for those who are willing and able to engage in such programs, Yoga can provide significant benefits in terms of building psychological resilience and improving overall wellbeing. The intervention of prenatal Yoga demonstrated significant improvement in the psychological health of pregnant women, as reflected by reduced levels of perceived stress, depression, anxiety, and psychological stress. Furthermore, the intervention contributed to an overall enhancement of the quality of life. The effect size for the differences observed in the Yoga group was moderate to large, with a Cohen's d value of 0.5 or greater. These findings suggest that the prenatal Yoga intervention had a substantial impact on the psychological well-being of pregnant women. In this study, we used a prenatal Yoga protocol that incorporated safe and gentle practices such as stretching, mild bending, meditation, breathing exercises, and relaxation techniques. These practices are considered to be beneficial to pregnant women and have been widely used for the general maintenance of their health. However, scientific evidence to support these claims has been limited until now. This study aimed to bridge this gap by designing a Yoga intervention that specifically focused on improving the attention and mental wellness of pregnant women. The results of our study suggest that this approach was effective in improving the psychological resilience and mental well-being of pregnant women, thereby highlighting the potential benefits of non-pharmacological interventions for this population. It should be noted that the practices used in the Yoga protocol were safe and adapted to the unique needs of pregnant women. Our study findings are in line with a previous study conducted by Abbas Rakhshani et al., which also reported improvement in psychological, social, and environmental domains of quality of life (QOL) through integrated Yoga practice during pregnancy (30). Our research further reinforces these findings by highlighting the positive impact of prenatal Yoga on the psychological and environmental domains of QOL, indicating a better outlook of pregnant women toward pregnancy after practicing Yoga. On the other hand, the usual care group reported a decrease in QOL domains of physical, psychological, and social health, indicating that physiological and psychological changes during pregnancy may have a greater impact on expectant mothers as pregnancy progresses, affecting their QOL and ultimately pregnancy outcomes. These changes can be better adapted by pregnant women if they integrate Yoga as a lifestyle during pregnancy, as our results show.

Kusuka et al. (17) have shown decreased salivary cortisol after each Yoga session in pregnant women. A negative indicator of mood

such as anxiety, depression fatigue, and confusion, it was decreased after Yoga practice (17). We also find that perceived stress, anxiety, psychological stress, anxiety, and depression were significantly decreased in YG, whereas we found a significant increase shift in perceived stress and anxiety in UCG. Mindfulness Yoga was also effective in reducing depression symptoms and increasing maternal-fetal attachment and mindfulness among psychiatrically high-risk women (31), in addition to those in healthy pregnancies.

According to a study conducted by Field et al. (16), Yoga has advantages for pregnant women, including reducing stress, anxiety, and physical complaints throughout pregnancy, reducing discomfort, minimizing birthing pain, and speeding up the opening of the birth canal during birth. Yoga during pregnancy is thought to promote nervous system control and physiological system function (immunity, endocrine, neurotransmitter, and cardiovascular) as well as improve mental health to achieve a balance between the body and mind (16).

When compared to a waitlist control group, an RCT by Vieten et al. (32) evaluated a psychosocial mindfulness-based intervention administered in the second half of pregnancy reporting a reduction in anxiety and negative mood, indicating mindfulness-based interventions are a possible mental health approach to managing pregnancy stressors (32). Women who underwent mindfulness Yoga courses grew more comfortable with their position as mothers and valued their interactions with the fetus, according to a study by Muzik et al. (31), and they concluded that the supporting environment given in prenatal Yoga promotes the transition to safe motherhood. Prenatal Yoga encourages pregnant women to envisage and speak with their unborn child, which may explain why women who participated in Yoga courses had higher maternal-fetal attachment scores (31). Telephonic survey with the study participants after delivery revealed that participants of YG felt more connectedness with the fetus, more willpower, confidence to deal with stress and situations, relaxation, calmness, and positive attitude, incidents of which were much less in UCG as compared to YG.

Quality of life during pregnancy affects the pregnancy outcomes and impacts both the mother and the developing fetus. Depression and anxiety are independently associated with poor quality of life and vice versa which implies the need for healthcare professionals to give attention to the quality of life of women visiting prenatal clinics. Mild muscle relaxation exercise combined with music therapy has been shown to significantly improve quality of life parameters in pregnant women with low back pain (33). Likewise, mindfulness helps in bringing more coping strategies and management toward negative psychological emotions of mood and anxiety, and improves the quality of life which can ultimately improve pregnancy outcomes. Mindfulness Yoga intervention significantly reduced psychological distress symptoms and improve quality of life as reported by previous studies (34).

PSS measures the degree to which an individual perceives life to be unpredictable, uncontrollable, and overloaded for the previous month which can impact the psychological state of the individual. To predict specifically the role of Yoga in changing the perception toward their situation we individually compared the questions in the PSS scale, which depicts that after Yoga practice women were able to control their emotions in challenging situations, handle anger, and face difficulties with a more positive attitude, as suggested by the results. The present study specifically examines the effects of Yoga on both psychological distress and quality of life during pregnancy. By focusing on both outcomes, our study provides a comprehensive assessment of the potential benefits of Yoga during pregnancy. Additionally, it adds to the limited body of research on this topic, which will help inform healthcare providers and pregnant women about the potential benefits of incorporating Yoga into their prenatal care.

Based on the findings, Yoga may be used as a primer to reduce or prevent stress, anxiety, and depression-like symptoms, and improve QOL during pregnancy. One of the limitations of the study is the small sample size. We suggest that similar kinds of studies can be done using similar Yoga protocols to evaluate the impact on psychological parameters, quality of life, and other pregnancy outcomes on a bigger sample size and using molecular markers of the same parameters assessed in the study. To gain a deeper understanding of the impact of prenatal Yoga on pregnant women, future studies may consider exploring the molecular-level changes by analyzing Umbilical Cord Blood. Various biological components like cells, serum plasma from Yoga practitioners can be transplanted into animals to see the changes driven by Yoga at cellular and molecular level.

Conclusion

Our study shows that the prenatal Yoga protocol used in this study was associated with reduced stress, anxiety, and depression among pregnant women. Therefore, this protocol can be used by pregnant women as a preventive as well as a therapeutic complementary measure for reducing pregnancy-induced stress, anxiety, and other psychological imbalances. Yoga appears to maintain good psychological health even in unhelpful emotional and mental states. Apart from psychological changes, our prenatal Yoga protocol was found to be helpful in alleviating overall quality of life by improving the quality of psychological and environmental health and balancing social and physical domains throughout the pregnancy.

Statistical analysis

Within-group analysis was done using paired *t*-test while between-group analysis was done using an independent *t*-test. Statistical significance was considered a two-tailed value of $p < 0.05$. The frequency of the PSS and DAS scales was analyzed using descriptive statistics. All analyses were performed using IBM SPSS Statistics 21 software.

Limitations of the study

Interpretation of our study outcome is made with caution given the number of limitations to our study design.

Lack of blinding

Blinding of participants and researchers was not possible in this study due to the nature of the intervention. This may introduce bias in the assessment of outcomes and influence the results.

Self-report measures

The study relied on self-report measures, which are subjective and can be influenced by participants' interpretation and response bias, which may potentially affect the validity of the results.

Sample characteristics

The study included only uncomplicated pregnant women aged between 18 and 35 years with a BMI < 30 and no associated anomalies. These narrow inclusion criteria may limit the generalizability of the findings to a broader population of pregnant women with different characteristics or complications.

Compliance and adherence

The study aimed to ensure compliance with the intervention through daily attendance records and submission of screenshots/videos of Yoga classes. However, the accuracy and completeness of self-reported compliance data may be influenced by participants' motivation, memory recall, and social desirability bias.

Online intervention

The Yoga intervention was delivered online via Google Meet, which may have limitations compared to in-person classes. Factors such as internet connectivity, video and audio quality, and participants' familiarity with technology could impact the effectiveness and engagement with the intervention.

Strengths of the study

Randomized controlled trial design

The study utilized a randomized controlled trial design, which is considered reliable for evaluating the effectiveness of interventions. Random allocation of participants into the Yoga group and usual care group helps minimize selection bias and increases the internal validity of the study.

Prospective registration

The study was prospectively registered in the Clinical Trials Registry-India, which promotes transparency and helps prevent selective reporting of outcomes. This enhances the credibility and reliability of the study findings.

Well-defined protocols

The study implemented two different Yoga protocols for the second and third trimesters of pregnancy, adapted from established sources and reviewed by an obstetrician and an institutional ethical committee. This standardized approach ensures consistency in the intervention delivery and allows for the reproducibility of the study in future research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Ethical Committee-Post Graduate Institute of Medical Education and Research (PGIMER). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AA conceptualized the whole study, edited the manuscript, and provided resources to complete the study. PN collected and sorted data, wrote the manuscript, and analyzed data. KK guided in doing neuropsychology of participants and reviewed and validated data and manuscripts. PS and VS provided the participants and assisted in the recruitment of participants. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2023.1201371/full#supplementary-material

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Empowerment of Mesenchymal Stem Cells in a Yoga-Practicing Woman

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KEY WORDS

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ABSTRACT

Mesenchymal Stromal/Stem (MSCs) cells possess a remarkable capacity as a therapeutic option for many diseases. These cells have immunomodulatory, proangiogenic, regenerative and anti-inflammatory capabilities. In spite of possessing such properties, these cells behave differently in the *in-vivo* environment in the diseased condition, and in many instances lose their therapeutic potential. This case report presents evidence about empowerment of MSCs from a pregnant woman who underwent a set of yogic exercises during her pregnancy. MSCs isolated from this woman were found to be in a better state post-cryopreservation, and also while mediating their immunomodulatory effect.

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Introduction

Mesenchymal stem/stromal cells (MSCs) exhibit various properties like self-renewal capacity, multilineage differentiation, angiogenesis and immunomodulatory properties. These features make them an extremely promising tool for translational research and clinical applications. MSCs are found in various adult tissues and the cues in the micro niche dictate their fate and function (1,2). It is known that various categories of exercises can affect the extracellular matrix composition, inflammatory milieu, and such changes in the niche lead likely to the alteration of tissue-specific stem cell populations and their functions post-exercise (3–5). The clinical application strategies of mesenchymal stem cells are still evolving, and in spite of their extra ordinary properties, the deployment of MSCs is not completely reflected in the clinical trials (6).

The requirement of the MSCs to be cultured *in vitro* for upto 3–4 weeks for their cultivation and expansion may be a deterrent to the realization of some of their biological functions. Furthermore, harsh environment *in vivo* post-injection in the recipient in its diseased state leads to them having shorter life-span (7). Licensing and optimization of MSC culture conditions are key strategies to improving the MSC functions *in vitro* and *in vivo*. All of these procedures reportedly contribute to enhancing the MSC transplantation efficacy in tissue engineering and regenerative medicine (8).

In this report, we have analysed the MSCs from the Wharton's jelly of a yoga-practising woman and found them to be possessing better properties. If tested and proved to be working in cells isolated from a larger sample size of yoga-practising pregnant women, such MSCs might be more effective when used for therapeutic purposes.

Yoga Protocol

The mother practised the yoga exercises as per (Table 1).

Table 1: Yogesta Protocol

2nd Trimester Practices, its sitting relaxation posture, *Siddhasana* instead of sitting relation posture, *Siddhasana* (60 minutes)	
Practices	**Duration**
Brief Invocation	2 min
Head Stretch, Side stretch, Hand in/out	1 min each
Loosening Fingers, Loosening wrist	1 min each
Ankle stretch	1 min
Neck exercises	1 min
Quick relaxation technique (QRT)	3 min
Side bending, Shoulder rotation	1 min each
Twisting	½ min
Instant Relaxation Technique (IRT)	2 min
Tadasana (Initial Standing Posture), *Ardhakati Cakrasana* (Right Bending), Standing Relaxation Posture	1 min each
Dandasna (Initial Sitting Posture), *Vajrasana* (Thunderbolt Pose), *Vakrasna* (side twist)	1 min each

(*Continued*)

Table 1: (*Continued*)

2nd Trimester Practices, its sitting relaxation posture, *Siddhasana* instead of sitting relation posture, *Siddhasana* (60 minutes)	
Practices	**Duration**
BadhaKonasana (Bound Angle Pose), *Upavista Konasana* (Wide angle seated forward bend)	1 min each
Sitting Relaxation posture, *Siddhasana* (Perfect pose)	1 min each
Deep Relaxation Technique (DRT)	5 min
Savasana (left lateral position)	2 min
Anulom Vilom (Alternative Nostril Breathing Technique)	3 min
Sitali, Sitkari, Sadanta (Cooling Practices)	3 min
Bhramari (bee breath)	2 min
Abdominal, Thoracic and upper lobar	1 ½ min each
Meditation	10 min
Trataka (Trotter-meditation)	2 min
Brief Invocation	2 min
3rd Trimester Practices (40 minutes)	
Brief Invocation	2 min
Head Stretch, Side stretch, Hand in/out	1 min each
Loosening Fingers, Loosening wrist	1 min each
Ankle stretch, neck exercise, shoulder rotation	1 min each
Instant Relaxation Technique (IRT)	3 min
Anulom Vilom (Alternative Nostril Breathing Technique)	3 min
Sitali, Sitkari, Sadanta (Cooling Practices)	3 min
Bhramari (bee breath)	2 min
Deep Relaxation Technique (DRT)	5 min
Meditation	10 min
Trataka (Trotter-meditation)	2 min
Brief Invocation	2 min

Case Presentation

Isolation of Mesenchymal Stromal Cells

Human umbilical cord tissue was taken from the full-term birth of patient P1 from the Department of Obstetrics & Gynecology, PGIMER, Chandigarh (The patient's consent was obtained and the respective approvals were taken from Institute ethics committee and Institute stem cell committee). P1 was 27 years in age and had no history of chronic infectious disease, STD or hepatitis. MSCs were isolated from the Wharton's jelly (WJ-MSCs) from the umbilical cord tissue using standardized explant method. WJ pieces were washed with Phosphate-Buffered Saline (PBS), seeded in T-25 flasks and cultured in complete α-Minimum Essential Medium (Sigma Aldrich™). Cells were kept in an incubator with 5% CO_2 at 37°C. After 70–80% confluence was achieved, cells were trypsinized and expanded till required passage number 2.

Characterization of MSCs

MSCs were characterized both phenotypically and functionally in accordance with the International Society for Cell Therapy (ISCT) guidelines (9). MSCs were phenotyped for standard markers including CD34, CD45, CD11b, CD19, HLA-DR, CD73, CD90, and CD105 (BD Stemflow™ Human MSC Analysis Kit) through flow cytometry (BD FACS ARIA II). Cell count and viability were determined by staining with the Annexin-V kit (Sigma Aldrich), as per manufacturer's protocol. Cells negative for annexin V and Propidium Iodide were counted and recorded as the viable population. MSCs were assessed for their multilineage differentiation potential to adipocyte, chondrocyte and osteogenic lineage.

Cryopreservation of MSCs

MSCs were cryopreserved in 10% Dimethyl Sulphoxide (DMSO) [Sigma Aldrich™] and 90% Fetal Calf Serum (FCS) [LONZA™] at 1°C/min cooling rate and stored in liquid nitrogen the following day. Their viability was analysed after 2 months.

Immunomodulatory Capacity of MSCs

Following the cryopreservation of two months, MSCs were analysed for their immunomodulatory capacity in a mixed lymphocyte reaction (MLR). CFSE (carboxyfluorescein succinimidyl ester) [Thermofisher Scientific™] labelled responder cells (peripheral blood mononuclear cells - PBMCs) were co-culture with mitomycin inactivated stimulator cells at a cell number of 0.3×10^6 for each to induce lymphocyte proliferation. Unprimed MSCs (Control MSCs) or yoga-conditioned MSCs (Y-MSCs) were added to the MLR at a 1:10 ratio (MSC: PBMC). Co-cultures were incubated for four days at 37°C in a CO_2 incubator, before analysing the proliferation of PBMCs in the cultures. The cell proliferation was analysed by acquiring the cells in flow cytometry and proliferation index was determined using Flow jo software.

MSCs stained with fluorochrome labelled antibodies showed >95% positivity for CD73, CD90 and CD105 in both the control MSCs (C-MSCs) and Y-MSCs (Figure 1). The pattern of both C-MSCs & Y-MSCs was similar for adipogenic, chondrogenic and osteogenic differentiation abilities.

Interestingly, post cryopreservation the viability of Y-MSCs was 96% as compared to 82% viability of C-MSCs (Figure 2). Moreover, the proliferation index of PBMCs was significantly reduced in YMSCs group when compared to the unprimed group (Figure 3).

Discussion

Physical exercise and yogic kriyas have known beneficial effects on overall healthy being. Considering the cellular level, endogenous MSCs contribute to tissue homeostasis but are largely insufficient in case of severely damaged tissues. Therefore, developing MSC therapeutics holds great promise for the regeneration and immune modulation for various disease conditions. They display unique immunomodulatory properties due to the paracrine factors secreted by them (10).

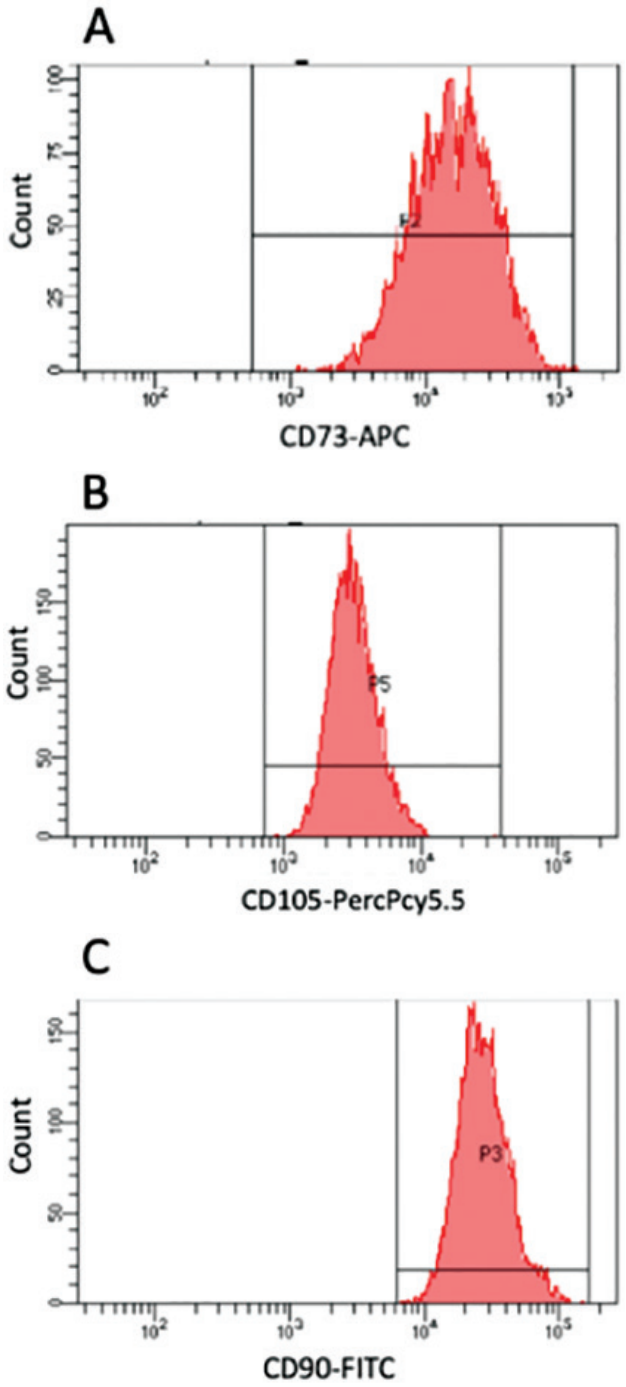

Figure 1: Phenotypic characterisation of Y-MSCs: 100% positive expression of CD73, CD90 & CD105 as analysed by flow cytometry.

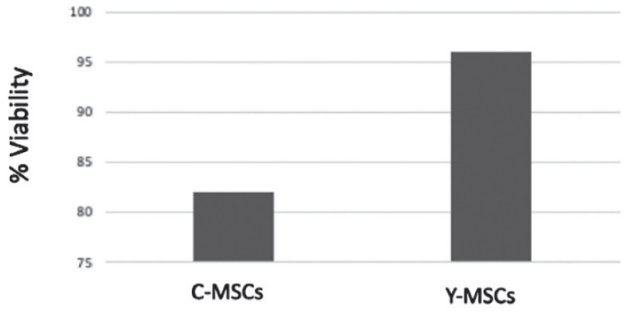

Figure 2: Comparison of viability of C-MSCs & Y-MSCs post cryopreservation for 2 months. The cells were stained with propidium iodide/annexin V and analysed by flow cytometry.

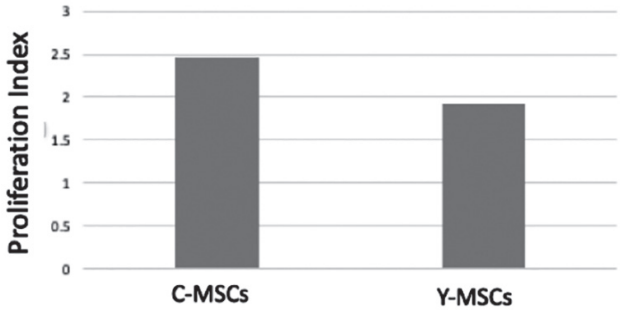

Figure 3: Comparison of responder PBMCs and their proliferation in response of C-MSCs & Y-MSCs. Flow cytometric analysis plots indication the percentage proliferation index of Responder cells, flow cytometry was performed on Day-5 post-coculture.

However, the complete efficacy of MSCs is not reflected adequately in terms of their clinical usage, and various regimens are being tried to license them to be functionally stable and more effective. They perform better if preconditioned in tailor made conditions according to the pathophysiology of the targeted diseased condition (11). Furthermore, for off-shelf supply, these cells have to be cryopreserved for on-demand availability. With the goal of understanding if yoga potentiates the capabilities of MSCs, this study was designed to understand the effect of cryopreservation on yoga-primed MSCs in terms of their viability and immunomodulation functional capacity. Various form of exercises have been reported to influence the biological properties of MSCs in various model systems (12–15), including their immunomodulation. Taken together, the results from our study provide a proof of concept indicating two significant findings which contribute to understanding the role of yoga in modulating properties of MSC. We propose that on account of having practiced a set of yoga exercises, the Y-MSCs revive in a better way with higher viability and, that the Y-MSCs become more potent immunomodulators.

Conclusion

This study forms a platform for testing the hypothesis in characterising WJ-MSCs from a larger cohort of yoga-practising pregnant women having genetic heterogeneity, and has implications in addressing pertinent issue of data gaps in the upcoming scientific field of evidence-based traditional medicine.

Authors' contribution

D: Performed the experimental part and collected the sample; PN: Conducted Yoga Intervention in the Pregnant Women; AR: Conceived the idea, and guided the experimental plan.

Informed consent

The study was verbally explained to the patient and written consent was signed by the patient.

Source of funding

None.

Conflicts of interest

None.

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IMCR
REV ARTICLE

Traditional Medicine as a part of Indian healthcare system: Challenges and Recommendations

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ABSTRACT

Background: Traditional Medicine (TM) is a system of medicine which is a combination of medical theories of various cultures, which can help in health maintenance, disease prevention and diagnostics. But this system of medicine has not been globally recognized and accepted, due to numerous reasons including, lack of research, technology, funding, etc.

Summary: The present review focuses on discussing the gaps and limitations at both academic and administrative levels in the acceptance of TM as a part of the Indian Healthcare system. Certain *in vivo* and *in vitro* studies have been discussed in the present review, showing the beneficial effects of TM on various health conditions. Based on the discussed studies and limitations, the authors have further proposed certain recommendations, including documentation, national policies, and academics that can be helpful in the implementation of TM as a part of the Indian healthcare system.

Key message: Through the present study, the authors have proposed that TM is an important part of the healthcare system, and this can be combined with conventional medicine to reduce the burden on the healthcare system in India as well as globally.

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Background

Traditional medicine (TM), as defined by the World Health Organization (WHO), is the combination of knowledge, skills, and practices which are based on the theories, beliefs, and experiences belonging to various cultures. These can be used in health maintenance as well as in the diagnostics, prevention, and treatment of physical and mental ailments (1). TM is the combination of health practices which comprises of plant, animal, and mineral extract-based medicine along with spiritual and manual techniques, and certain exercises with the combined aim of treatment, diagnosis, and prevention of illness along with the maintenance of well-being (2). TM has always been an important system of medicine that is essential for maintaining global world health needs. In the Indian scenario specifically, six systems of medicine are recognized in this field: Ayurveda, Yoga and Naturopathy, *Unani*, *Siddha*, and Homeopathy. Each system of TM is important in its context (3).

Besides each of these systems having its advantages, these are not globally accepted in the current scenario and face challenges in being accepted as an important system of Medicine. Though the above-mentioned systems of medicine have originated in India, the acceptance and recognition of these are not ubiquitous (4). Many factors have led to the current scenario with allopathic medicine taking the front end of the medicine system and other TM systems are not being commonly recognized as a system of medicine for disease prevention and cure.

Though a huge volume of studies is available in support of the TM system (5), many factors limit the potential of the TM system to make it globally acceptable. Through the current study, the authors wanted to highlight the challenges in the implementation of TM in the current system of medicine, specifically in the Indian context. Further, the authors have also provided certain recommendations for the implementation of TM along with the current healthcare system.

TM system faces many challenges in the implementation of TM in daily lifestyle as a part of disease preventive and curative strategy. Following are some of the challenges which are faced by policy members in the following context (6).

Academic limitations

Lack of research and development in the field

The evidence-based studies are lacking in the field of traditional medicine. Small sample numbers, inconsistent or varied outcomes, and poor research methods are some of the key factors that render studies defective and insufficient. Other issues include weak controls, inconsistent descriptions of the treatment or product, low statistical power (perhaps due to small sample sizes), and a lack of comparisons with other therapies, a placebo, or both (7). Folk traditions and wisdom of traditional medicine are handed over from generation to

generation in India and are termed as 'people's health culture' with the scarcity of documentation and patents in the field of traditional medicine. As per the announcement by the Ministry of Commerce and Industry, any readymade traditional ayurvedic formula cannot be patented, however, substantial improvement and modification in this area can be patented, hence the number of patents in the field of TM is required to generate more data and evidence-based documentation (8) and hence patent in the field of TM can be used as a tool of evidence and market awareness. Obtaining patents with modified and improved TM components also enhances entrepreneurship potential.

Lack of technology to preserve the research data: While there is an increasing trend with the use of TM worldwide, the research in this field is inadequate with serious difficulties in data acquisition and preservation. The research data generated is not safeguarded and preserved in a way that it can be retrieved and reproduced. The data once acquired has to be stored in a way so that it can be retrieved from the repository.

Lack of SOPs (Standard Operating Procedure): Despite the rising research and acceptance of the field of TM, certain studies are reporting adverse health effects of TM, this may be due to the variable quality, efficacy, and contents of herbal products as a class of medicinal products. In this regard, the development of SOPs for carrying out research studies based on TM could help generate evidence-based research data, also the data generated could be patented based on standard operating protocols used (9).

Lack of funding: There is a lack of higher education support system in traditional medicines such as Ph.D. and Post Docs. Traditional medicine is primarily practiced by folk people or indigenous communities and from here only limitations appear and hence, the general population access gets restricted (10). When government will promote Ph.D. research fellowships and Post Doc fellowships, only then a large number of communities will become part of the standardization and quality assurance in traditional medicine (11). Medical institutes should bring courses for learning as well as training of TM so that from here only the development of collaboration of modern medical system with traditional medicine can start (12).

Lack of high-impact TM journals: For the wide acceptance of research, publication in high-impact journals is paramount, but a limited number of high-impact journals consider publishing research data on TM due to limitations in the research data, and also due to the lack of approval to TM research (13).

Administrative limitations

Lack of administrative bodies: There is a lack of administrative policies specially made for traditional medicines. In Medical institutions, there should be a separate ethical committee and Dean for approval of doing Traditional medicine research (9). These committees should contain medical experts as well as people who are experts in traditional medicine. This collaborative method might yield good results as well as be helpful in the standardization of outcomes of every traditional medicine study (14).

Policies and regulations, development and enforcement: In TM, there is a wide range of products, techniques, and practitioners. Some of these techniques are aimed to provide health benefits, while others have their risks or are solely motivated by business interests. Government should choose where to concentrate its efforts given its limited resources to give consumers the greatest and safest type of healthcare while meeting the requirement to protect consumer choice and it must be supervised within their jurisdiction. In TM systems that are referred to as codified medical systems, policymaking, and standardization are arguably the most challenging issues (15). For instance, some courses might place more emphasis on the physical parts of the healing system than others, which might place more emphasis on the mental and spiritual aspects. For this to be done correctly, it would be necessary to have policies and particular nodal agencies to control and offer guidance (16). As per the WHO report in 2004, to implement TM in any country's healthcare system, formulation and implementation of national policies and laws as per the country's situation are needed (17).

Lack of awareness among medical practitioners about TM: For the integration of TM into the conventional healthcare system, medical practitioners should be made aware of the system of TM, which could generate more evidence.

Lack of documentation of TM leading to lack of transfer of knowledge of TM to future generations

Lack of documentation is one of the major hurdles in the acceptance of TM, which could be due to the limited documentation of traditional medicine-based medicine through, research papers, clinical trials, and well-documented libraries, which could preserve the information. The preserved information could have then been passed on to future generations. Due to lack of proper documentation, knowledge transfer has been majorly impacted leading to less acceptance of the TM system of medicine in the masses. To overcome the issue, Government has now initiated the Traditional Knowledge Digital Library (TKDL), which is a digital repository of knowledge of TM. This repository is currently under the AYUSH ministry.

Lack of awareness and acceptability of the consumers concerning TM

In contrast to Western biomedicine, these medical traditions have a distinctive understanding of physiology, aetiology, pharmacology, and medicines (18). These medical systems have recently become professionalized, maybe as a result of this systematic approach. Traditional medicine refers to those traditional knowledge systems that are more frequently passed down orally, were developed by communities over many years, and utilize readily available and accessible elements of the local ecosystem (15). Government should focus

on advertisements, researchers, applicability, and implementation methods for the optimal use of TM.

Industrial development: Due to a lack of patents and entrepreneurship in the field of TM, this stream has not been established well in the field of industries, and hence people self-medicate as per the oral transfer of the knowledge of the field which may generate negative health effects. There is a need of enough evidence to generate optimum industrialization in this field through patents, documentation of SOPs, and storage of data to stimulate standardized drug industrialization in the field of TM.

Quality: Implementation and functioning of Inter-University and inter-medical institute nodal centres are required to generate enthusiasm and data out of collaborative research between various Institutions through student impart training and Inter-University projects.

AYUSH and health secretariat collaboration- The anticipated unification of the nation's Traditional Health and Modern Medical systems can be achieved through the implementation of a clearly defined procedure (18). AYUSH and the modern health secretariat should collaborate for access to generalized facilities, and find task forces and administrative portfolios which are already available. To further the process of coordinated action and achieve complete integration of both ministries at all functional and conceptual levels, a monthly joint review mechanism might be created (19).

Lack of Integration between Western Medicine and Traditional Medicine- Integrating traditional medicine into a modern healthcare system can benefit industrialized nations as well (20). There should be a Centre for Training and Learning established inside every hospital. To improve the staff's knowledge, skills, and general capacity, the Institutions should hold frequent academic meetings of various kinds related to traditional medicine so that their knowledge can embark with current knowledge in the field (21). A significant barrier to the incorporation of TM into mainstream medical practices is the absence of pharmacological and clinical data on the bulk TM items. Pharmacological and, in particular, comparative effectiveness, clinical research, must be done (22).

Integration of TM into National and Primary Healthcare

A Joint health secretary must be appointed to support and direct the execution of national policies on indigenous medical practices and to promote the resurgence of those practices (23). The development of India's national health strategy should include traditional medicine experts.

Comparative *in vitro* and *in vivo* studies on scientific validation of TM

A double-blind, placebo-controlled randomized study, tested the efficacy of pennogenyl extracted from French maritime pine bark extract which has been known for its clinical efficacy in lowering blood glucose levels recruited N = 147 pre-diabetic participants above the age of 18 with FPG between 5.5–6.9 mmol/L and BMI >25 kg/m^2 and compared this with standard placebo who were given an extract containing NaCl with other excipients except for maritime pine bark extract. The participants were tested for the efficacy of pine bark extract by measurement of FPG and other parameters but in this study, the authors were not able to find any improvement after 12 weeks of intervention. However, the study had its limitation concerning the duration of intervention, non-stringent recruitment criteria and the participants had a wide initial FPG range (24). As per a study published in the JAMA network in 1998, which investigated by a survey of 1035 individuals for examination of choosing traditional alternative medicine over conventional treatment, it was reported that the major contributors to choosing traditional medicine were higher education and poorer health status, also it was reported that one of the major reason for choosing traditional medicine over conventional was being dissatisfied with conventional medicine also alternative medicine was as per their values, beliefs and philosophical orientation towards life (25). A survey-based study on the usage of traditional medicine over conventional medicine among the general population in a city in Malaysia reported that 31.7% of the total recruited population having traditional medicine over conventional for self-management of cardiovascular health conditions as they were not prescribed to take the traditional medicine, which highlights the need of research-based studies on traditional medicine to avoid self-mismanagement of cardiovascular conditions (26). A study randomized controlled study in 2019, identified the effectiveness of adjunct yoga therapy over conventional therapy in diabetic lung patients where N = 72 participants were randomized in adjunct yoga and control group. The adjunct yoga group was given yoga training thrice a week for 4 months and assessed for the efficacy of adjunct yoga in the improvement of pulmonary function in diabetic lung patients. It was observed that the yoga group showed a significant change in weight and BMI after 4 months, also the yoga group showed a significant improvement in pulmonary functions i.e., FEC1 (Forced expiratory Volume), FVC (Forced Vital Capacity), and in case of conventional therapy, these parameters worsened with time (27). Another yoga-based study identified the efficacy of yoga-based traditional medicine in a primary care setting, where participants with high blood pressure (Systolic Blood Pressure of ≥140 mmHg and <160 mmHg or Diastolic Blood Pressure of ≥85 mmHg and <100 mmHg) or those who were taking medication for high blood pressure were recruited and randomized into control and yoga groups, the control group was following the conventional lifestyle or medication (if any), the yoga group was given initial 5 days physical yoga intervention in the primary care centre followed by at least 30 minutes of yoga practice to be done at home for 90 days, after yoga based traditional medical intervention, a significantly reduced systolic and diastolic blood pressure was observed. Based on these results it can be hypothesized that the addition of yoga as a standard treatment approach could be preventive for the development of major NCDs like hypertension (28). A study assessed the

response of neem leaf extract inoculation on animals with Ehrlich Carcinoma (EC) which was inoculated in animals by regular *in vivo* intraperitoneal passage under sterile conditions and Murine B16 melanoma cell line was also maintained under standard culture conditions, when the C57 animals and B16 cell were inoculated with (1 unit/mice/week for 4 weeks) Neem Leaf extracts, significantly reduced tumour growth was observed in both Ehrlich Carcinoma and B16 melanoma cell line, no *in vitro* cytotoxic effects of neem leaf extract was observed towards both EC and B16 Mel tumour cells. Another study identified the anti-tumour effect and immune-modulating effects of an extract of the plant *Calendula Officinalis* (Asteraceae) on cell lines derived from leukaemia, melanomas, fibrosarcomas and cancers of the breast, prostate, cervix, lungs and pancreas by BrdU incorporation and analysis of total cell count. Also, nude mice which were subcutaneously injected with human Ando-2 melanoma cells were tested for anti-cancerous effects of plant extract *Calendula Officinalis* (Asteraceae). The plant extract showed a potent tumour inhibition in all the tested cell lines, further when the nude mice were provided with the extract obtained from the plant, it also showed inhibition of *in vivo* tumour growth (29). Adding on a few more studies related to Ayurveda and COVID-19, one study on an innovative herbs-mineral formulation called ZingiVir-H was created as an add-on therapy for adult patients with mild to moderate COVID-19. ZingiVir-H was proven to be efficient and secure in treating COVID-19 infections and postponing the disease's progression from mild to moderate and moderate to severe in a randomized controlled single-blinded multicentre clinical trial (30). In one another study, It has been demonstrated that the Ayurvedic formulation AYUSH 64 works well in easing the intensity of COVID-19 symptoms. AYUSH 64 was proven to be both safe and beneficial in lowering the length of hospital stays and the risk of hospitalization in a thorough multi-centre clinical investigation for the care of mild to moderate COVID-19 patients (31). In mild to moderate COVID-19, a pilot clinical evaluation of an add-on Ayurvedic formulation combining *Tinospora cordifolia* and *Piper longum* revealed that adding this formulation to standard therapy shortened hospital stays and recovery times. However, additional study is required to validate these results (32).

Recommendation for optimal TM use in Indian health system

As traditional medicine has been a topic of discussion for many now. It is a challenge to preserve, maintain and maximise the usage of the ancient science of healing.

There are 15 agroclimatic zones in India, with 47,000 plant species and 15,000 medicinal plants. Around 7,000 of the 150,000 medicinal plants are used in Ayurveda, 700 in the Unani system, 600 in the Siddha medicine system, and approximately 30 are used in the modern medicine system. This makes India one of the mega bio-diverse countries in the World (33). The recommendations for enhancing the usage of TM in the Indian health system need the correction of flaws discussed in the challenges. The national health system in India is being integrated with traditional medicine (TM) using a two-pronged strategy. The main strategy is to advocate for the use of TM as an additional or alternative therapy, and the second strategy is to incorporate TM into the established healthcare system. The National AYUSH Mission, which began operations in 2014, is carrying out the main strategy. Through several activities, such as the creation of AYUSH dispensaries and polyclinics, the education of AYUSH practitioners, and the manufacture of AYUSH medications, the mission seeks to promote the use of TM. The National Accreditation Board for Hospitals and Healthcare Providers (NABH) is carrying out the secondary plan. Hospitals and healthcare organizations are accredited by NABH, an organization supported by the government. A new set of requirements for hospitals integrating TM was introduced by NABH in 2017. A few key points are covered by these standards such as the accessibility of TM professionals, accessibility of TM drugs, the instruction of medical professionals in TM, the inclusion of TM in a patient's entire care plan etc. It takes a lot of work to incorporate TM into the Indian healthcare system. The government's two-pronged strategy, though, is a promising beginning. The government is working to guarantee that all Indians have access to quality healthcare by encouraging the use of TM as a complementary or alternative medicine and by incorporating TM within the established medical system.

Advanced technology and documentation

1. Indian traditional medicine being the ancient science of healing need maintenance, preservation and curation for reducing the economic burden, which can be done through the advanced approach of technology like artificial intelligence, machine learning and the development of a database for information (34).
2. There is a lack of IP Protection or standard documentation for traditional medicine knowledge. The documentation is complicated and a potential challenge, which needs continuous effort for resolving the issue. Unresolved issues can lead to the loss of IP protection, lack of resources, legal challenges for ownership and failure in the utilization of traditional medicine knowledge (35).

Collaborations

1. The Ministry of Health, AYUSH, Science and Technology should be encouraged to collaborate with different institutes for more clinical, research, technical and Scientific growth and to Produce more evident based ancient science of healing.
2. Therapies under traditional medicine are valuable and effectively used worldwide, especially in the United States and other Latin nations. Considering that a collaboration workshop was conducted in March 2016 between the Ministry of AYUSH, Govt of India and different Institute of US like NCI (National cancer

institute), NIH (National Institutes of Health), and Office of Global Affairs, US Department of Health and Human Services (36). The result of the workshop decided standardization of TM products and make them more reliable and more scientific with the production of research and clinical trials.

3. Collaboration with other countries and different government agencies will also generate the resource for funding. External collaboration can enhance the ideas, approach and motivation for new concepts (35).
4. The time-to-time validation and assessment of information on traditional knowledge applicable to the Indian Health System.
5. There is unrecognised work by Ground innovators, who have been working in the field for years, should be encouraged and supported for registration, filing the patents, Claiming of IPR (Intellectual property rights) and other legal knowledge associated with it by the government.

National policies for traditional medicine

1. One of the reasons that lead to decreased demand for TM could be extensive national policies for ancient medicine. The role can be defined effectively and efficiently, by developing national policies needed in the health sector. Lack of policies and lack of government oversight, reduce the usage for people around the nation. Policies can build a necessary regulatory and legal mechanism, to promote and maintain good practices, that make TM equitable and accessible with more authenticity, safety and efficacy of therapies used (37).
2. Many developing countries all over the world have emerging TM policies. The Indian health system should make policies to assure the preservation and maintenance of Traditional medicine through different advanced techniques like artificial intelligence, Machine learning and Developing software to secure our ancient science of healing.
3. According to a survey done by WHO, only five nations had policies for TM in early 1990, by 2003 the number have reached 45 nations and 51 nations were still making policies for TM (38).

Integration of TM into national and primary healthcare

A joint health secretary must be made to support and direct the execution of national policies on indigenous medical practices and to promote the resurgence of those practices. The development of India's national health strategy should include traditional medicine experts.

Conclusion

TM is an important system of medicine which could be an addition to conventional medicine if integrated and can also help reduce the burden on conventional medicine in the current system. TM is not a new era or new concept towards health. However, with the acceptance of TM in the Indian healthcare system, various challenges are currently in the acceptability of the TM medicine system which the authors have highlighted in the present review. The authors have tried to provide certain recommendations towards the acceptance of TM in the current Indian Healthcare system. For the implementation of the suggested recommendations, both state and national policies have to be implemented for the integration of TM with the conventional medical system in Indian Healthcare.

Authors' contribution

KPS: Writing and editing; MG: Writing and editing; SKC: Writing; AA: Conceptualization and editing.

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Commentary

Yoga for Control of Progression in the Early Stage of NCDs

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Non-Communicable Diseases

Non-communicable diseases (NCDs) are diseases or body ailments that cannot be communicated or transferred to another person through physical or biological contact. NCDs pose a greater threat to human society more than communicable diseases. NCDs are challenging to treat and are characterized as chronic. However, some chronic diseases, such as cervical cancer, are caused by viral infections as an exception. These diseases have a prolonged course. NCDs usually have complex etiology, and it is difficult to trace the exact cause of these diseases. NCDs can also be called multi-factorial diseases, that is, they have multiple risk factors. NCDs are challenging to diagnose at the early stages of the disease and are generally diagnosed after causing significant damage and at the late stages of the disease. The disease keeps spreading during the latent period. According to the World Health Organization (WHO), nearly 41 million people succumb to the burden of NCDs. Out of all the global deaths, 74% occur because of NCDs.[1]

Classification of NCDs

NCDs are commonly classified as seven types of disorders. These diseases are mostly life-threatening. *Diabetes* is an NCD that mainly occurs as a result of a sedentary lifestyle. Other types of NCDs are chronic respiratory disease, cancer, cardiovascular disorders (such as stroke and coronary heart disease), musculoskeletal disorders (such as amyotrophic lateral sclerosis and multiple sclerosis)/arthritis, chronic neurological disorders, and unintentional injuries because of certain accidents that result in permanent physical or mental disabilities (Figure 1).

Status of NCDs in India

It is estimated that chronic NCDs are India's leading cause of death. Despite the lack of standard methods to estimate NCD data, according to the Sample Registration System (SRS-1998), approximately 32% of deaths are caused by these diseases.[2] A series of chronic diseases (chronic disease 3) reported by Reddy et al. estimates deaths (53%) and disability-adjusted life years (44%) due to chronic diseases. It has been reported that there is a 3%–4% prevalence of cardiovascular diseases in rural regions and 8%–10% in urban areas. Data from six cancer centers of the ICMR has reported approximately 800,000 new cancer cases every year.[3] India consists of the largest number of people with diabetes, which was estimated at 19.3 million in 1995 and is estimated to be 57.2 million by the year 2025.[4] Hypertension is also increasing among the Indian population drastically, which is a risk factor for many other cardiovascular and coronary diseases. A high prevalence of hypertension among urban adults was reported from 1995 to 2000, which was 30%–37% in Jaipur, 44%–45% in Mumbai, 31%–36% in Thiruvanthapuram, 17%–24% in Rajasthan, 4.5% in Haryana, and 14% in Chennai. Polling of epidemiological studies showed that the prevalence of hypertension was higher, approximately 25% in urban areas and 10% among the rural population. In the ICMR study, hypertension and inactivity were found to be higher in both males and females in urban areas compared to rural areas in Tamil Nadu, Jharkhand, Chandigarh, and Maharashtra.[5] It should be noted that this data is an approximation, and the actual number may be higher than this, as indicated by the

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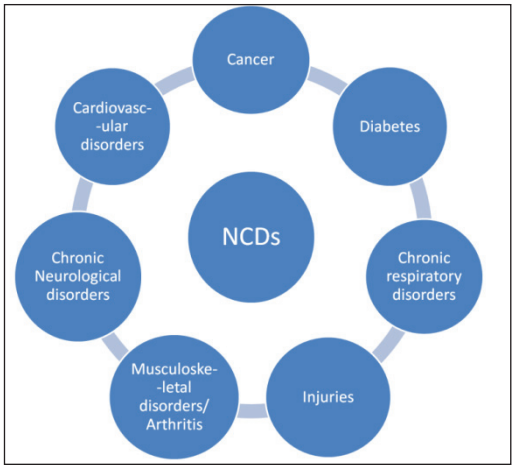

Figure 1. Classification of NCDs.

growing demand for healthcare professionals, hospitals, and allopathy-based treatments.

Economic Burden

Besides individual behavior and lifestyle modifications, several other factors, like economic, social, and political approaches, also act as critical factors for NCDs.[6–8] NCDs are more prevalent in developed nations. In comparison, developing nations with middle- and low-income economies face a major challenge as the numbers continue to increase. The low-income economy is directly related to poor health status, which contributes to unhealthy food consumption and expensive treatments. NCDs pose a significant economic burden on the growth and development of a nation. As per the WHO estimates, the average pocket expenditure in India, called out-of pocket expenditure for NCDs, is higher than that in other developing nations. The rate of hospitalization increased from 36.3% (in rural areas) to 43.9% (in urban areas) between 2014 and 2017–2018. During this period, the hospitalization cost due to NCDs also increased by ₹4461. In 2017, 81% of the population in urban areas and 86% of the population in rural areas were covered under different health schemes. There are already several government programs running for the prevention and control of NCDs. The 2017 recommendations by the National Health Policy proposed increasing the expenditure from 1.15% to 2.5% of GDP by 2025.[9]

Management of NCDs

According to WHO, around 41 million people lose their lives due to these NCDs annually, equivalent to almost 71% of all global deaths.[1] The critical strategy for reducing the global concern is adequate prevention and related strategies as well as better management. The critical components of management include screening, detection, and treatment. The accessibility of available resources to palliative care for the needy is essential. The primary healthcare system can be strengthened, and timely treatment can be delivered. Reducing the use of modifiable risk factors, like alcohol, tobacco, and unhealthy diets. Also, a lifestyle change, like adopting a balanced diet and engaging in regular physical activity, can reduce the risk. It can significantly prevent NCDs.

Control of NCDs Through Yoga

As a traditional form of practice, yoga benefits the human body by encouraging physiological and psychological well-being, as well as preventing the development of NCDs.[10] Yoga can be incorporated as part of a daily lifestyle routine to overcome sedentary lifestyles, one of the main contributors to NCDs. The importance of physical activity for a healthy lifestyle is highlighted in the Global Action Plan on Physical Activity (GAPPA) 2018–2030 with a tagline of "more active people for a healthier world". They set a target to reduce physical inactivity by at least 15% by the end of 2030 by implementing policies and plans within a period of 12 years. Dance, Yoga, and Tai Chai, along with walking, cycling, and other sports, if done regularly and at a particular intensity, have been recommended by GAPPA for being physically active throughout the day.[11] With the advancement in technology, transportation, economic development, and urbanization, the rate of physical inactivity also increases as lifestyle habits, whether at work or home, become more sedentary. Yoga is the most diverse form of physical activity where not only skeletal muscles but also smooth muscles are involved at different intensities, which can be customized as per an individual's requirements. Similar or different yoga poses and practices can be practiced by adolescents, adults, and the elderly with varying frequencies from beginning to advance as per their body form and type.

An unhealthy lifestyle, which is the leading cause of the development and progression of NCDs, is a result of both physical inactivity and an unhealthy diet, the prevalence of which is increasing with time. *Ashtanga Yoga*, a concept given by Rishi Patanjali, includes eight components generally known as limbs of yoga, which make a perfect recipe for a healthy lifestyle if followed conventionally. These components are *Yama*-restraint, *Niyama*-observances, *Asana*-postures, *Pranayama*-breathing, *Pratyahara*-senses withdrawal, *Dharana*-concentration, *Dhyana*-meditation, and *Samadhi*-absorption.[12] Most NCDs are preventable, and these aspects of yoga can help build a strong foundation for the body and mind, which can further prevent many lifestyle disorders, including NCDs, from occurring. One of the crucial ways to reduce the death rate due to NCDs is by controlling the risk factors, which include an inactive lifestyle and consumption of unhealthy food, both of which can be attained by practicing *Ashtanga yoga*, as discussed previously in the text. Yoga is not only cost-effective but also a feasible form of exercise for individuals of all ages.

It can potentially reduce the risk factors responsible for the development of NCDs, such as obesity, impaired glucose metabolism, psychological imbalance, high cholesterol levels, and blood pressure. More strategies are required for risk reduction, prevention, and progression of NCDs, which support healthy aging and lower the premature death rate caused by NCDs. There is a lack of effective treatment for most NCDs, and management is also costly, contributing to the increased economic and global disease burden.[13] Being healthy (mentally and physically) prevents the body from becoming a suitable target for NCDs. Different dimensions of mental and physical wellness can be achieved by yoga as follows:

1. *Asanas*— *Asanas* are body postures where the body holds specific positions for some duration to increase muscle strength, endurance, and stimulation of organs by increasing blood flow to a particular part of the body.
2. *Pranayama*—*Pranayama* is a regulated, controlled breathing technique to increase lung capacity and harmony.
3. *Dhayana*—*Dhayana* is meditation for increasing self-awareness and controlling thoughts.

Yoga affects different systematic axes of the body. The pronounced effect of yoga is to decrease the activity of the HPA axis, which gets activated during stress and adverse conditions.[14] The *pranayama* practice also shows the potential of yoga in regulating heart rate and the cardiac axis.[15] The psycho-neuro-immune axis is involved in immune system-related functions such as inflammation and mind-body communication. Yoga helps normalize biomarkers of the neuro-immune axis not only at the molecular level but also at the genetic level.[16] Metabolic syndrome (MetS) is a cluster of risk factors for most NCDs, such as higher blood pressure levels, increased fasting glucose and triglycerides, central obesity, and a low level of HDL. The Ghrelin axis, which gets upregulated in MetS, has been shown to get modulated after the practice of yoga.[17] Therefore, based on the above evidence, it can be said that the yoga practice can achieve a standard concept of health and a healthy lifestyle.

Implementation Strategies

The biggest hurdle in implementing strategies and their acceptance among the population after implementation is the need for more evidence-based research. More evidence provides a solid foundation for its implementation. Following are a few preparatory steps that can be kept in mind during the implementation of yoga as complementary and alternative medicine in different policies.

1. *Generating More Evidence*—Without the available evidence, profound research, and action plan, it is neither safe nor feasible to implement any new strategy (rule, medicine, intervention, and education system). Therefore, the first step in implementing new policies should focus on generating more reproducible, evidence-based research. It can be done by providing resources to the institutes involved in the particular field of interest and providing more financial support, infrastructure, and other required facilities. Besides, quality research should be assured by following good laboratory practices (GLP) so that the evidence produced is reliable and can be implemented.[18]
2. *Training of Tutors and Educating Children*—A special policy can be made for the training of tutors where teachers are trained in yoga and related techniques, including the benefits, practices, and adaptations in daily routine to make it a lifestyle. It will not only spread awareness, but most of the children will also learn about yoga at a very young age. This will add more value to education and, at the same time, increase awareness at a very early stage of life, which will act as a preventive tool for most lifestyle disorders. Also, even if resources are available, people need to be made aware of the importance of the resources. Therefore, raising awareness at an early stage with the right mentors (teachers at the school and college levels) can make a big difference.
3. *Awareness*—Unless people are themselves aware and experienced, awareness cannot be spread. There is no reason why yoga cannot be included as a compulsory subject in all educational systems, regardless of whether they are medical or not. The main reason is that medical students who practice medicine can practice yoga, which should be integrated into their curriculum.

The steps mentioned above are of primary importance at the start of an implementation process. Several other steps should be taken before a strategy is planned and can be implemented in all sectors to benefit most of the population.

Status and Potential of Yoga in the Healthcare System in India

A majority of the Indian population lives an unhealthy lifestyle. It is exposed to the risk factors associated with NCDs. Middle-income countries with limited health professionals tend to have a higher prevalence of NCDs, which are not diagnosed at pre- or early disease stages, which places a heavy burden on health systems. Other than allopathy, the AYUSH healthcare system of Ayurveda, Yoga, Naturopathy, Unani, Siddha, and Homeopathy is being practiced in different parts of India. The AYUSH system of indigenous medicine is not only involved in the treatment but also focuses more on preventive approaches. AYUSH was started by a national rural health mission to help solve the shortage of human resources in the available

Table 1. List of Evidence-Based Yoga Studies.

S. No.	Condition	Research Institute	Study Type	Sample Size	Region
1.	Diabetes and pre-diabetes	SVYASA, Bengaluru	Non-randomized controlled trial	896	Karnataka, Maharashtra, Gujarat, Rajasthan, and Tamil Nādu[24]
2.	Healthy individuals	Patanjali Research Foundation, Haridwar, Uttarakhand	A cross-sectional survey	3135	North-western state of Rajasthan[25]
3.	Pre-diabetic and Type 2 diabetes	Regional Ayurveda Research Institute for Infectious Diseases, Patna	Multi-centric, open-labeled study	3044	Bihar[26]
4.	Pain, anxiety, and depression in chronic low back pain	SVYASA, Bengaluru	Randomized control, single-blind active study	80	Bengaluru[27]
5.	Pre-diabetes	Srinivas Institute of Medical Science and Research Centre, Mangalore	Randomized-controlled trial	29	Mangalore, Karnataka[28]
6.	Cognitive function: pre-dementia	NIMHANS, Bengaluru	Single-blind controlled study	87	Bengaluru[29]
7.	Digestive health and sleep	SVYASA, Bengaluru	Randomized-controlled trial	96	Bengaluru[30]
8.	Age-related changes in healthy individuals	Defence Institute of Physiology and Allied Sciences (DIPAS), New Delhi	Randomized-controlled trial	104	New Delhi[31]
9.	Mild cognitive impairment	SVYASA, Bengaluru	Non-randomized-controlled trial.	88	Bengaluru[32]

healthcare system.[19] The shortage of healthcare professionals can be solved by providing more human resources and promoting a preventive healthcare system through AYUSH personnel, which will spread awareness among people about lifestyle management and ultimately decrease the prevalence of disorders.[20]

By preventing NCDs and risk factors with yoga, alternative medicine can potentially reduce the number of patients and the burden on healthcare systems.[21] The government of India designed various strategies for mainstreaming the AYUSH system into the existing healthcare system in the country. These strategies include the integration of the Indian system of medicine and homeopathy with the existing healthcare system, establishment of various centers of Indian system medicine, quality research in this field focusing on standardization of interventional research, advocacy for AYUSH, and establishing links of AYUSH in different sectors.[22] AYUSH mainstreaming is still in progress among the general population, but to make this healthcare system available and accessible for all, there is a need for stringent strategies and implementation, along with a robust monitoring mechanism.[23]

Status of Yoga-based Research in India

After the government established resources for yoga-based research, various institutes started producing evidence using different research study designs on varied populations. Some of the studies are given in Table 1.

India has many institutes where research related to effect of yoga on different health conditions and its efficacy as a preventive intervention is being explored. There is a need for new strategies to implement and policies that can spread more awareness and acceptance among the population for the acceptance of Yoga as a preventive and therapeutic intervention for NCDs.

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CLINICAL TRIAL REPORT

Common Yoga Protocol Increases Peripheral Blood CD34+ Cells: An Open-Label Single-Arm Exploratory Trial

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Purpose: Physical inactivity can be a cause of various lifestyle disorders including atherosclerosis, diabetes, hypertension, and cardiovascular diseases (CVDs). Lifestyle modification by the inclusion of Yoga and similar activities has shown beneficial effects on disease prevention and psychological management. However, the molecular mechanism at the cellular level is unknown. This study aims to identify the molecular response at systemic level generated after three months of Common Yoga Protocol (CYP) practice.

Methods: A total of 25 healthy adult females were recruited for this study (25 to 55 years). After the drop out of 6 participants at baseline and 2 participants after 1 month; blood samples of 17 participants were assessed. Blood samples were assessed for lipid profile, CD34+ cell enumeration and angiogenesis markers (ie, VEGF, Angiogenin and BDNF) at baseline (before intervention), after one month and after three months of Common Yoga Protocol (CYP) practice. The psychological health of the participants was assessed at baseline and after three months of CYP practice. The psychological tests used were General Health Questionnaire (GHQ), State-Trait Anxiety Inventory (STAI), Trail Making Test A & B, Digit symbol test, Digit symbol substitution test.

Results: After 3 months of intervention, blood samples of 17 participants were collected and following results were reported (1) percentage of CD34+ cells increased significantly after 3 months of CYP practice (from 18.18±7.32 cells/μL to 42.48±18.83 cells/μL) (effect size: W, 0.40; 95% CI, $p = 0.001$) (2) neurogenesis marker, ie, BDNF showed a significant change with time after 3 months of CYP intervention (effect size: W, 0.431, 95% CI; $p = 0.002$), (3) HDL showed an increasing trend (non-significant) after three months of CYP practice (53.017±1.28 mg/dl to 63.94±5.66 mg/dl) (effect size: W, 0.122; 95% CI; $p = 0.126$) (4) General Health score (10.64 ± 3.53 to 6.52 ± 3.12) (effect size: d, 0.98; 95% CI; $p = 0.001$) along with visual and executive function improved (69.94±26.21 to 61.88±28.55 (time taken in seconds)) (effect size: d, 0.582; 95% CI; $p = 0.036$), also stress and anxiety showed reduction (effect size: d, 0.91; 95% CI; $p = 0.002$) (5) a significant positive correlation was found between: HDL with VEGF ($r = 0.547$, $p = 0.023$) and BDNF ($r = 0.538$, $p = 0.039$) after 3 months of intervention; also, a significant positive correlation was found between VEGF with BDNF ($r = 0.818$, $p \leq 0.001$) and Angiogenin ($r = 0.946$, $p \leq 0.001$), also, BDNF was also positively correlated with Angiogenin ($r = 0.725$, $p = 0.002$) at both 1 month and 3 months after intervention. Also, VEGF and BDNF showed a significantly negative correlation with stress and anxiety questionnaire after the intervention.

Conclusion: The current study provides insights into the molecular response to CYP practice at systemic level. The results suggest that CYP practice indeed increased CD34+ cells in peripheral blood and BDNF also showed a significant change after the intervention. An overall improvement in general health and psychology of the participants was also observed.

Keywords: common yoga protocol, stem cells, angiogenesis, psychology, lipid profile

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Introduction

Physical inactivity can have serious implications leading to various lifestyle-related disorders and the incidence of these disorders increases with age. This may occur due to the dysregulation of the metabolic and molecular pathways, which may cause Non-Communicable Diseases (NCDs) either via overactivation or via inhibition of the molecules involved. To cite an example, in cancer overactivation of angiogenic mechanism occurs while via inhibition there is a reduced blood vessel development, halted stem cell proliferation and cardiac complications. The reason for these conditions can be physical inactivity along with other contributing factors. It has been shown that one-third of the adult population in the world is leading a sedentary life with insufficient physical activity.[1–3] In India, this population is also high, and women are more prone to physical inactivity.[4] As per a report published in 2019, on a global average, women are more physically inactive in comparison to men (31·7% for inactive women vs 23·4% for inactive men),[5] which makes women more prone to developing NCDs, with an impact on their quality of life[6] and cognition,[7,8] these studies underscore the importance of awareness and practice of physical activity among women globally.

Angiogenesis is described as the sprouting of new blood vessels from preexisting ones, and this process is mediated through molecular signals like VEGF and Angiogenin.[9] Angiogenesis is known to influence neurogenesis mechanism mediated via cross-talk between VEGF and BDNF.[10,11] Alteration in angiogenesis-related pathways is pivotal to the development of lifestyle disorders like cancer, diabetes, hypertension, atherosclerosis, stress and depression which is cross linked to the dysregulated angiogenesis.[12–17] Physical activity is known to primarily regulate angiogenesis molecular mechanism and therefore may help in prevention of NCDs.[18,19] Increased vascular density after exercise enhances cognition and quality of life.[19] The major molecular players involved in this mechanism are markers of angiogenesis (VEGF and Angiogenin),[20–22] Neurogenesis (BDNF),[23] Lipid profile,[24] stem cell mechanisms (CD34+ Hematopoietic stem cells (HPCs))[25] which lead to the development of new cells in the system and these altogether lead to an overall development of better health.

CD34+ cells are a type of hematopoietic stem cell (HPCs) with the potential of developing into endothelial cells.[26,27] These bone marrow-derived cells have been found in circulating peripheral blood, and their role in pro-angiogenic therapies has been studied extensively.[25] Circulating HPCs enhance the regenerative potential of blood and tissue cells, more specifically in circulation, which shows that these correlate with vascular endothelial function.[28] Studies have also shown that a deteriorating number of CD34+ along with angiogenic markers increases the risk of cardiovascular diseases (CVDs) reflecting reduced vascular capacity.[25] Also, physical exercise has been known to enhance the mobilization of CD34+ cells into circulation.[29]

Lipid metabolism is associated with CVDs like atherosclerosis, coronary heart disease, etc.[30–32] An increase in lipid metabolites above the normal range can inhibit the process of angiogenesis and further lead to blockage in arteries which is a significant cause of CVDs.[33] Together, these molecular responses to physical activity are known to influence and improve general health and cognition.[34,35]

Yoga is a branch of physical activity that focuses on the mind and body, and evokes relaxation through stress and anxiety resistance techniques. It leads to an overall enhancement in physiological, psychological, and physical health. Studies have shown that the practice of Yoga reduces inflammatory markers, improves immune responses and T effector cell function, and improves the overall quality of life and psychosocial health.[35] Wu et al in 2020 reported an increased proportion of CD34+ cells after Innovative Mind-Body easy exercise.[36] Another similar study reported that sustained one-year Tai chi practice showed significant elevation in peripheral CD34+ cell number in young adults.[37] In our previous study, we have reported an increase in angiogenesis markers, ie, Angiogenin and VEGF after 1 month of Common Yoga Protocol (CYP) intervention along with and elevation in HDL, as an extension of previous study we wanted to explore the effects of CYP practice for a longer time duration, ie, 3 months and also wanted to explore and correlate the effects of CYP through angiogenesis and stem cell mechanisms.[38]

The risk factor for high disease frequency in females affecting their quality of life is the prevalence of sedentary lifestyle which is high worldwide and also in India. Therefore, we primarily aimed to identify the angiogenic response of Common Yoga Protocol, CYP[39] (a generalized yoga protocol introduced by Govt. of India on International Yoga Day for the general population) in sedentary adult women by evaluation of CD34+ cells, angiogenesis markers and lipid profile in

peripheral blood as angiogenic mechanism is the preliminary response of cell proliferation and growth. We also aimed to identify the psychological response to the involvement of CYP in daily lifestyle amongst these sedentary adult females. The study's hypothesis was to identify the response of inclusion of CYP in daily routine to improve and manage overall health and to identify the psychological aspects in response to CYP practice in sedentary adult women. This study was planned to identify the potential of CYP as an adjunct therapy in daily lifestyle for overall health management and decipher the molecular response associated with the practice of CYP in sedentary adult females.

Methodology

Study Design

This study is an open-label single-arm exploratory trial to investigate the effects of CYP practice for three months.

Subject's Characteristics

A total of 25 healthy female subjects (without any co-morbidity) between the age group of 25–55 years were recruited for this 3-month yoga intervention study based on their willingness to participate (Figure 1), after 3 months eight participants dropped out and 17 participants gave their follow-up samples. Recruitment of participants was based on self-reported sedentary lifestyle of the participants since last 1 year, those who were not performing any vigorous/moderate physical activity were recruited for the study (these details were acquired at the time of recruitment). The participants were residents of urban areas of Chandigarh city, India. The participant's primary language was Hindi, with an understanding of the basic English language. The education of all the participants was above secondary school.

Recruitment of participants was done between January 2021 and June 2021 (all the participants were recruited at different time points). All the recruited participants were informed about the purpose of the study and informed consent was obtained from all individual participants.

The participant's blood samples were taken at three time points: Baseline (before the intervention), after 1 month, and after 3 months. Blood obtained was used for lipid profile assessment, assessment of angiogenesis markers, and also for CD34+ cell enumeration. Ethical approval was obtained from the PGIMER, Chandigarh Ethical Committee (IEC No. IEC-03/2020-1541). The study was registered in CTRI (CTRI No. CTRI/2020/09/027747). The study complies with principles of Declaration of Helsinki.

Intervention

45–50 minutes of Yoga intervention (Common Yoga Protocol) (Table 1) was given to the participants 5 days/week for 3 months through online interface (Google meet). Common Yoga Protocol (CYP), which includes Loosening practices, Asanas (standing, sitting, prone and supine), Pranayama, and Meditation practice, was used[39] as an intervention. The intervention was given in the morning (6–6:45 am) and evening (5:30–6:15 pm) timings depending upon the suitability of the participant. Daily attendance of the participants was recorded.

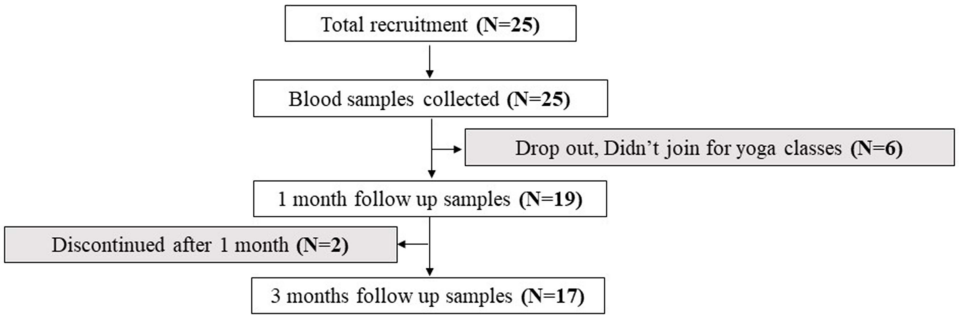

Figure 1 Participant information.

Table 1 Shows the Details of Common Yoga Protocol (CYP) Intervention

S. No.	*ASANAS*	Protocol
1.	Invocation/ Prayer (1 minute)	To enhance the benefits of practice.
2.	Loosening practices (5 minutes)	• Neck bending • Shoulder's movement • Trunk movement (*Katishaktivikasak*) • Knee movement
3.	*Yogasanas* (Yoga postures) (1 minute per asana)	**Standing postures** • *Tadasana* (Palm tree pose) • *Vrksasana* (Tree posture) • *Padahastasana* (The hands and feet posture) • *Ardhacakrasana* (The half wheel posture) • *Trikonasana* (The Triangle Posture) **Sitting postures** • *Bhadrasana* (The firm auspicious posture) • *Vajrasana* (Thunderbolt posture) • *Ardhaustrasana* (The half camel posture) • *Ustrasana* (Camel Posture) • *Sasakasana* (The Hare posture) • *Uttana mandukasana* (Stretched up frog posture) • *Vakrasana* (The spinal twist posture) **Prone postures** • *Makarasana* (The Crocodile posture) • *Bhujangasana* (The Cobra posture) • *Salabhasana* (The Locust Posture) **Supine postures** • *Setubandhasana* (The Bridge Posture) • *Uttanapada Asana* (Raised feet posture) • *Ardha Halasana* (Half plough posture) • *Pavanamuktasana* (The Wind releasing Posture) • *Savasana* (The Dead body Posture)
4.	Kapalbhati (3–4 minutes)	Forceful exhalation by contracting the abdominal muscles (30 strokes/round)
5.	*Pranayama* (2 minutes each)	• *Nadishodhana* or *Anulom Viloma Pranayama* (Alternate nostril breathing) • *Sitali pranayama* • *Bhramari pranayama*
6.	*Dhyana* (Meditation) (5–10 minutes)	For stress free deep relaxation and silencing of mind.
7.	*Sankalpa* (1 minute)	Commitment to be healthy, happy, peaceful and joyful human being.
8.	*Shanti path* (1 minute)	Prayer for happiness, health and peace for all.

Outcome Measures

Attendance Rate

Daily attendance of the participants was recorded.

Anthropometric Assessment

Age, weight, height, and BMI of the participants were recorded before and after the intervention.

Biochemical Assessment

One mL blood sample of the participants was assessed for lipid profile at baseline, after 1 month, and after 3 months of intervention.

Blood Serum Isolation

A fasting blood sample (approx. 3mL) was collected in a clot activator SST tube and was kept at room temperature for 30 minutes to allow clotting of the sample. The sample was processed at 2500 rpm for 30 minutes in a density gradient centrifuge. The upper yellowish layer was separated, aliquoted, and stored at −80°C.

CD34+ Cells Enumeration by Flow Cytometry

The flow cytometry sample preparation and gating strategy was based on published protocols (ISHAGE).

Briefly, 4mL of blood from the participants was collected in EDTA-coated vials. These vials were kept at room temperature for 45–60 minutes. The upper layer containing plasma was then layered on Hisep 1077 (Hi-Media) and centrifuged in a density gradient centrifuge at 1500 rpm for 30 minutes. The middle buffy layer containing PBMCs was then separated. From the separated PBMCs, approximately 1 million cells were suspended in 20 µL of Fc Blocker and kept at 4°C for 30 minutes. CD45 FITC and CD34 PE Fluorochrome labeled antibodies were added per requirement and incubated at 4°C for 1 hour. Washing of the cells with 1X PBS was then done, and finally, the pellet was resuspended in 200 µL of PBS and analyzed on FACS Calibur (BD Bioscience, USA) for 4 hours of processing.[40]

The cells were enumerated using ISHAGE guidelines. The acquisition was mainly based on forward, and side scatters analysis, including lymphocytes excluding debris. Manual gating procedure was followed keeping a negative (cells alone) control for each sample to avoid autofluorescence and false detection. After gating, CD34/CD45 dim cells were analyzed. ISHAGE guidelines were used to calculate estimates of CD34 concentration.

Elisa

Assessment of angiogenesis markers, ie, VEGF (Vascular Endothelial Growth Factor), Angiogenin, and BDNF (Brain-Derived Neurotrophic Factor) in blood serum of the participants was done by sandwich enzyme-linked immunoassay technique ELISA (Kinesis Dx). The procedure was followed as per the manufacturer's instructions. Briefly, after adding the samples, a biotinylated antibody was added, and the plate was incubated for 1 hour. The plate was then washed, the substrate was added, and the plate was again incubated for 10 minutes, after which stop solution was added. Reading was taken at 450 nm with an ELISA reader (Bio-Rad Laboratories). A standard curve was plotted for each experiment, and the respective protein concentration was calculated. $R^2 \geq 0.98$ was considered for the analysis.

Total protein assessment was done to normalize the concentration of the target protein. The Bradford method was used for total protein, and BSA was considered standard. Serum samples were diluted at a concentration of 400X. Coefficient of Variation (CV%) for total protein intra assay assessment was measured using formula $(\sigma/\mu)*100$. For ELISA, samples were assayed in singlets hence no CV% is reported for that.

Neuropsychological Assessment

Participants were assessed with neuropsychological tests before and after three months of intervention. The tests used were as follows: DST (Digit Substitution Test), which measures attention and verbal memory,[41] DSST (Digit Symbol Substitution Test), which measures the information processing capacity of the participant,[42] TMT A & B (Trail Making Test A & B) which measures the visual attention and task switching,[43] SLCT (Six Letter Cancellation Test).[42]

State-Trait Anxiety Inventory, which assesses the anxiety of the participant,[44] and the Short General Health Questionnaire (GHQ-12) to assess the participant for mental health and overall general health of the participant[45] were also administered to the participants. These tests were selected as these tests are quick, short, and reliable for research studies based on the general population.[46,47]

Statistics

Statistical analysis was performed by using SPSS 21 (IBM corp.). Shapiro Wilk test was used to test the normality of the data. Friedman test was used to analyze the non-parametric repeated measures data (lipid profile, CD34+ cell enumeration, and ELISA data). For the parametric pre-post data (psychological assessment, weight, and BMI) paired *t*-test was used. Correlation assessment was done using spearman's rho test to correlate the change between CD34+ cells, lipid

parameters, and angiogenesis markers after 1 month and 3 months of CYP practice. The effect size was reported using Kendall's W concordance coefficient for repeated measures of non-parametric data.

Using formula $W = X2/N(K-1)$, where W is Kendall's W value; X2 is the Friedman test statistic value; N is the sample size. k is the number of measurements per subject.

For the parametric pre-post data of psychological assessment along with weight and BMI assessment, Cohen's d effect size calculation was done using the formula

$$t/\sqrt{N}$$

Where t represents the t value, and N represents the number of participants.[48]

Results

Demographic and Anthropometric Characteristics

A total of 25 healthy females who met the inclusion criteria were recruited for the study. Six participants did not join the yoga classes and were thus excluded, and two discontinued after one month; therefore, 17 were assessed for the final analysis. The mean age of the participants was 40.82 ± 10.11 years.

All the participants were of Indian nationality recruited from Chandigarh city of India with education status of Higher Secondary School or above and an understanding of basic Hindi and English. The socio-economic status of all the study participants was above middle income.

The weight and BMI of the participants were assessed at baseline and after 3 months of CYP intervention, and it was observed that both weight (p = 0.019) and BMI (p = 0.017) reduced significantly after 3 months of intervention (Table 2).

Attendance Rate of the Participants for Intervention

For the present study, a total of 25 participants were recruited, out of which six did not join the yoga class after showing their willingness at the time of recruitment, and two others dropped out after 1 month of intervention. Two dropout participants attended classes even after 1 month for the next 15–20 days, after which they discontinued without giving any apparent reason. Participants with attendance ≥30 (43%) out of 70 classes were excluded from the study.

Table 2 Demographics and Anthropometric Details. Data Was Analyzed Using Paired *t*-Test. N = 17, **p <0.01

Demographics of the Participants					
Average age (in years)	40.82 ± 10.11				
Occupation	11 working professionals, 6- non professional				
Ethnicity	Asian Indian				
Nationality	Indian				
Education	Higher secondary school or above				
Primary Language	Primary Language: Hindi Understandable Language: English				
Socio economic status	All the participants belonged to middle income salary status (Monthly income ≥Rs 45,000/-)				
Co morbidity	2 had migraine				
Diet (self- declared)	4 non-vegetarians, 13 vegetarians				
	Pre (Mean ± SD)	Post (Mean ± SD)	*p* value	t value	Effect size (95% CI)
Weight (kg)	66.48 ± 7.82	65.32 ± 6.92	0.019**	2.607	0.16 (2.16 to 2.10)
BMI (kg/m^2)	26.36 ± 3.05	25.92 ± 2.82	0.017**	2.659	0.16 (0.090 to 0.80)

Daily attendance was recorded; 13 out of 17 participants attended more than 60% of the classes, whereas the other 4 participants joined 60% and 50% of classes (Figure 2).

Quantification of Absolute CD34+ Cell Count

After CYP practice, the CD34+ cell number increased over time. CD34+ cell number increased significantly after 3 months of CYP intervention (42.48±18.83 cells/μL) as compared to baseline (18.18±7.32 cells/μL) ($p = 0.001$), which is more than two times increase. However, this change was not observed at 1 month follow-up time point (Figure 3).

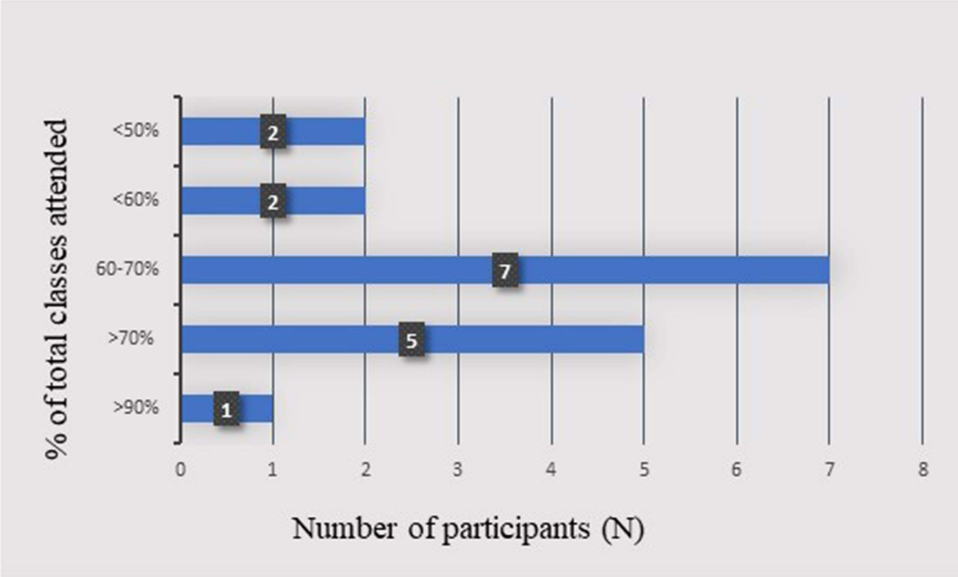

Figure 2 Figure showing attendance record of the participants for 3 months of intervention.

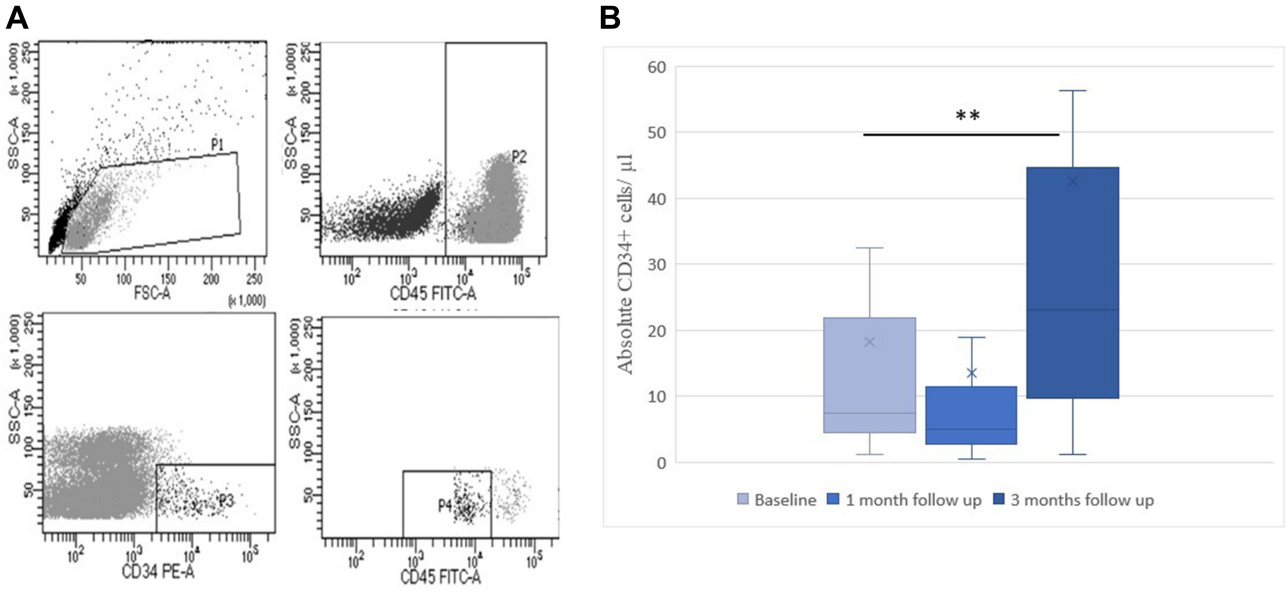

Figure 3 Enumeration of CD34+ cells before and after 1 month and after 3 months of CYP practice. (**A**) Scatter plot of enumeration CD34+ cells total blood cells, P1 shows total leukocyte population, P2 depicts the total CD45+ population, P3 is the CD34 population from the total CD45 population and P4 is the dim CD45+ (**B**) Box plot depicting quantified CD34+ cell population. **$p \leq 0.01$, Degrees of Freedom=2, Effect Size, W= 0.405.

Abbreviations: FSC, Forward Scatter; SSC, Side Scatter; PE, Phycoerythrin; FITC Fluorescein isothiocyanate.

Quantitative Biochemical Measurement

The lipid profile of the participants revealed no significant difference before and after the intervention. However, mean HDL (Baseline 53.01±5.28, 1-month follow-up 54.48±4.37, 3 months follow-up 63.93±23.33) has shown an increasing trend after 3 months of CYP practice (Effect Size, W = 0.122 (p = 0.126)) (Figure 4).

Protein Expression Quantification

ELISA assessment for angiogenesis markers was done from blood serum samples obtained from the participants. VEGF and Angiogenin showed a non-significant trend of increment after 1 month and 3 months of CYP practice. BDNF, which is a marker of neurogenesis, showed a significant decreasing trend following the intervention (Effect size = 0.431, p = 0.002) (Table 3). CV% for intra assay total protein assessment was 8.96%.

Psychological Assessment

Psychological assessment of participants was done at baseline and after 3 months of intervention. Participants showed a significant improvement in general health score (Effect size, d = 0.98; p = 0.001) and a reduced anxiety score post-intervention (Effect size, d = 0.91; p = 0.002). Also, participants showed a significant improvement in Trail making test B (Effect size, d = 0.582; p = 0.036), a visual and executive function parameter. Participants also showed an increasing trend in SLCT, DST, TMT A (parameters of attention and information processing) tests, though not significant, which are parameters of attention and information processing (Table 4).

Correlation Analysis

To determine the effects of change in CD34+ cell count on Angiogenesis markers and lipid profile of the participants, we correlated the values obtained after 1 month and 3 months of CYP practice for all the parameters mentioned above. We found a positive correlation of VEGF with BDNF and Angiogenin after both 1 month (Table 5) and after 3 months

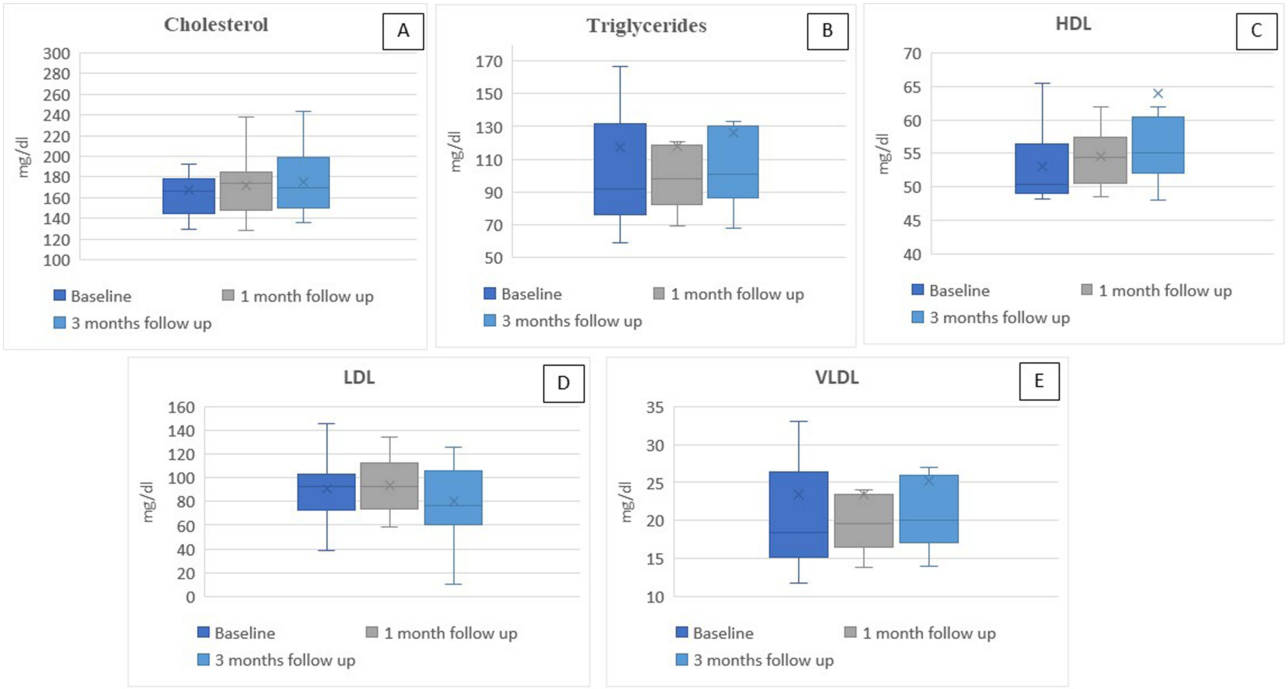

Figure 4 Box plot of Lipid profile at baseline, after 1 month and after 3 months of CYP practice (**A**) Cholesterol, Degree of Freedom = 2; Effect size, W = 0.027 (p = 0.630). (**B**) Triglycerides, Degree of Freedom = 2, Effect size, W = 0.064, p = 0.336. (**C**) HDL, Degree of Freedom = 2; Effect size, W = 0.122 (p = 0.126). (**D**) LDL Degree of Freedom = 2; Effect size, W = 0.010 (p = 0.838). (**E**) VLDL Degree of Freedom = 2, Effect size, W = 0.064, p = 0.336. Data was analysed by using SPSS Friedman K related samples test, N = 17.

Abbreviations: HDL, High-Density Lipoprotein; LDL, Low-Density Lipoprotein; VLDL, Very Low-Density Lipoprotein; CYP, Common Yoga Protocol.

Table 3 Table Showing Levels of Angiogenesis Markers, ie, VEGF, Angiogenin and BDNF at Baseline, After 1 Month and After 3 Months of CYP Practice. Data Was Analyzed Using SPSS Friedman Related Sample KS Test. N = 17, **p = 0.002

	VEGF (pg/µg)			Angiogenin (pg/µg)			BDNF (ng/µg)		
	Baseline	After 1 Month of CYP Practice	After 3 Months of CYP Practice	Baseline	After 1 Month of CYP Practice	After 3 Months of CYP Practice	Baseline	After 1 Month of CYP Practice	After 3 Months of CYP Practice
Median	30×10^{-4}	45×10^{-4}	39×10^{-4}	71×10^{-5}	69×10^{-5}	70×10^{-5}	14×10^{-6}	13×10^{-6}	7×10^{-6}
Minimum	3×10^{-4}	18×10^{-4}	16×10^{-4}	15×10^{-5}	30×10^{-5}	20×10^{-5}	8×10^{-6}	6×10^{-6}	4×10^{-6}
Maximum	7×10^{-2}	7×10^{-2}	6×10^{-2}	14×10^{-3}	23×10^{-3}	19×10^{-3}	12×10^{-5}	15×10^{-5}	12×10^{-5}
25th percentile	2×10^{-3}	3×10^{-3}	2×10^{-3}	39×10^{-5}	49×10^{-5}	36×10^{-5}	93×10^{-7}	80×10^{-7}	55×10^{-7}
75th percentile	20×10^{-3}	12×10^{-3}	14×10^{-3}	33×10^{-4}	32×10^{-4}	54×10^{-4}	58×10^{-6}	56×10^{-6}	40×10^{-6}
Chi square	1.412			1.529			12.933		
***p* value**	0.494			0.465			0.002**		
Degree of freedom	2			2			2		
Effect size (Kendall's W)	0.042			0.045			0.431		

Table 4 Table Showing Pre and Post Effects of Psychological Assessment. Data Was Analyzed Using SPSS Paired Sample *t*-Test. N = 17, *p < 0.05, **p <0.01

Psychological Assessment	Before Intervention (Mean ± SD)	After 3 Months of CYP Practice (Mean ± SD)	t value	Effect Size (Cohen's d)	95% CI		Degree of Freedom	*p* value
					Lower	Upper		
General Health Questionnaire score (GHQ-12)	10.64 ± 3.53	6.52 ± 3.12	4.07	0.98	1.97	6.259	16	0.001**
State Trait Anxiety Inventory (STAI)	29.23 ± 8.62	23.11± 3.40	3.78	0.91	2.69	9.542	16	0.002**
DST (Digit Span Test) Score (forward and backward)	16.88±5.06	16.70±4.52	0.65	0.15	−17.36	32.778	16	0.524
SLCT (Six Letter Cancellation Test)	30.82±12.26	32±13.23	0.23	0.05	−1.42	1.774	16	0.818
DSST (Digit Symbol Substitution Test) Time in seconds	241.17±87.5	233.47± 103.1	−0.49	−0.11	−6.27	3.917	16	0.631
TMT A (Trail Making Test A)	33.41±13.53	31.41±11.16	0.71	0.17	−3.93	7.932	16	0.485
TMT B (Trail Making Test B)	69.94±26.21	61.88±28.55	2.28	0.55	0.582	15.534	16	0.036*

(Table 6). Also, BDNF and Angiogenin were found to be significantly correlated. After 1-month, lipid parameters were found to be correlated with each other (Table 5). A positive correlation of HDL with VEGF and BDNF was also observed after 3 months (Table 6). Also, neuropsychological assessment parameter STAI showed a significant negative correlation with BDNF and VEGF (Table 6). Parameters of neuropsychological assessment were found to be inter correlated (Table 6).

Table 5 Table Showing Correlation Between the Change in CD34+ Cells, Lipid Parameters and Biochemical Parameters After 1 Month of CYP Practice. Data Was Analyzed Using SPSS Spearman Correlation Analysis. N = 17, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001. the table alignment should be proper, the empty boxes can be deleted.

CD34 F1	ρ=1.000								
Cholesterol F1	ρ=−0.087 P=0.740	ρ=1.000							
Triglycerides F1	ρ=0.218 p=0.400	ρ=0.524* p=0.031	ρ=1.000						
HDL F1	ρ=0.342 p=0.179	**ρ=0.549** **p=0.022***	ρ=0.447 p=0.072	ρ=1.000					
LDL F1	ρ=−0.368 p=0.146	**ρ=0.888** **p≤0.001****	ρ=0.191 p=0.462	ρ=0.291 p=0.257	ρ=1.000				
VLDL F1	ρ=0.200 p=0.442	**ρ=0.533** **p=0.028***	**ρ=0.999** **p≤0.001****	ρ=0.438 p=0.079	ρ=0.201 p=0.439	ρ=1.000			
VEGF F1	ρ=0.262 p=0.309	ρ=0.120 p=0.646	ρ=0.196 P=0.451	ρ=0.053 p=0.841	ρ=0.050 p=0.848	ρ=0.197 p=0.448	ρ=1.000		
BDNF F1	ρ=0.189 P=0.499	ρ=0.173 p=0.537	ρ=0.300 p=0.277	ρ=0.048 p=0.864	ρ=0.154 p=0.585	ρ=0.302 p=0.274	**ρ=0.929** **p≤0.001****	ρ=1.000	
Angiogenin F1	ρ=0.257 P=0.319	ρ=0.155 p=0.554	ρ=0.324 p=0.205	ρ=0.082 p=0.754	ρ=0.070 p=0.790	ρ=0.326 p=0.201	**ρ=0.917** **p≤0.001****	**ρ=0.896** **p≤0.001****	ρ=1.000
	CD34 F1	**Cholesterol F1**	**Triglycerides F1**	**HDL F1**	**LDL F1**	**VLDL F1**	**VEGF F1**	**BDNF F1**	**Angiogenin F1**

Note: Parameters showing significant correlation is represented in bold.

Discussion

The present study demonstrates that the inclusion of CYP practice in the daily lifestyle routine provides physiological health benefits by enhancing the level of hematopoietic and endothelial progenitor cells, CD34+; and influences angiogenesis markers (VEGF, Angiogenin and BDNF). We have previously also reported a similar trend with respect to CYP practice in sedentary adults after 1 month.[38] We also report an improvement in general health, reduced anxiety and improved visual and executive function after 3 months, which could be attributed to the change in BDNF after 3 months of CYP practice and a negative correlation of STAI with BDNF and VEGF, other cognitive parameters did not show any significant improvement after CYP practice, which implies a longer duration of CYP practice could be assessed for cognitive parameters. Overall, these results depict an improvement in the physical, physiological, and general well-being of the participants with the inclusion of a standardized yoga protocol, ie, CYP, in the participants daily routine.

The average age of the participants was 40.82±10.11 years. In the Indian context, this age group of females has high prospects of high BMI and abnormal lipid profile,[49] indicating the need for lifestyle moderation. Studies have shown that women in their middle age are prone to more sedentary and leisure activities make them susceptible to various lifestyle-related disorders.[50,51] Furthermore, it has been seen that women in their middle age have deteriorated quality of life compared to men of the same age, which accentuates the need for lifestyle modification in women's lifestyles.[52,53]

In the present study, we have found a significant reduction in body weight (66.48 ± 7.82 to 65.32 ± 6.92) (p = 0.019) and BMI (26.36 ± 3.05 to 25.92 ± 2.82) (p = 0.017) after 3 months of CYP practice, the BMI of the participants has moved towards overweight from the obese category.[54] Since the recruited participants did not have any co morbid condition, their lipid profile did not show any significant change, except for HDL, which has shown an increasing trend, though not significant, it has a role in cardiovascular repair mechanism and is also associated with an increase in CD34+.[55,56]

CD34+ cell population was consistent with previous studies, which shows that the detection technique and enumeration method followed were similar to other studies.[57] A significant increase in the total CD34+ population in peripheral blood after 3 months of CYP practice shows an enhancement in the cells regenerative potential and angiogenesis.[36,58] Also, a decrease in CD34+ cells represent a marker of aging; we found the enhancement in CD34+ cells, which depicts a curtailed cellular aging.[56,59]

Table 6 Table Showing Correlation Between the Change in CD34+ Cells, Lipid Parameters and Biochemical Parameters After 3 Months of CYP Practice. Data Was Analyzed Using SPSS Spearman Correlation Analysis. N = 17, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001the table alignment is not proper.

CD34 F2	ρ=1.000										
Cholesterol F2	ρ =- 0.083 P=0.750	ρ=1.000									
Triglycerides F2	ρ= 0.267 P= 0.300	ρ=0.254 P=0.326	ρ= 1.000								
HDL F2	ρ= −0.145 P=0.578	**ρ= 0.661 P=0.004****	ρ= 0.044 P= 0.866	ρ=1.000							
LDL F2	ρ= 0.065 P=0.804	ρ=0.381 P=0.132	ρ = −0.082 P= 0.754	ρ= −0.033 P= 0.899	ρ=1.000						
VLDL F2	ρ= 0.245 *P*=0.344	ρ=0.285 P=0.267	**ρ= 0.997 P≤.001*****	ρ= 0.074 P= 0.778	ρ= −0.065 P=0.804	ρ=1.000					
VEGF F2	ρ= −0.020 P=0.940	ρ=0.150 P=0.567	ρ=0.000 P=1.000	**ρ=0.547 P=0.023***	ρ= −0.163 P= 0.531	ρ= 0.005 P= 0.985	ρ=1.000				
BDNF F2	ρ= −0.275 P=0.321	ρ=0.146 P=0.603	ρ = −0.089 P= 0.752	**ρ=0.538 P=0.039***	ρ= −0.342 P=0.213	ρ= −0.086 P=0.761	**ρ= 0.818 P≤0.001*****	ρ=1.000			
ANGIOGENIN F2	ρ= 0.125 P=0.633	ρ=0.197 P=0.448	ρ= 0.088 P= 0.736	ρ=0.407 P=0.105	ρ= −0.061 P= 0.815	ρ= 0.086 P= 0.743	**ρ= 0.946 P≤ 0.001*****	**ρ= 0.725 P= 0.002****	ρ=1.000		
GHQ POST	ρ= −0.359 P=0.158	ρ= −0.257 P=0.319	ρ= −0.022 P= 0.932	ρ= −0.116 P=0.656	ρ= 0.082 P= 0.754	ρ= 0.002 P= 0.992	ρ= −0.305 P= 0.234	ρ= −0.480 P= 0.070	ρ= −0.449 P= 0.070	ρ= 1.000	
STAI POST	ρ= −0.118 P=0.651	ρ= −0.180 P= 0.489	ρ= −0.024 P= 0.928	ρ= −0.305 P= 0.234	ρ= 0.184 P= 0.480	ρ= −0.006 P= 0.981	**ρ= −0.483 P= 0.049***	**ρ= −0.585 P= 0.022***	ρ= −0.458 P= 0.064	ρ= 0.481 P= 0.051	ρ= 1.000

(*Continued*)

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Table 6 (Continued).

DSST POST	ρ= 0.104 P=0.690	ρ= 0.117 P =0.654	ρ=0.299 P=0.243	ρ= 0.260 P= 0.313	ρ= −0.038 P=0.885	ρ= 0.286 P= 0.267	ρ= 0.211 P= 0.416	ρ= 0.071 P= 0.800	ρ= 0.180 P= 0.488	ρ= 0.061 P= 0.816	ρ= −0.509* P=0.037	ρ= 1.000				
DST POST	ρ= −0.290 P=0.260	ρ=0.271 P=0.292	ρ= −0.152 P= 0.561	ρ= 0.197 P= 0.449	ρ= −0.018 P=0.946	ρ= −0.123 P= 0.638	ρ= 0.144 P= 0.581	ρ= 0.382 P= 0.160	ρ= 0.100 P= 0.703	ρ= −0.258 P= 0.317	ρ= 0.089 P= 0.734	**ρ= −0.711 P=0.001*****| ρ= 1.000			
SLCT POST	ρ= −0.243 P= 0.348	ρ= −0.172 P= 0.510	ρ= −0.278 P= 0.279	ρ= −0.478 P=0.052	ρ= 0.157 P= 0.549	ρ= −0.278 P= 0.280	ρ= −0.240 P= 0.353	ρ= 0.038 P= 0.894	ρ= −0.210 P= 0.419	ρ= −0.148 P= 0.570	ρ= 0.219 P= 0.399	**ρ= −0.786 P≤0.001*****| **ρ= 0.678 P=0.003****	ρ= 1.000		
TMT A POST	ρ= 0.244 P=0.346	ρ= 0.220 P= 0.397	ρ= 0.154 P= 0.555	ρ=0.324 P=0.205	ρ= 0.070 P= 0.791	ρ= 0.169 P= 0.516	ρ= 0.142 P= 0.588	ρ= −0.160 P= 0.569	ρ= 0.167 P= 0.521	ρ= 0.062 P= 0.814	ρ= −0.218 P= 0.401	**ρ= 0.742 P= 0.001*****	**ρ= −0.593 P=0.012***	**ρ= −0.861 P≤0.001*****	ρ= 1.000	
TMT B POST	ρ=0.075 P=0.775	ρ= −0.057 P= 0.827	ρ= 0.246 P= 0.341	ρ=0.255 P=0.323	ρ= −0.339 P= 0.183	ρ= 0.247 P= 0.338	ρ= 0.176 P= 0.499	ρ= 0.079 P= 0.780	ρ= 0.080 P= 0.760	ρ= 0.152 P= 0.560	ρ= −0.264 P=0.306	**ρ= 0.760 P≤0.001*****	**ρ= −0.662 P=0.004****	**ρ= −0.788 P≤0.001*****	**ρ= 0.735 P=0.001*****	ρ=1.000
	CD34 F2	**Cholesterol F2**	**Trigly cerides F2**	**HDL F2**	**LDL F2**	**VLDL F2**	**VEGF F2**	**BDNF F2**	**ANGIO GENIN F2**	**GHQ POST**	**STAI POST**	**DSST POST**	**DST POST**	**SLCT POST**	**TMT A POST**	**TMT B POST**

Note: Parameters showing significant correlation is represented in bold.

Our study has found a significant positive correlation of HDL with VEGF and Angiogenin after 3 months of CYP practice, which signifies that CYP induces a mechanism of elevation in angiogenesis and cardiovascular repair. Furthermore, a positive correlation was also found between VEGF, BDNF, and Angiogenin after both 1 month and 3 months of CYP practice (Table 5 and Table 6) which signifies that the response is interrelated between these angiogenesis and neurogenesis molecules. No positive correlation was detected for CD34+ cells with any other markers analyzed. Furthermore, a negative correlation of STAI assessment with BDNF and VEGF was reported (Table 6) which signifies that with decrease in stress and anxiety after the CYP practice, an increment in VEGF and BDNF could be anticipated. However, studying these responses with a larger sample size and longer duration would depict more precise information.

Yoga may be beneficial with aging by increasing the CD34+ cells and angiogenesis, thereby reducing the risk of CVDs. Yoga may influence this response by immediate induction of intermittent hypoxia through breathing techniques and thereby sympathetic response and increasing blood flow at the time of practice.[37,60] Consequently, in the present study, we found a significant increase in CD34+ cells, and VEGF and Angiogenin followed an increasing trend after CYP for 3 months which is consistent with our previous study. BDNF showed a significant decreasing trend which may be due to the inverse response of resting BDNF levels to the long term of practice.[61]

The present study employs CYP as the standardized Yoga intervention (recommended by Govt. of India for International Yoga Day) as an adjunct inclusion to the daily routine of the recruited adult sedentary females who did not participate in any physical activity in their daily routine. Through this study we confer that CYP protocol mediates its health benefits through angiogenic mechanism via activating the endothelial stem cell niche and further activating the angiogenic molecular response to the practice of CYP. An enhancing level of HDL further enhances the angiogenic activation response via its function in cardiovascular repair. We also found an improvement in general health, reduced stress and anxiety score, and increment in information and visual processing cognitive function, however overall neuro psychology did not show any significant improvement after the intervention.

Overall, the current study shows that the practice of a validated and standardized 45–50 minutes of Yoga protocol, ie, CYP (which is freely available on AYUSH Ministry website) which includes the practices, can be performed by individuals of any age

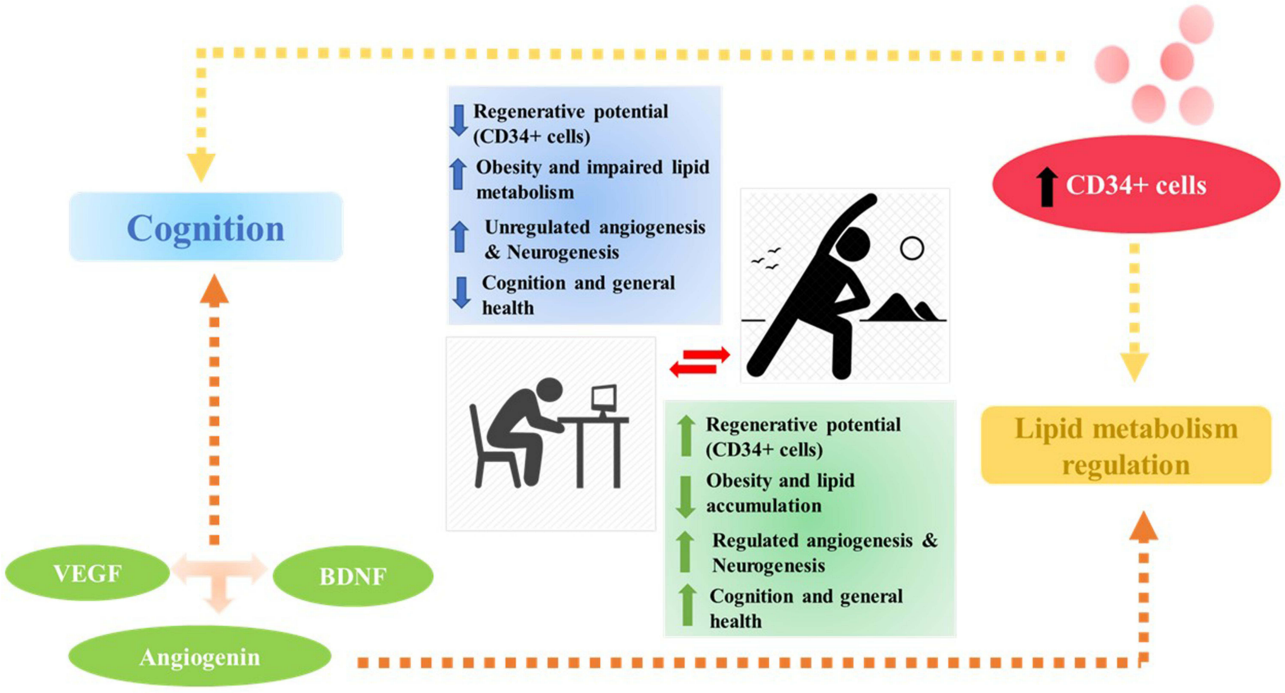

Figure 5 Schematic showing effects of Yoga induced through the regulation of neurogenesis and angiogenesis pathways via CD34+ cells number and Lipid metabolism. ↑ depicts increase, ↓ depicts decrease,----► depicts the pathway.
Note: the arrows in the figure are distorted and not properly alinged

(with no comorbid condition) as an adjunct in daily lifestyle. This can enhance the overall quality of life by boosting general health and improving cognition and also may be beneficial in prevention of NCDs (Figure 5). The possible mechanism of these benefits could be the intermittent hypoxic mechanism activated with the practice of Yoga which activates the stem cell niche from the bone marrow into the peripheral blood. This would also enhance the growth of blood vessels through angiogenesis activation.

Limitations

Small sample size and lack of a control group were the significant limitations of the present study.

Conclusion

We demonstrated that when sedentary adults included 45–50 minutes of Yoga practice in their daily lifestyle, it led to an overall physical, physiological, and psychological health benefits. These health benefits could be escalated through stem cell proliferation prompted by the intermittent hypoxia induced by the Yoga practice. Hence, including CYP as a daily lifestyle habit may provide health benefits and may prevent NCDs.

Data Sharing Statement

The authors confirm that the data confirming the findings of the study are available within the article. The raw data that supports the finding of the study can be made available from corresponding author (AA) on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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Brief Article

Randomized Controlled Trial of Isha Kriya versus Observation to Improve Quality of Life in Hematopoietic Cell Transplantation Recipients

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A B S T R A C T

Hematopoietic cell transplantation (HCT) impacts recipients' quality of life (QoL). Few mindfulness-based interventions (MBI) in HCT recipients have shown feasibility, but heterogeneous practices and outcome measures have called into question the actual benefit. We hypothesized that self-guided isha kriya, a 12-minute guided meditation based on the principles of yoga focusing on breathing, awareness, and thought, as a mobile app would improve QoL in the acute HCT setting. This single-center, open-label, randomized controlled trial was conducted in 2021 to 2022. Autologous and allogeneic HCT recipients age ≥18 years were included. The study was approved by our Institutional Ethics Committee and registered at the Clinical Trial Registry of India, and all participants provided written informed consent. HCT recipients without access to smartphones or regular practitioners of yoga, meditation, or other mind-body practices were excluded. Participants were randomized to the control arm or the isha kriya arm at a 1:1 ratio stratified by type of transplantation. Patients in the isha kriya arm were instructed to perform the kriya twice daily from pre-HCT to day +30 post-HCT. The primary endpoint was QoL summary scores as assessed by the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) and the Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) questionnaires. The secondary endpoints were the differences in QoL domain scores. The validated questionnaires were self-administered before the intervention and at days +30 and +100 post-HCT. The analysis of endpoints was done on an intention-to-treat basis. Domain and summary scores were calculated for each instrument as recommended by the developers. A P value $< .05$ was considered to indicate statistical significance, and Cohen's d effect size was used to determine clinical significance. A total of 72 HCT recipients were randomized to the isha kriya and control arms. Patients in the 2 arms were matched for age, sex, diagnosis, and type of HCT. The 2 arms showed no differences in pre-HCT QoL domain, summary, and global scores. At day +30 post-HCT, there was no difference between the arms in the mean FACT-BMT total score (112.9 ± 16.8 for the isha kriya arm versus 101.2 ± 13.9 for the control arm; $P = .2$) or the mean global health score (global mental health, 45.1 ± 8.6 versus 42.5 ± 7.2 [$P = .5$]; global physical health, 44.1 ± 6.3 versus 44.1 ± 8.3 [$P = .4$]) in the 2 groups. Similarly, there were no differences in physical, social, emotional, and functional domain scores. However, the mean bone marrow transplantation (BMT) subscale scores, which addresses BMT-specific QoL concerns, were statistically and clinically significantly higher in the isha kriya arm (27.9 ± 5.1 versus 24.4 ± 9.2; $P = .03$; Cohen's d = .5; medium effect size). This effect was transient; mean day +100 scores showed no difference (28.3 ± 5.9 versus 26.2 ± 9.4; $P = .3$). Our data indicate that the isha kriya intervention did not improve the FACT-BMT total and global health scores in the acute HCT setting. However, practicing isha kriya for 1 month was associated with transient improvement in the FACT-BMT subscale scores on day +30 but not on day +100 post-HCT.

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INTRODUCTION

The hematopoietic cell transplantation (HCT) procedure is associated with significant morbidity and mortality risks from regimen-related toxicity, infections, and graft-versus-host disease. These risks cause significant distress and impact the health-related quality of life (HR-QoL) of HCT recipients [1]. Up to 22% to 43% of patients report difficulty living with uncertainty, fear of recurrence, loneliness, memory concerns, and somatic preoccupation [2]. Several studies of mindfulness-based interventions (MBIs) in HCT recipients have shown the feasibility and usefulness of such interventions [3,4]; however, heterogeneous intervention practices with low uptake and tools to measure outcomes have called into question the tangible benefits of MBIs [5,6]. We hypothesized that a culturally acceptable self-guided meditation method as a mobile app will have greater acceptance and adherence and a clinically significant impact on HCT recipients' QoL in short-term follow-up post-transplantation. Isha kriya is based on the science of yoga and incorporates actions aimed at promoting a feeling of connection with universal existence. The practice essentially focuses on breath, awareness, and thought. It reminds practitioners to not be identified by their body and mind and to be a watcher to cease bodily suffering. Isha kriya has been shown to reduce stress levels and improve immunity in healthy volunteers and other disorders by modifying the immune system [7]. The present study aimed to evaluate the impact of an MBI with isha kriya on HCT recipients' HR-QoL in the acute post-HCT setting.

METHODS

This single-center, open-label, randomized controlled trial (RCT) was conducted at the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, from January 2021 to December 2022. PGIMER is a large-volume HCT center and an academic institution of national importance under the Indian Ministry of Health. The PGIMER Institutional Ethics Committee approved the study, which was registered at the Clinical Trial Registry of India (CTRI/2021/09/036667). All included patients provided written informed consent.

Autologous and allogeneic HCT recipients age $\geq$18 years were included in the study. HCT recipients without access to smartphones or regular practitioners of yoga, meditation, or other MBI practices were excluded. One study author assessed the patients for study eligibility, and another author was involved in patient randomization and intervention administration. Recipients were randomized to the isha kriya arm or control arm at a 1:1 ratio using a table of random numbers. Randomization was done using a fixed block size of 4 and stratified by type of transplantation. In this open-label study, both the patients and the investigators were aware of the allocation.

Isha kriya is 12-minute guided meditation available as a free app in several regional languages in the Apple and Android stores [8]. Patients in the isha kriya arm were instructed to perform the kriya twice daily (at least once daily) from pre-HCT to day +30 post-HCT. The nursing team ensured adherence to the kriya at least once daily while the patients were admitted and during once-weekly outpatient visits or phone calls after discharge from the transplantation ward.

The study's primary endpoint was the QoL summary score at day +30 post-HCT as assessed by the Functional Assessment of Cancer Therapy-Bone Marrow Transplantation (FACT-BMT) and the Patient-Reported Outcomes Measurement Information System Global Health (PROMIS-GH) questionnaires. The secondary endpoints were the QoL domain scores at days +30 and +100 post-HCT and summary score at day +100 post-HCT. The QoL questionnaires FACT-BMT version 4 [9] and PROMIS-GH Scale version 1.2 (mental and physical) [10] are validated in Indian languages and were self-administered on paper at baseline before the intervention (pre-HCT) and at days +30 and +100 post-HCT.

The sample size of 36 patients per arm was determined based on an assumption of an actual difference in the experimental and control means of 10 with a standard deviation of 15, a type I error probability of .05, power of 80% [5]. The analysis of endpoints was done on an intention-to-treat basis. Domain and summary scores were calculated for each instrument as recommended by the developers. The QoL scores were compared between the 2 arms using the unpaired *t* test. A P value $< .05$ was considered to indicate statistical significance, and Cohen's d effect size was used to determine clinical significance.

RESULTS

A total of 90 HCT recipients were screened for eligibility over the study period, of whom 72 were randomized 1:1 to the isha kriya arm or control arm (Figure 1). There were 4 deaths in the isha kriya arm and 2 deaths in the control arm before day +100; these patients were included in the analysis, which was done on an intention-to-treat basis.

The median patient age was 32.5 years (interquartile range [IQR], 27 to 49 years) in the isha kriya arm and 31 years (IQR, 22 to 49 years) in the control arm (P = .6) (Table 1). There was a male predominance in both arms (61% versus 64%; P = 1.0). The proportions of patients who underwent HCT for myeloma (28% versus 31%), lymphoma (28% versus 31%), and leukemia (36% versus 30%) were similar in the 2 arms (P = 1.0), and were the proportions of patients undergoing autologous HCT (53% versus 56%) and allogeneic HCT (47% versus 44%; P = 1.0). There were no differences between the 2 arms in the pre-HCT QoL domain (physical, social, emotional, functional well-being, and bone marrow transplantation [BMT] subscales), summary (FACT trial outcome index [TOI], General [G] total, and BMT total) scores, and global (mental and physical) scores (Table 2). At post-HCT day +30, there also were no differences between the arms in the mean FACT-BMT total score (112.9 $\pm$ 16.8 versus 101.2 $\pm$ 13.9; P = .2) or mean global health scores (global mental health, 45.1 $\pm$ 8.6 versus 42.5 $\pm$ 7.2 [P = .5], global physical health, 44.1 $\pm$ 6.3 versus 44.1 $\pm$ 8.3 [P = .4]) and no differences in the physical, social, emotional, and functional domain scores. However, the mean BMT subscale score was statistically significantly higher in the isha kriya arm compared with the control arm (27.9 $\pm$ 5.1 versus 24.4 $\pm$ 9.2; P = .03). The difference was clinically significant, with a Cohen's d of .5 implying a medium effect size. The mean difference of 3.5 points also was clinically meaningful within the 10-item BMT subscale [9]. The FACT-TOI, which is a sum of physical, functional and BMT subscale scores, was nonsignificantly higher in the isha-kriya arm at day +30 (66.2 $\pm$ 16.3 versus 61.5 $\pm$ 18.6; P = .3). The FACT-G total score, which is a sum of the physical, social, emotional, and functional scores, also was nonsignificantly higher in the Isha-kriya arm at day +30 (84.9 $\pm$ 13.4 versus 76.8 $\pm$ 23.1; P = .09). This effect of isha-kriya on the BMT subscale was transient, as the day +100 scores showed no difference (28.3 $\pm$ 5.9 versus 26.2 $\pm$ 9.4; P = .3). There were no differences between the arms in the FACT-BMT total/domain scores or PROMIS global scores at day +100 post-HCT (Table 2).

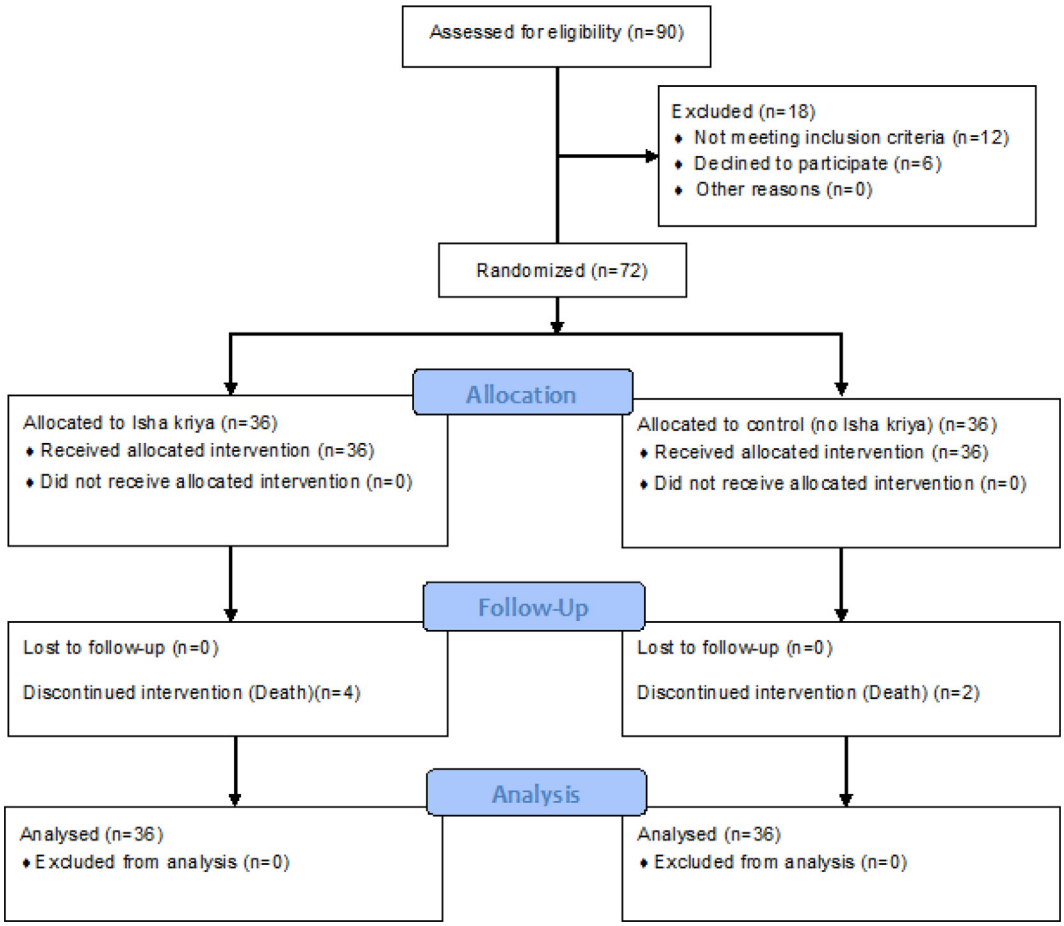

Figure 1. Enrollment, allocation, follow-up, and analysis of study participants.

DISCUSSION

Conducting RCTs of MBI in the HCT setting has several inherent challenges. Foremost are the choice of intervention and acceptance of and adherence to the prescribed intervention. The heterogeneity of tools for assessing QoL, distress, anxiety, and depression makes it difficult to compare studies and draw meaningful conclusions. In one of the largest RCTs conducted by the Blood & Marrow Transplant Clinical Trials Network, a mix of exercise and stress management training programs was found to be ineffective [5]. However, smaller RCTs either have been plagued by low intervention uptake [6] or have shown some benefit in QoL [4].

For this small RCT, we consciously chose a culturally acceptable meditation, isha kriya, which is based on the science of yoga and is available as a mobile app for self-guided practice. We also chose the Indian language validated FACT-BMT and PROMIS-GH tools to assess the domain and total scores for a comprehensive assessment of the impact of isha kriya. Although the practice of isha kriya for a short (1-month) period did not lead to differences between the study arms in

Table 1
Patient Characteristics

Characteristic	Isha Kriya Arm (N = 36)	Control Arm (N = 36)	*P* Value
Age, yr, median (IQR)	32.5 (27-49)	31 (22-49)	.6
Sex, n (%)			
Male	22 (61)	23 (64%)	1.0
Female	14 (39)	13 (36%)	
Disease, n (%)			
Myeloma	10 (28)	11 (31%)	1.0
Lymphoma	10 (28)	11 (31%)	
Leukemia	13 (36)	11 (30%)	
Aplastic anemia	3 (8)	3 (8%)	
Type of HCT, n (%)			
Autologous	19 (53)	20 (56%)	1.0
Allogeneic	17 (47)	16 (44%)	

Table 2
QoL Scores in the Isha Kriya and Control Arms

QoL Domain	Pre-HCT	Day +30 Post-HCT	Day +100 Post-HCT	Pre-HCT	Day +30 Post-HCT	Day +100 Post-HCT	*P* Value, Isha Kriya vs Control, Pre-HCT	*P* Value, Isha Kriya vs Control, Day +30	*P* Value, Isha Kriya vs Control, Day +100
Physical well-being	19 ± 6.4	19.7 ± 6.3	20.6 ± 5.7	19.6 ± 6.2	19.3 ± 7.8	20.7 ± 8.0	.7	.8	.3
Social well-being	24.1 ± 2.6	24.2 ± 3.5	22.9 ± 6.0	23.3 ± 4.2	21.5 ± 7.2	22.5 ± 8.1	.9	.1	.9
Emotional well-being	19.5 ± 3.8	21.1 ± 2.7	19.7 ± 6.2	18.3 ± 5.7	18.6 ± 6.5	18.1 ± 7.3	.7	.2	.3
Functional well-being	19.3 ± 6.2	19.9 ± 5.5	20.7 ± 6.6	19.3 ± 5.1	17.5 ± 7.1	18.7 ± 7.5	.9	.1	.3
BMT subscale	26.9 ± 6.9	27.9 ± 5.1	28.3 ± 5.9	26.7 ± 5.4	24.4 ± 9.2	26.2 ± 9.4	.8	.03	.3
FACT-BMT TOI	41.3 ± 13.0	66.2 ± 16.3	68.0 ± 18.0	41.1 ± 10.5	61.5 ± 18.6	64.2 ± 23.7	.9	.3	.7
FACT-G total score	81.9 ± 13.9	84.9 ± 13.4	82.7 ± 20.6	80.6 ± 16.3	76.8 ± 23.1	78.5 ± 27.9	.8	.09	.8
FACT-BMT total score	108.9 ± 19.5	112.9 ± 16.8	109.0 ± 29.3	107.3 ± 20.1	101.2 ± 13.9	103.9 ± 37.2	.7	.2	.8
PROMIS-global mental health	45.7 ± 7.3	45.1 ± 8.6	45.9 ± 7.3	44.6 ± 6.6	42.5 ± 7.2	43.8 ± 7.2	.7	.5	.4
PROMIS-global physical health	45.5 ± 6.4	44.1 ± 6.3	44.6 ± 7.8	46.8 ± 7.5	44.1 ± 8.3	46.1 ± 8.9	.6	.4	.3

Data are mean ± SD. Bold type indicates statistical significance.

the primary endpoint of FACT-BMT total and PROMIS-GH scores, there was a clinically meaningful difference in the FACT-BMT domain, which addresses BMT-specific QoL concerns. The FACT-BMT scale is sensitive to psychosocial interventions and allows the evaluation of treatment effects in a clinical trial [11]; however, in our cohort, the impact of the kriya was transient during the intervention period, with no difference seen at day +100 post-HCT. The PROMIS global health questionnaire contains questions overlapping with global assessment of the physical, social, emotional, and functional health subscales of the FACT-BMT questionnaire, possibly explaining the lack of differences in global scores.

A limitation of this study was the difficulty of ensuring adherence to the isha kriya practice twice daily. Another limitation was the lack of measurements of symptom burden and psychological outcomes, which are more likely to improve using MBI in cancer survivors [12,13]. The intervention period needs to be longer and could be continued at home after discharge to observe an effect in other QoL domains and global health [14]. Mobile health technology can be used to administer QoL interventions in cancer survivors [15]. It is also important to consider patient preference in the design of clinical trials [16] and suitable endpoints in subsequent RCTs to confirm the effect of MBI on QoL in HCT recipients.

In conclusion, this study demonstrates that the app-guided practice of isha kriya is feasible and acceptable for HCT recipients and shows promise in managing BMT-related stress and improving some aspects of the QoL of HCT recipients.

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Data availability statement**:** Data will be made available on reasonable request by contacting the corresponding author.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2023.05.010.

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REVIEW ARTICLE

Ayurvedic Herbal Therapies: A Review of Treatment and Management of Dementia

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Abstract: Dementia has been characterized by atypical neurological syndromes and several cognitive deficits, such as extended memory loss, strange behavior, unusual thinking, impaired judgment, impotence, and difficulty with daily living activities. Dementia is not a disease, but it is caused by several neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Lewy's bodies. Several drugs and remedies are indicated for alleviating unusual cognitive decline, but no effective pharmacological treatment regimens are available without side effects. Herbal drugs or traditional medicines like Ayurveda have been known for facilitating and corroborating the balance between mind, brain, body, and environment. Ayurvedic therapy comprises 600 herbal formulas, 250 single plant remedies, and natural and holistic health-giving treatments that relieve dementia in patients and increase vitality. Ayurvedic Rasayana herbs [rejuvenating elements] strengthen the brain cells, enhance memory, and decrease stress. The current medicine scenario in the treatment of dementia has prompted the shift in exploring the efficacy of ayurvedic medicine, its safety, and its efficiency. This review presents the literature on several herbal treatments for improving dementia symptomatology and patients' quality of life.

Keywords: Ayurveda, dementia, ashwagandha, turmeric, brahmi, Shankhapushpi.

1. INTRODUCTION

Dementia, characterized by the ongoing decline of brain functioning, such as reasoning, thinking, and memory, has become the most significant global challenge [1]. Dementia is a syndrome [a group of symptoms], and the normal aging process does not necessarily cause dementia [2]. Instead, it is caused by the damage to brain cells by several factors and diseases, such as Alzheimer's and stroke [1]. Almost 60% - 70% of dementia cases are Alzheimer-induced dementia, followed by 20%-25% of vascular dementia and 5% of Lewy Body dementia [2, 3]. Age is one of the significant risk factors in people with dementia; however, other differential factors have also been discerned, and younger people in their 30s, 40s, and 50s [below 65] are also at risk, constituting 9% of dementia cases [1, 4]. Although the causes of Alzheimer's disease have not been fully understood, the age-related changes in the human brain, genetics, and environmental factors, including lifestyle, are associated with this progressive brain disease [3, 5]. The late-onset of Alzheimer's disease is the most common type appearing in the mid-60s compared to early-onset [between the 30s and 60s] [6]. Alzheimer's is the leading cause of dementia and is highly correlated with age, raising the incidence of dementia later in people's lives [7]. However, several studies project the primary etiology of early dementia is Alzheimer's disease, followed by Vascular Dementia and Frontotemporal Lobar Degeneration, highlighting the significant role of environmental factors leading to epigenesis, but those perturbations do not get manifested until later life [8-10].

The prevalence of dementia may double every 5-6 years after 60-65 years of age until 90, and approximately 30% of individuals over 85 years may also be at risk of developing dementia [2, 3, 7]. Some of the common risk factors besides neurogenetics that have been found associated with dementia are diabetes mellitus, hypertension, obesity, unbalanced diet, social isolation, alcohol use, and tobacco consumption [11-14]. According to the WHO report, around 50 million people have dementia worldwide, and approximately 9.9 million new dementia cases are found every year [1]. The increment in the neurological disorder will multiply and may turn 82 million by 2030 and 152 million by 2050, according to the WHO report [5]. Comparatively, low and middle-income countries have reported a higher incidence of dementia than

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developed countries [15]. Dementia has been recognized as the second highest disability syndrome and constitutes the seventh primary cause of death of individuals above 70 years [5, 16]. WHO estimates that 50% of subjects experiencing dementia remain undiagnosed, and almost one-third of patients discharge from the hospital without much improvement in functional capabilities [17].

There has been a lot of debate regarding the pathogenesis of Alzheimer's disease, in particular the difference in pathogenesis between early and late-onset Alzheimer's and dementia. A consensus among researchers has been noticed that the pathogenetic cause of early-onset Alzheimer's, which can have familial roots, is the premature excessive deposition of amyloid beta plaques due to various mutations, such as PSEN1, PSEN2, or APP mutations [18, 19, 20], whereas the pathogenesis of sporadic Alzheimer's disease is mainly undetermined [10, 21]. Late-onset Alzheimer's was thought to be associated with amyloid beta; however, unlike its early-onset counterpart, amyloid beta does not seem to have an etiological relationship [21, 22]. Schneider *et al.* reported mixed brain pathologies for most dementia cases in older adults [21-23]. Gorelick *et al.* suggested the importance of vascular contributions to cognitive impairment and dementia in later life and reported that the neuropathology of cognitive impairment could be a complex interplay of Alzheimer's disease and microvascular brain damage in later life [23]. Furthermore, global cerebral hypoperfusion has been noticed to be associated with the increased progression of late-onset Alzheimer's disease [24], and the study by Moon *et al.* showed a correlation between Carotid intima-media thickness [CIMT] and progression of dementia after adjustment for various baseline risk factors for cognitive impairment [25]. Atherosclerosis and vascular phenomenon have been indicated to be the significant co-contributors to cognitive impairment and dementia, and any intervention that can reduce the burden of atherosclerosis can, in turn, reduce the burden of late-onset Alzheimer's progression [7].

Over the last five decades, numerous pharmacological and non-pharmacological approaches and interventions have been used to treat, stop progression, and manage dementia effectively; however, there are no effective ways to cure dementia. Pharmacological treatments could be expensive and potentially hepatotoxic, requiring patients to undergo regular liver checkups and appropriate dose modifications [26, 27]. The absence of specific medical treatment to manage dementia patients' neurological, behavior, and neurodegenerative diseases has been challenging for clinicians and caregivers. Providing adequate care to dementia patients requires a collaborative approach between healthcare professionals and family members, which could be expensive, challenging, and emotionally taxing for all stakeholders [28]. Almost 20% of healthcare professionals providing care to dementia patients may be at risk of experiencing mental health problems [17, 29]. These challenges and the growing number of dementia cases have motivated healthcare workers to emphasize early diagnosis and find evidence of alternative treatments for dementia patients with comorbid medical and/or mental health conditions, which may also be preventive in nature. Additionally, rigorous scientific research is required for any alternative treatments to be included in evidence-based best practices to optimize people's physical, emotional, psychological, and cognitive well-being. Ayurvedic medicine's use globally has surged, and research to quantify evidence has also been growing [8]. As a result, this study has attempted to present an overview of the Ayurvedic medicine system and approach and evaluate the recent evidence found in the literature to treat and/or manage dementia. The current review has excluded herbs that do not come under Ayurvedic medicine purview. However, clinical trials and the use of herbal medicine in clinical treatments of diseases have several challenges.

Although plants are the source of almost a quarter of medicines globally, a few countries [like India, ancient Greece, Egypt, and China] where alternate herbal medicine originated still practice traditional herbal medicine [30]. Ayurvedic medicine is well known in India, but due to a lack of established funding, effective government policies, and Ayurvedic operational, clinical, and quality management standards, the clinical trials and standardized Ayurvedic medicine manufacturing could not take off until recently [30, 31]. Ayurvedic medicinal plants have also been labeled as dietary supplements, and the lack of awareness among people regarding the safe and unsafe use of herbal medicine and its interactions with allopathic [modern] medicine has created practical barriers to demand and supply and clinical trials [30]. Lately, with shifting focus and policy changes in India, evidence of clinical trials of Ayurvedic medicine is burgeoning. As a result, it is important to provide people, researchers, and clinicians with adequate updated information and an overview of the Ayurvedic medicine system to bring changes in their lives and help deal with the growing challenges of dementia, which is the focus of the current review.

2. AYURVEDIC MEDICINE

Among several medicinal sciences, Ayurveda is the oldest medical system that originated in India from one of the Vedas called Atharvaveda and has discussed dementia and age-related problems. Ayurveda is medical knowledge system of holistic healing, emphasizing natural plant-based medicine and living in balance with nature for the health and well-being of human beings [32, 33]. Ayurveda has discussed various classifications of diseases, treatment modalities [including behavioral interventions], surgeries [mentioned in Sushruta Samhita by Nagarjuna], and lifestyle changes to improve ailments, health, and general well-being [33]. Ayurveda also elaborates on the knowledge of energy points on the body [marma] to be used as diagnostic and treatment tools of diseases through therapeutic massages [33, 34].

The mechanics of the Ayurvedic approaches in the therapeutic application of Ayurvedic herbs is integrative, harmonizing biological, neurological, and behavioral diseases and disorders and spiritual aspects of human life. Ayurveda [Ayur Vidya] is called the Knowledge or Science of Life, which emphasizes integrating mind, body, social, psychological, and spiritual aspects of human existence while maintaining balance with nature [35]. Ayurveda believes that life consists of five basic *panchamahabhutas* [five elements of life; linguistically translated as air, fire, water, earth, ether] and spirit, the consciousness, which is the reflection of the pure consciousness [36]. Fire holds an

essential place in Ayurvedic medicine and corresponds to metabolism and metabolic stress generated by the interaction of various body parts/organs, such as brain electromagnetic waves and the digestive system [37]. Air denotes gaseous movements and motion, such as heart beating, breathing, and neural transmissions; water represents liquid in the body, such as blood, digestive, tongue, and genital secretions; earth denotes anatomical and mechanical structures in the body; ether corresponds to space, such as pores in the body and spiritual energy [37]. These are the foundational blocks of understanding Ayurvedic medicine, as their disbalance cause *doshas* [biohumors].

Ayurveda takes a functional approach to human anatomy, which is the interplay of different organs corresponding to different sensory inputs [38]. Ayurveda views disease as the imbalance of metabolic processes consisting of five basic *panchamahabhutas* [five elements of life], and imbalances distress physical, psychological, spiritual, and environmental systems of human life [32, 33, 36]. To attain the highest level of health and well-being, an individual must take responsibility [follow the doctrine of karma] and understand themselves as part of the macrocosm to harmonize one's existence with the surrounding environment and nature. Ayurveda holds that salvation [Moksa] is the epistemological transformation toward self-actualization, transcending mundane life toward higher consciousness [39]. This journey is identified as spiritual, epistemological, intellectual, social, and psychological evolution towards self-actualization, promoting happiness [decreasing stress and anxiety], love, compassion, physical and mental health, and harmony with the environment and nature [39]. It emphasizes the importance of valid knowledge achieved through analytical decision-making processes of perception, inference, comparison, testimony, and intuition and recommends using valid knowledge for diagnostic analysis and understanding of general 'truth' [32, 33, 36, 40].

Furthermore, yoga, which is the oldest recorded behavioral treatment modality, recommends cognitive and behavioral interventions for various medical and mental health problems, emphasizing mental modification and perfecting the human body [39]. Yoga views the mind as an aggregate of biopsychosocial experience known through introspection, creating self-awareness. Self-awareness can promote a healthy lifestyle, spiritual well-being, and balance with the immediate environment and nature, which are holistic and promotive approaches to well-being (Fig. **1**). Righteous actions and behaviors conjoined with a mindful and balanced diet, nutrition, and food digestion can have therapeutic preventive and restorative effects on disease (Fig. **1**). Lastly, identification of treatment and management of ailments, such as dementia and cognitive problems, may need remedial approaches and can also have compensatory effects (Fig. **1**). Thus, the Ayurvedic wellness framework is grounded in the person-in-environment perspective. In Ayurveda, patients' non-diseased states are separated from diseased states, and it emphasizes balancing the life forces to decrease mind and body distress and increase well-being (Fig. **2**). Furthermore, Ayurveda distinguishes patients by diseased states of patients' phenotypical constitutional specificity based on three *doshas* [biohumors - fluid/semi-fluid excitant secretions] - *Vata, Pitta,* and *Kapha*, representing all movements in the body and mind, all metabolic processes in the body impacting at physical and mental levels, and all stability functions in the body respectively; these three factors constitute the state/inclination of mind and body [38].

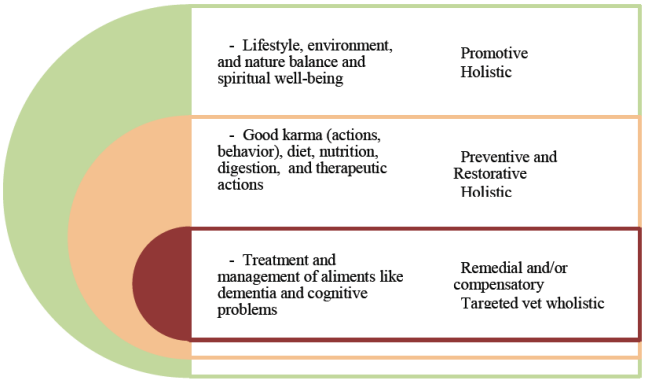

Fig. (1). Ayurvedic diagnostic and treatment approaches. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

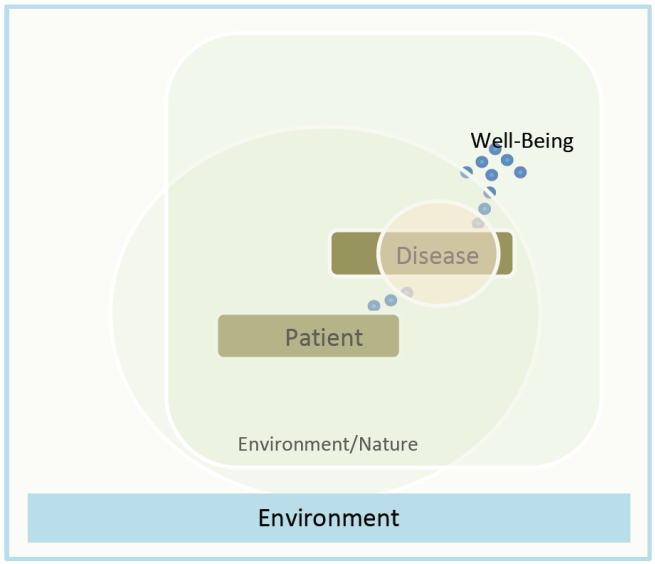

Fig. (2). Ayurvedic framework. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Ayurvedic approaches are similar to what Evidence-Based-Practice [EBP] modern science claims. Ayurveda advocates basing the clinical decision-making process on analytical reasoning and evidence in testimonies [recorded practice wisdom as evidence], understanding of the client's unique problems and preferences [including connection with social environment and nature], and the utilization of the clinician's expertise. Ayurveda maintains that therapeutic approaches to treating diseases and helping patients maintain or achieve optimal wellbeing are possible by harmonizing mind, body, and environment processes, which resembles the integrative health approaches.

3. DEMENTIA AND AYURVEDA

According to Ayurveda, dementia is caused by the imbalance of three doshas [biohumors] – Vata, Pitta, and Kapha [functions of motion, digestions, and cumulation, respectively] [41]. Imbalanced Vata components of the body are predominantly associated with dementia [42, 43]. Dietary factors have a critical role in the pathogenesis of dementia [40], and constipation has a higher incidence rate in dementia patients and has been observed to accelerate the progression of neurodegenerative pathology [44]. Different lifestyles, sleeping, and eating preferences/patterns have also been associated with the age-related issues of the predominance of Vata dosha, and Vata dosha dominance is the prime factor associated with constipation [Krura Kostha] and neuropsychological disturbances in dementia patients [40]. Sleep disorders and sleep disturbances due to napping during the day and waking up at night increase Kapha and Vata dosha, respectively [40]. Kapha sustains body mass, structure, and versatility [45-47], especially for the Vata imbalance [35]. Ayurvedic medicine has explained the different usage and qualities of 700 herbs and 6,000 formulations for curing various disease sufferers [34]. It illustrates approximately 5,000 signs and symptoms of several disorders and has several ayurvedic medicines for treating dementia. Herbal medicine may be free from chemicals, additives, and preservatives, with low side effects and beneficial outcomes. This review attempts to describe different ayurvedic processes and remedies for the management of dementia.

4. AYURVEDA TREATMENT: MEDICINAL PLANTS USED FOR DEMENTIA TREATMENT

Ayurveda has been using herbal plants since 5,000 B.C. as medicinal resources and considered them health promoters, restorators of dosha imbalances, and curators of ailments [48]. Two of the Vedas, Rigveda [4500 to 1600 B.C.] and Atharvaveda, have demonstrated different medicinal plants, their uses, and their effects on the body. Ayurvedic herbalism targets to improve the neuro-endocrine-immune system by increasing anti-inflammatory and antioxidant derivatives [49, 50]. Traditional remedies also stimulate patients' memory and cognitive function in an enhanced state [51, 52]. Some of the herbal remedies have been mentioned for the treatment of dementia. Adjunct therapies, social and spiritual dimensions, diets/nutrition, and yoga have been excluded from this review.

5. ASHWAGANDHA [WITHANIA SOMNIFERA]

Ashwagandha is a predominant analeptic ayurvedic medication that belongs to the Solanaceae family and has been used for thousands of years [53, 54]. Alkaloids like alanine, withananine, somnine, and steroidal lactones are the most important compounds of *Withania Somnifera* compositions; its roots have frequently been used for medicines [53, 55]. Research indicates that the ashwagandha root influences nerve functions, antioxidant activities, free radicals, and inflammatory ventures to support defense mechanisms, enhance sexual performance, and reduce stress reactivity [55, 56].

As a *rasayan* [medicine], its overall alkaloid extraction from the root portion helps different mammalian families' central nervous systems to remain calm [55]. Additionally, roots prohibit NF-kB dynamization and obstruct mass-production of β- amyloid, which lessens apoptotic cell death and revitalizes synaptic functions [57]. Furthermore, its WL-A compound [steroid lactone] strengthens antioxidant activities by transferring Nrf2 to the nucleus [57-59]. WL-A also promotes the regeneration of nerves by reducing semaphorin 3A.

In a recent study, Ashwagandha was also found to facilitate the level of cholinergic like acetylcholinesterase and dopaminergic activities in the brain, and the memory and cognitive activities of dementia patients were improved [60, 61]. Another study has demonstrated that applying methanolic extracts of Ashwagandha to human neuroblastoma cells with a proper dose and time resulted in nerve growth, developed synapse patterns, and caused regeneration of axons and dendrite [53, 57, 62, 63]. According to Elhadidy, oxidative stress in rats due to aluminum trichloride [$AlCl_3$] in the cortex, hippocampus, and striatum can be prevented by the daily consumption of ashwagandha extract. This medication also prevents lipid peroxidation and the production of NO [64]. In addition, Ashwagandha prevents mitochondrial disruption, rejuvenates energy levels, and decreases brain inflammation.

6. CHEMICAL STRUCTURE OF ASHWAGANDHA

Ashwagandha is a 2 m tall and 1 m wide woody perineal shrub with tomentose branches whose structure is radially expanded from the central stem and produces green bell-shaped flowers. The brownish stem of this shrub also consists of small, green elliptic leaves located at the opposite side of flowering shoots and generates orange-red fruits, which shape like spherical berries with multiple pale brownish seeds, encircled by inflated calyx [5-8mm in diameter]. When the ashwagandha fruit reaches the ripe stage, it becomes red in color. Generally, the calyx [5mm long] of this shrub is found to be shorter than the corolla [5-8 mm long] [65].

Ashwagandha is composed of numerous chemicals with major characteristics for use in the pharmacotherapeutics medicinal department. The most important chemical components are steroidal lactones formed by "withanolides, withaferin A, 27-deoxywithaferin A, withanolide-D, withanosides, and withasomniferols A-C. It also contains countless alkaloids like anaferine, anahygrine, cushohygrine, dl-isopelletierine, 3-tropyltigloate, *etc*. The different parts of this shrub consist of various chemicals; for example, in the stem, Withasomnilide, withasomniferanolide, somniferanolide, somniferawithanolide, somniwithanolide; leaf part: 24,25-Dihydrowithanolide A, withanolide A, withanone, withaferin A, 27-hydroxy withanone, and 17-hydroxy withaferin A, 27-deoxy-16-en-withaferin A, 2, 3-dihydro-3*β*-hydroxywithanone, *etc*.; root segment: Withanolide E, withanolide F, withanolide G, withanolide H, withanolide I, withanolide J, withanolide K, withanolide L, withanolide M, and even fruits contain withanamide F,withanamide G, withanamide H, withanamide I, and many more [66, 67].

7. TURMERIC [CURCUMA LONGA]

Turmeric, an herbaceous medicinal plant, belongs to the Zingiberaceae family and possesses antioxidant, anti-septic, and anti-inflammatory preventive properties. As a derivative of curcuma longa, turmeric is a rhizome and root. It carries powerful biological properties that decrease oxidative stress and reactivity and enhances cognitive activities associated with aging procedures [55, 57]. In addition to curcumin, additional turmeric ingredients, including odorous turmerones like α - turmerones, β- turmerones, α - santalene, *etc.,* have significant anti-inflammatory and antioxidant characteristics to be used as a medicinal remedy for different purposes [68].

By activating the Nrf2- keap1 pathway, turmeric exerts antioxidant effects to decrease genomic variability. Curcumin interacts with keap1 [ECH-associated protein1] and liberates Nrf2 [which is primarily found in the cytoplasm] to move towards the nucleus, where it binds with antioxidant components of DNA to facilitate gene expression. Genes governed *via* Nrf2 comprising antioxidant enzymes, DNA revivify enzymes, and anti-inflammatory proteins strengthen the cell's capacity to repair the damage caused by repression of pro-inflammatory cytokines like ROS, IL-8, and TNF-α [57, 69, 70, 71]. In addition to this, curcumin decreases inflammatory activities by suppressing PLA2 [phospholipaseA2] and COX-2 [cycloxygenase-2] enzymes, which metabolize neural phospholipids and prostaglandins. Furthermore, through the Aβ-induced rat model of AD, it has been shown that curcumin improves memory by decreasing GFAP and COX-2 manifestation [57, 72], but the effectiveness of amyloid treatments in humans needs to be established.

Whenever turmeric [Curcumin] was given to AD mice, they displayed reduced plaque deposition and decreased oxidative and inflammatory activities [55, 57, 73, 74]. According to Brondino, curcumin defends PC12 and endothelial cells against Aβ toxicity and tau hyperphosphorylation in AD transgenic mice, decreasing Aβ oligomer and fibril formation [73,75]. In addition to this, curcumin decreases the rate of oxygen species like ROS, which blocks APP cleavage and revitalizes synaptic flexibility in AD mice [75, 76, 77, 78]. Furthermore, turmeric can decalcify the liver, normalize cholesterol levels, suppress allergies, and promote the digestive and immunity systems [55, 79, 80].

8. CHEMICAL STRUCTURE OF TURMERIC

The height of turmeric plant is 1 mm tall with highly branched but has a short stem and long leaves. The leaves of this ayurvedic plant are alternatively arranged in two rows and produce pale yellowish flowers. Again, the leaves are separate to form a leaf sheath, petiole, leaf blade, and the false stem also developed from the leaf sheath. The petiole length is 50-115 cm, whereas the leaf blade is 75-115 cm long. The most important part is the yellowish-orange colored rhizome, whose upper part is rough and segmented skin, approximately 2.5-7.0 cm long, and diameter measures about 2.5 cm [1 inch] [5, 6].

The major ingredient of turmeric is carbohydrate, i.e., 69.9%, remaining like 6.3% protein, 3.5% minerals, 5.1% fat, and 13.1% moisture are present [81]. Like Ashwagandha, the rhizome of turmeric contains different chemicals like curcuminoids and possesses demethoxycurcumin, curcumin, bisdemethoxycurcumin, and sesquiterpenoids including germacrone, bisacumol ar-turmerone, curlone, curcumene, curcuminol, β-bsabolene, α and β termerones, zingiberene, *etc*. [81, 82]. Another constituent of the rhizome is a volatile oil that can be acquired by a known process called steam distillation but also incorporated by borneol, d-sabinene, d-α-phellandrene, cineol, sesquiterpenes, and zingiberene [82, 83]. These chemicals are available in turmeric, but it also contains L-beta-curcumene, limonene, manganese, niacin, nickel, norbixin, pcymene, phosphorous copper/zinc, potassium, calcium, *etc*. [84].

9. BRAHMI [BACOPA MONNIERI]

Another ayurvedic herb related to the Scrophulariaceae family is primarily found in swampy and marshy regions of Southeast Asia, tropical Asia, sub-tropical United States, tropical Africa, and Australia [57,85]. Bacopa Monnieri is used to improve memory and intelligence and decrease stress and anxiety. It has also been used for the treatment of various diseases like epilepsy, asthma, and insomnia. Additionally, Brahmi possesses antioxidant, anti-inflammatory, anti-diabetic, and anti-arthritis properties. It also has gastrointestinal and muscle tranquilizer effects. Furthermore, it has been used as a fever reducer, pain reliever, lowering hypertension agent, and displays neuronal and liver-protecting properties. The main chemical components of Brahmi are saponins and triterpenoid saponins, including bacosides A and B, bacosaponins A, B, and C, and alkaloids containing nicotine, herpestine, and brahmine. Other primary constituents of this nootropic herb are betulinic acid, aspartic acid, glutamic acid, serine, stigmasterol, stigmastanol, β- sitosterol, and saponin glycosides like pseudo-jujubogenin glycosides [85, 86].

Brahmi's components exhibit antioxidant properties [especially bacoside A and B] and defend the brain from oxidative stress and various age-related cognitive decline [87]. Recently, it has been proven that bacosides expanded expressions of antioxidant molecules like SOD, GSH, and HSP70 and acted as a free radical scavenger by preventing lipoxygenase activities in the brain [42, 57, 87, 88]. Additionally, this advancing mode of various antioxidant enzymes was found in the prefrontal cortex, hippocampus, and striatum of the rat brain when treated with Brahmi for 21 days [85]. In AD dementia cases, these bacosides also provide neuroprotection to specific regions, such as the prefrontal cortex, hippocampus, and striatum of the brain, from cytotoxicity and DNA damage [85, 89]. The extracts of Brahmi [*i.e.,* bacosides] also possess a higher potential for inhibiting lipid peroxidation, chelating irons, and other divalent metals, which lead to reduced oxidative stress associated with β-amyloid [85, 90]. Due to bacosides and glutathione peroxidase, iron chelation increases in the brain [57, 85, 91], which improves cerebral vasodilation and enhances memory and learning ability [57, 85]. Due to the vasodilator property of Brahmi, which is mediated by nitric oxide, it controls systolic and diastolic pressure and ca+ fluctuations without influencing cardiac rhythm [85, 92].

Even bacosides can appear as regulators for membrane phosphorylation and dephosphorylation processes [57, 93] due to enhancing protein and RNA turnover activities in different brain areas like the hippocampus [94]. A combination of bacosides A and B protects the brain from smoking-induced neurological damage [57, 95]. Brahmi acts as an herbal neuroprotective agent that reduces the inflammatory levels in the brain by decreasing microglia-induced interleukin, TNF-α, and caspase-10 levels [42, 96-98]. Brahmi's betulinic acid also acts as a triterpenoid, which decreases COX-2 expression and production of prostaglandins due to minimizing the rate of inflammation in the brain cells [42]. As a therapeutic herb, Brahmi interacts with neurotransmitters, improves memory [99, 100], and enhances brain plasticity by increasing BDNF by 1.3 times and Arc by 2 times the expression of the brain cells [85, 101]. Research shows that Brahmi's anticholinergic effects in the AD of rat model increased cognitive functions [55, 102]. It has also been shown that Brahmi treatment inhibited acetylcholine and choline acetyltransferase activities in hippocampal and frontal cortexes muscarinic cholinergic receptors [55, 89]. Another study showed that neurons are protected from beta-amyloid-induced cell apoptosis by suppressing cellular acetylcholinesterase activities using Brahmi extracts [55]. Bacosides of Brahmi reduce hypobaric-hypoxia-induced cognitive dysfunction and other associated neurological disorders [88, 103].

Brahmi also plays a critical curative role in treating amnesia in dementia, Alzheimer's, and schizophrenia patients in various ways. For example, Brahmi can reverse amnesia and function like benzodiazepines, scopolamine, quinoline derivatives, and phenytoin, for which disruption of long-term potentiation [LTP] occurs. It has been shown by different tests that Brahmi inhibited the increased levels of mitogen-activated protein kinase [MAP kinase], phosphorylated CREB [pCREB], and inducible nitric oxide synthase [iNOS] in patients with amnesia induced by diazepam, while other proteins like cAMP [cyclic adenosine monophosphate], total CREB, total nitrate, and nitrite PDE were unaffected or normalized [104]. By utilizing Brahmi extracts, amnesia patients showed that their nitrite levels were normal. Additionally, Brahmi reversed amnesic effects caused by L-NNA-induced anterograde and retrograde amnesia but did not reverse amnesia in rats induced with MK-1 [104]. Brahmi may perform as a neuroprotective medicinal herb for Parkinson's, stroke, and epilepsy as it has been observed to enhance serotonin levels and activate CREB and 5-HT3A receptors in the hippocampus in postpartum rats, promoting learning abilities [100, 104, 105].

10. CHEMICAL STRUCTURE OF BRAHMI

Brahmi is a perineal herb that is 60-90 cm long, highly branched, and extended up to 5-35cm. This non-aromatic herb has well-expanded yellow-colored roots and has a 1 mm thick, greenish stem with nodes and internodes, but the taste is somehow unsweetened. Brahmi leaves are 8-15 mm long, 4 mm broad, and oblong-shaped. Its leaf blade is attached to the stem, which is called sessile; the lower surface is covered with dots and produces different colored five-petal flowers like white, pink, purple, *etc*. Bracteoles are broader than pedicles and 6-30mm long [85, 106].

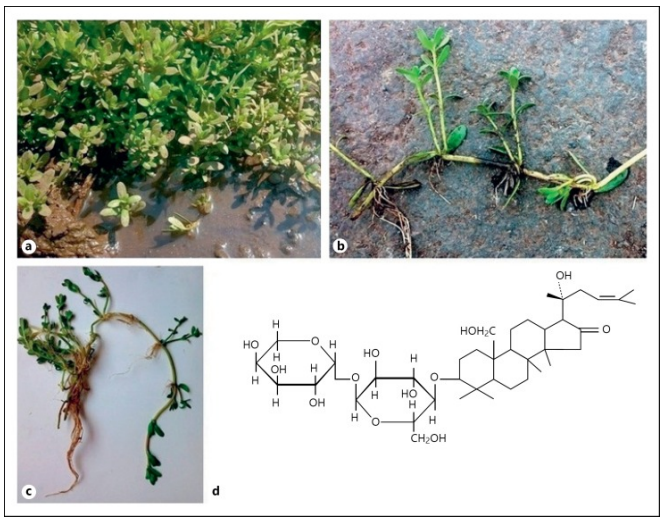

Fig. (3). Plant botanical morphology and Bacosides chemical composition [85]. Reprinted from Annals of Neurosciences, 24(2), Chaudhari KS, Tiwari NR, Tiwari RR, Sharma RS., Neurocognitive effect of nootropic drug Brahmi (Bacopa Monnieri) in Alzheimer's Disease, 111-22, 2017, with permission from S. Karger AG, Basel." *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

11. SHANKHAPUSHPI [CONVOLVULACEAE PLURIC-AULIS]

Shankhapushpi, an ayurvedic medicinal herb, belongs to the family of Convolvulaceae, which enhances learning, memory, and intelligence [57, 107]. Every part of Sankhapushi plants bears medicinal properties of strengthening memory acquisition, retention, and retrieval [107]. Generally, it is found in India and contains different secondary metabolites, such as triterpenoids, flavonol, glycosides, and steroids, which help in alleviating various nervous disorders like stress, anxiety, mental fatigue, and insomnia. Sankhapushpi also facilitates diverse neuropharmacological processes [55, 57, 108], and it has soothing effects on the body due to its effectiveness in regulating stress hormones like cortisol and adrenaline [57, 109, 110]. The presence of different chemicals, such as glucose, sucrose, starch, coumarins, sitosterol, convolvine, and convolidine, minimizes various ulcers and pain, controls neurotoxicity levels, enhances bone marrow quality, and increases nerve tissues [108, 111].

Ethanolic extract of CP decreases cholesterol, LDL cholesterol, triglycerides, and phospholipid levels in serum and provides antioxidant effects on the body [57, 109, 112, 113]. It has also been proven that ethanolic extraction of Shankhapushpi enhances brain nourishment by increasing acquisition and raising brain protein contents [109, 114, 115]. Additionally, CP acts as a muscle relaxant by decreasing the ethyl acetate portion [109] and acting as an antidepressant through interacting adrenergic, dopaminergic, and serotonergic systems utilizing ethanolic extrication [108, 116, 117]. It is also found that ethanolic extraction of CP enhances acetylcholine activities in the hippocampal CA1 and CA3 regions, dendritic intersections, and branching point numbers to support brain development, plasticity, and cognitive activities [57, 118-120]. Furthermore, methanolic extracts of CP, especially from stems and leaf callus, enable the body to defend against

tonic convulsion and show anti-convulsant activities [108, 121, 122]. CP also provides nutrition to every single layer of skin and is used in beauty products [109].

There are three different varieties of Shankhapusphi, such as Canscora Decussata (CD), Clitoria Ternatea (CT), and Evolvulus Alsinoides (EA). Sethiya [2018] verified the four traditional herbs' neuropharmacological activities *in vitro* to understand the antioxidant potential, AchE inhibition, 5-LOX enzyme inhibition, β- amyloid-induced neurotoxicity on neuro-2A, and *in vivo* assays like scopolamine-induced memory retrieval. After testing various parameters, he found different pharmacological potency in these four botanical herbs, and the order of activity was found as EA> CD>CP>CT [123].

12. CHEMICAL STRUCTURE OF SHANKHAPUSHPI

This medicinal herb consists of several branches, usually expanding widely on the ground and extending up to 30cm. Branched roots are cylindrical, and their color is also converted from brown to light brown. Even stems are found to be cylindrical, having nodes and internodes, while the length of the light green leaves is found to be 10.5-2cm and 0.1- 0.5 cm broad. Shankhapushpi flowers are primarily white and purple in color [124].

The whole Shankhapushpi plant is enriched in several medicinal properties as its different part contains several types of chemical constituents like kaempferol, taraxerone, taraxerol, N-hexacosanol, delphinide, *etc*. Another chemical group of alkaloids is also found in this plant, including sankhapusine, convosine, convolidine, confoline, phyallbine, convolamine, subhirsine, *etc.* This plant also consists of other groups like flavonoids, glycosides, phenolic compounds, steroids, *etc*. [125]. It also contains carbohydrates consisting of maltose, sucrose, rhamnose, *etc.,* besides myristic acid [39.9%], palmitic acid [66.8%], and linoleic acid [2.3%] [126].

13. GOTU KOLA [CENTELLA ASIATICA]

Gotu Kola [Centella Asiatica] is a herbaceous perennial plant that grows mostly in temperate and swampy areas in several regions of the globe [57, 127]. CA has a long and dense stem with smooth leaves of green to reddish-green color. Stems are interconnected and belong to the family Apiaceae [55, 57, 127]. In addition to scentellin, asiaticin, and centillicin, GK consists of pentacyclic triterpenoids, such as Asiatic acid (AA), madecassoside acid (MA), asiaticoside, and madecassic acid, which purify the blood, enhance memory, boost learning abilities, promote longevity, and decrease high blood pressure [57, 128-130].

AD and dementia patients have lower levels of phosphorylated CREB, which is an essential factor in the progression of memory and cognitive functions. Yanan [2008] observed that water extract of GK improves CREB phosphorylation and increases BDNF levels, facilitating axon regeneration and neuronal dendritic arborization, indicating neuroprotection in rats. He also identified the increasing molecular mechanism of memory and cognitive activities caused by the enhancement of CREB phosphorylation. Using GK treatment, Yanan [2008] specified some definite pathways that stimulate CREB phosphorylation, such as PKA [protein kinase A], nitric oxide signaling, and MAPK/

Fig. (4). Shankhapushpi. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

ERK/RSK pathways [129]. In another study, it has also been found that AA of GK decreases the glutamate-induced cognitive deficits and controls the lipid peroxidation, GSH, and superoxide dismutase levels in the hippocampus and cortex of the brain [130-132]. Additionally, it was found that AA of GK protects the body from glutamate-induced dementia and increases memory retrieval [132,133].

Furthermore, GK derivatives, such as AA and asiaticoside, can minimize hydrogen peroxide-induced cell death and lessens the number of free radicals. These proficient derivatives were also able to inhibit AD type of dementia and Aβ toxicity, which causes neural death *in vitro* [134-136]. Gray [2015] noticed that the GK treatment protects the body from Aβ-induced mitochondrial dysfunction and oxidative stress by using MC65 and SH-SY5Y neuroblastoma cells but also shows higher ATP production and the stimulation of antioxidant response genes, such as NFE2L2, GCLC, and NQO1 [136]. Furthermore, Gray [2017] found that using GK extraction treatment, both brains of the aged Tg2576 and WT mice possessed enhanced synaptic plasticity, increased dendritic arborization, and spine density [137]. Justin [2018] reported the GK's CWA neuroprotection capability against aluminum toxicity. He claimed that AA of GK decreases Al 3+ induced intracellular ROS production and mitochondrial membrane depolarization and prevents apoptosis activities and disruption of DNA in *in vitro* models of AD disease [138]. The use of GK extract also shows a substantial impact on patients with epilepsy disorder [57].

14. CHEMICAL STRUCTURE OF GOTU KOLA

Gotu kola is not only a perineal but also identified as a creeper herb growing 15 cm long. The stem of this medicinal herb starts at the rooting points, morphologically thin, striated, and greenish in color. Generally, the kidney-shaped leaves are covered with crenate margins and possess lengths of 1-5 cm and 2-6 cm broad. Small 3-4 white or purple flowers are found in the umbels [139].

There are different chemical groups present in this medicinal herb. Gotu kola consists of multiple types of triterpenic acids, including Madasiatic acid, Madecassic acid, Thankunic acid, Indocentoic acid, Euscaphic acid, Terminolic Isothankunic acid, Asiatica acid, *etc.* Different chemicals that constitute triterpenic sugar esters are available, such as Asiaticoside [A, B, C, D, E, F], Braminoside, Brahmoside, Brahminoside, Thankuniside, Centellasaponin A, Centellasapogenol, *etc.* Even steroid groups of triterpenoids are found in which stigmasterol and sitosterol are included. By analyzing Gotu kola, other chemical groups are also identified like flavonoids, such as kaempferol, astragalin, catechin, Rutin, *etc.,* vitamins: nicotinic acid, ascorbic acid, β -carotene, minerals, calcium, phosphorus, iron, potassium, magnesium, manganese, zinc, sodium, and copper. In addition to this, different essential oil, chemicals, and amino acids are also found [139, 140].

15. GUGGULU [COMMIPHORA MUKUL]

Guggulu is an exotic plant and belongs to the Burseraceae family. It is widely distributed from northern Africa to central Asia. It is a herb with an average height of about 3m and thin and peppery bark, and it grows mostly in arid and semi-arid climates [141]. Its juice [oleo gum resin] is extracted from cracks and fissures of the bark of different plant species [Commiphora Mukul, C. Molmol, C. Abyssinica, C. Burceraceae, and C. Whighitti] [55]. Aromatic oleogum resin is a pale yellow-brown color substance with a sharp, bitter taste [57, 142]. The oleoresin of Guggulu has been found to contain complex mixture compounds, such as water-soluble gum [30% to 60%], alcohol soluble resins [20% to 40%], and volatile oils [8%], which harbor numerous pharmacological activities [55, 57]. The major constituents of water-soluble gum are mucilage, sugar, and proteins, whereas alcohol-soluble gum consists of comiphorinic acids and heerabomyrrhols. Volatile oils are composed of terpenes, sesquiterpenoids, cuminic aldehyde, eugenol, ketone steroids Z- and Eguggulsterone, and guggulsterols I, II, and III [143, 144]. Additionally, Guggulu includes ferulic acids, phenols, and other non-phenolic aromatic acids that possess antioxidant activities against hydroxyl radicals and are used to treat different neurodegenerative and oxidative stress-related disorders [145, 146].

Fig. (5). Morphology of Gotu kola. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Additionally, Guggulusterone is a potent antagonist of the nuclear hormone receptor involved in cholesterol metabolism to lower total cholesterol levels. The administration of guggulipid [Z- Guggulsterone] has been found to decrease LDL cholesterol and triglyceride levels in serum of both animal and human models [147, 148]. These biological activities can also explain the hypolipidemic effects of Guggulu extraction [149]. The efficacy of Guggulu in hypolipidemic activities has been found, and it acts as an efficacious antagonist ligand for the farnesoid X receptor, a nuclear receptor that is activated through bile acids [147, 150]. A number of findings suggest a strong association between APP [amyloid precursor protein] processing, cholesterol, and AD [18, 151]. During *in vitro* and *in vivo* experimentation, it was observed that different cholesterol pools within the plasma membrane bilayer were affected by modulating membrane cholesterol levels and these cholesterol pools were differen-

tially sensitive to Aβ disrupting effect [152]. The evidence in the literature indicates an association between the utilization of cholesterol-lowering drugs and decreased prevalence of dementia [18,55,153]. Gugulipid acts as a substantial cholesterol-lowering, antioxidant, and anti-acetylcholine esterase antagonist against the streptozotocin-induced memory deficit model of dementia in rats [55, 154].

16. CHEMICAL STRUCTURE OF GUGGULU

The height of this medicinal tree ranges between1.2 to 1.8 m, with several branches producing brownish-red flowers but possessing shorter pedicles. This dwarf plant has palmately compound leaflet and bears drupe-type fruits containing one seed. In the ripe stage, fruits become red [155].

Like other herbs, this therapeutic tree also contains multiple varieties of fatty acids, myristic acid, palmitic acid, steric acid, arachidic acid, and oleic acid [156, 157].

17. MUSKROOT/SPIKENARD [NARDOSTACHYS JATAMANSI]

Nardostachys Jatamansi [NJ] is a flowering plant and belongs to the valerian family. It grows in Nepal, India, and Bhutan and is also known as muskroot or spikenard. Its rhizomes and roots are used for ayurvedic therapies. Different phytochemical components produced by muskroot include Acaclin, Ursolic acid, Octacosanol, Nardosinonediol, Oleanolic acid, and β- Sitosterol. It also contains other terpenoids, such as spirojatamol, nardostachysin, jatamols A and B, and calarenol. This medicinal plant is also used for preparing perfumes due to its intense aromatic essential oils.

NJ herbal extract has antioxidant properties. It decreases chronic fatigue syndrome [CFS], lipid peroxidation, nitrite and superoxide dismutase levels and increases low catalase levels. Furthermore, NJ alcoholic extract improves memory and learning capacity and reverses the amnesia induced by diazepam [1 mg/kg] and scopolamine [0.4mg/kg] in young and aged rats. NJ was reported to reverse the aging-induced amnesia in mice. It has established itself as a powerful and useful memory enhancer in both older individuals and patients experiencing age-associated dementia [55, 157, 158].

18. CHEMICAL STRUCTURE OF MUSKROOT

Muskroot is a perennial plant that is hairy and grows up to 10-60 cm long. Generally, this medicinal herb's roots [2.5 to 7.5 cm] are used for therapy and pharmaceutical applications. Narrow, long leaves of muskroot are rosy and slightly pink in color. Bilateral flowers not only possess bisexual characteristics but also develop the capacity to form clusters. The rhizomes of this herbal plant are 2.5 to 7.5 cm long and covered with reddish-brown tufted fibers. The upper surface of 4 mm lengthy muskroot fruits is hairy.

This herbal medicinal plant contains volatile oil, like sesquiterpenes, which also comprise other chemicals, such as nardostachone, jatamol, nardosinone, jatamansic acid, pyrnocoumarin A and B. Through chemical analysis, it has been

Fig. (6). Guggulu plants and rasins of Guggulu. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Fig. (7). Rhizomes of muskroot. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

Table 1. Drugs with clinical trials models and their benefits.

Drugs Name	Disease	Model	Benefit	Refs.
Ashwagandha	Chronic stress	Human	Decreases stress and anxiety	[160]
	Cognitive dysfunction	Human	Reduces cognitive impairment level	[161]
	Neurodegeneration, Cognitive disability	Rat	Re-establishing neurite growth, defend neurons from apoptosis	[162]
	Inflammatory mechanism	Rat	Reduces inflammation for long term	[163, 164]
	Memory disorder		Enhances memory	[164, 165]
Turmeric	Dementia	Rat	Enhances cognition, improve memory	[166]
	Memory disorder	Non-demented adults	Increases memory and attention	[167]
	Alzheimer's	Human	Enhances cognition, depression agitation	[168]
Brahmi	Dementia	Human	Improves cognition	[169]
	Dementia	Human	Reduces stress, improves memory and cognition	[170]
Shankhapushpi	Cognitive dysfunction	Rat	Cognition level	[171]
	Poor Memory	Children	Increases alertness of mind, attention, and memory level	[172]
	Neurotoxicity, memory disorder	Rat	Decreases neurotoxicity level, strengthen memory	[123]
Gotukola	Alzheimer's	Rat	Improves behavior	[173]
		Healthy people	Increases working memory, cognition function	[174]
Guggulu	Hypercholesterolemia	Human	Decreases total cholesterol level	[149]
	Neuroinflammation	Rat	Decreases behavior abnormality, inflammation level	[175]

Table 2. Drugs mechanism in clinical trials.

Drugs	Disease	Mechanisms Observed in the Clinical Trial	Refs.
Brahmi	Memory disorder	Increases memory level	[176]
		Improves cognition level	[177, 178]
Gotukola		Increases working memory, cognition function	[124, 179, 180]
Centella Asiatica		Improves cognitive and mood disability and enhance working memory	[175]
Ginko Biloba	Alzheimer's Vascular dementia	Increases cognition function and reduces high blood pressure, headache, and dizziness.	[181]
Withania somnifera	Cognitive dysfunction	Increases level of functionality, attention, cognition, and even reaction time also changes	[161]
Muskroot	Cognitive disorder, depression, memory disturbance	Regulates nervous functions, increase learning, memory, reduce depression and express normal cognitive effects	[182]
Turmeric	Dementia, memory impairment	Improves memory and cognition level	[183]

confirmed that sesquiterpenes also include other chemicals like sitosterol, angelicin, elemol, and calarene. Muskroot also contains unstable oils, gum, sugar, starch, ketone, lupeol, propionate, and cyclohexanol ester [159].

The following two tables summarize clinical trials and drugs efficacy in different clinical models (Tables **1** and **2**).

CONCLUSION

The evidence in the literature illustrates that ayurvedic medicinal plants, such as Ashwagandha, Gotu Kola, Guggulu, Turmeric, and Brahmi, have valuable therapeutic properties in the treatment of dementia. Using these medicinal plants based on the evidence in the literature to provide person-specific treatment regimens can significantly be helpful in addressing dementia symptomatology and improving quality of life. Furthermore, these herbal remedies have a low toxicity threshold compared to other pharmacological drugs. Dementia involves neurodegeneration and can be addressed using herbal medicines; however, Ayurveda recommends Rasayana [herbal remedies], adjunct therapies [like panchakarma therapy], and lifestyle changes for managing dementia effectively. Yoga and meditation may also help rejuvenate the brain cells and improve memory and confidence. With the growing acceptance and use of herbal medicine worldwide, Ayurveda offers natural, cost-effective, well-tolerated, and holistic treatment regimens to manage dementia. However, there are many challenges to overcome in accessing Ayurvedic treatment. Several issues that need attention are manufacturing pharmaceutical-grade herbal medicine, conducting new RCTs to generate evidence, and evaluating the efficacy of ayurvedic medicine administration along with many available pharmacological drugs, quality control, and safety.

LIST OF ABBREVIATIONS

PSEN1 = Presenilin-1

PSEN2 = Presenilin-2

APP = Amyloid Protein Precursor

NF-kB = Nuclear Factor Kappa B

Nrf2 = Nuclear Factor Erythoid 2 Related Factor 2

ROS = Reactive Oxygen Species

IL-8 = Interleukin-8

TNF-alpha = Tumor – Necrosis Factor -Alpha

GFAP = Glial Fibrillary Acidic Protein

APP = Amyloid Protein Precursor

SOD = Superoxide Dismutase

HSP70 = Heat Shock Protein 70

BDNF = Brain Derived Neurotrophic Factor

CP = Convulvulus Pluricaulis

GK = Gotukola

NJ = Nardostachys Jatamansi

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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