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Yoga maintains Th17/Treg cell homeostasis and reduces the rate of T cell aging in rheumatoid arthritis: a randomized controlled trial

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The pathogenesis of rheumatoid arthritis (RA) is characterized by a Th17/Treg cell imbalance. A pro-inflammatory cytokine milieu that promotes the continued proliferation of Th17 cells is related to the development of autoinflammation. In RA, T cells have several hallmarks of cellular aging, and they accumulate DNA damage, predisposing to the occurrence of mutations and epigenetic alterations. Since the onset, progression, and treatment response are influenced by a variety of external stressors and environmental factors, this study aimed to evaluate the impact of 8-week yoga practice on disease severity, T cell subsets, markers of T cell ageing and inflammation, epigenetic alterations and gene expression patterns in active RA patients on standard disease-modifying anti-rheumatic drugs (DMARDs). A total of 64 participants with active RA were randomized into 2 groups, yoga group (n = 32) or non-yoga group (n = 32); that were assessed for disease severity, at baseline and after 8 week duration, for Disease Activity Score (DAS28-ESR), T cell subsets [Th17 (CD3+CD4+IL17+RORγt+) cells and Treg (CD3+CD4+CD25+CD127-Foxp3+) cells], markers of T cell aging [aged Th17 cells (CD3+CD4+IL17+RORγt+CD28−) and aged Treg cells (CD3+CD4+CD25+CD127-Foxp3+CD28−)], pro-inflammatory markers [IL-6, and IL-17], anti-inflammatory markers [TGF-β, and IL-10], epigenetic alterations [5-methyl cytosine, 5-hydroxymethyl cytosine, and HDAC1] and gene expression patterns [*RORγt*, *FoxP3*, *IL-17*, *IL-6*, *TGF-β*, *CXCL2*, *CXCR2*, and *JUN*]. In yoga group, there was a significant improvement in DAS28-ESR scores at the end of 8-weeks of yoga program. The Th17 cells and aged T cell subsets showed a significant decline whereas Treg cell population showed a significant elevation in yoga group. There were significant improvements observed in epigenetic markers as well as inflammatory markers post 8-weeks of yoga practice. The yoga group showed downregulation of *RORγt*, *IL-17*, *IL-6*, *CXCL2*, *CXCR2*, and upregulation of *FoxP3* and *TGF-β* transcripts. Yoga enables the maintenance of immune-homeostasis as evident by increased Treg cell population and reduced Th17 cell population. Yoga reduces the rate of immunological aging in T cells, as seen by the reduction in population of aged Th17 cells and aged Treg cells. Yoga positively modifies transcriptome and epigenome by normalization of various inflammatory markers, gene expression patterns and epigenetic alterations. Taken together, yoga reduces RA severity, and aids in immune-modulation and hence can be beneficial as an adjunct therapy.

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease of multifactorial origin that develops due to unfavorable coincidence of genetic, immune, and environmental factors[1]. A fragile state of dynamism persists between pro-inflammatory and anti-inflammatory forces. Loss of tolerance to self-antigens is the

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hallmark of autoimmune disorders leading to the production of autoantibodies[2]. The pathogenesis of RA is heavily influenced by immune cells, particularly B-cells, T-cells, and macrophages[3]. T-cells activate macrophages and fibroblasts to become tissue-destructive cells and release a wide range of cytokines and chemokines to support joint inflammation[4].

T helper 17 (Th17) and regulatory T cells (Treg cells) are both differentiated from the same naive CD4+ T cells, but in separate cytokine environments and with distinctive gene expression profiles[5]. Pro-inflammatory Th17 cells cause joint injury and autoimmune-derived tissue inflammation by inducing proinflammatory cytokines[6]. Treg cells inhibit the activity of Th17 cells as well as other effector T cells. Treg cells suppress the immune system, maintain self-tolerance, and prevent autoimmune disease by producing anti-inflammatory cytokines[7]. The retinoic acid-related orphan receptor gamma t (RORγt), a lineage-defining transcription factor unique to Th17 cells that produce interleukin (IL)-17, has been linked to a variety of autoimmune diseases[8]. Foxp3 (forkhead transcription factor) plays a crucial role as a lineage specification factor of Treg cells that produce transforming growth factor (TGF)-β, which maintains immune tolerance and homeostasis of the immune system[9]. Th17 cells mediate the pro-inflammatory response through the release of IL-17A and tumor necrosis factor-alpha (TNF-α), which results in tissue destruction as well as damage to bone and cartilage[8]. In contrast, Treg cells mediate the anti-inflammatory response through the release of IL-10 and TGF-β, which aid in maintenance of immune-tolerance[9]. The key immune cells, Treg cells are functionally impaired in RA[10]. The importance of the Th17/Treg cell imbalance in the etiology of RA was highlighted by their opposing behaviors as well as their reciprocal plasticity.

An aberrant Treg cell response with a shift towards a Th17 cell response characterizes the disease onset and course. The relationship between the imbalance of Th17/Treg cells and the production of pro- and anti-inflammatory cytokines is important for the onset and/or course of autoimmunity, chronic inflammation, and articular damage in the joints of RA patients[11]. Age-inappropriate telomere shortening is a hallmark of premature aging in the T cells of RA patients[12]. In RA, the rate of immunosenescence is accelerated[13]. T cells become susceptible to aging as there is enormous proliferative stress due to antigenic exposure, homeostatic proliferation due to thymic involution and their long lifespan as they serve as the carriers of immune memory[14]. The peculiar features of prematurely aged RA T cells include loss of CD28 expression, shrinking naïve and expanding memory repertoire, shortened telomeres, gain of cytotoxicity, DNA damage accumulation, lack an irreversible cell cycle arrest, more vulnerable to apoptosis, altered tissue trafficking, excess pro-inflammatory cytokine secretion[12,15,16]. The inefficient DNA damage sensing and repair machinery of RA T cells are linked to premature T cell aging and arthritogenic effector functions[16].

Epigenetic alterations like DNA methylation and histone acetylation accumulate with aging and provide a mechanistic link between immunosenescence and development of autoimmune diseases such as RA. T cell landscape is influenced by epigenetic mechanisms such as alteration in the global 5-methyl cytosine (5-mC) DNA, global 5-hydroxymethyl cytosine (5-hmC) DNA and histone deacetylase 1 (HDAC1) levels, which are susceptible to systemic factors, external stressors and environmental stimuli[17]. Yoga is an integrated ancient mind–body practice that is increasingly recognized to have beneficial effects on immune system functioning[18–23]. Yoga practice may exert positive impact on overall health by boosting cell-mediated and mucosal immunity[23]. Our previous studies evaluated the role of yoga as an effective intervention to assist the management of RA with respect to various systemic inflammatory biomarkers, immune-modulatory markers, acute phase reactants, clinical symptoms, depression severity, functional status, pain acuity and quality of life[19,20,24,25]. Yoga aids in regression of inflammatory processes by reducing the pro-inflammatory cytokines and elevating anti-inflammatory cytokines[21]. Nevertheless, the research on exploration of molecular, cellular and epigenetic aspects following yogic practices is rare, hence a possible mode of action underlying the immune-modulatory effects of yoga needs an active exploration. Further investigation is needed to determine how regular yoga practice impacts the T cell subsets that secrete these cytokines, and the associated transcription factors, gene expression and epigenome. There is currently insufficient data to relate yoga's multifaceted therapeutic targets and its molecular mode of action with a malfunctioning immune system as in RA.

Keeping in mind the multifactorial etiology, diverse pathogenesis of RA, heterogeneous clinical phenotypes and the therapeutic potential of yoga, we hypothesized that yoga improves clinical outcome in RA by bringing changes in all interconnected biological components and at various levels—molecular, cellular, organ systems, and the person as a whole. With this novel context in mind, this study aimed to investigate the immune-modulatory effects of 8-weeks of yoga practice on disease severity, T cell sub-sets [Th17 (CD3+ CD4+ IL17+ RORγt+) cells and Treg (CD3+ CD4+ CD25+ CD127-Foxp3+) cells], markers of T cell aging [aged Th17 (CD3+ CD4+ IL17+ RORγt+ CD28−) cells and aged Treg (CD3+ CD4+ CD25+ CD127− Foxp3+ CD28−) cells], inflammatory markers [IL-6, IL-17, TGF-β, and IL-10], epigenetic alterations [5-mC, 5-hmC and HDAC1] and gene expression [*RORγt, FoxP3, IL-17, IL-6, TGF*-β, C-X-C motif chemokine ligand 2 (*CXCL2),* C-X-C motif chemokine receptor 2 (*CXCR2),* and *JUN*].

Results

Overview of enrollment. A total of 105 individuals were screened for eligibility, out of which 64 were randomized into 2 groups (each group $n = 32$). Figure 1 shows the CONSORT flowchart of intervention. All 32 randomized participants were included in intent-to-treat analyses of outcome measures.

Participants' baseline characteristics. Baseline demographic and clinical characteristics of all randomized participants are shown in Table 1. There were no statistically significant differences between the two intervention groups, except stratification of disease severity.

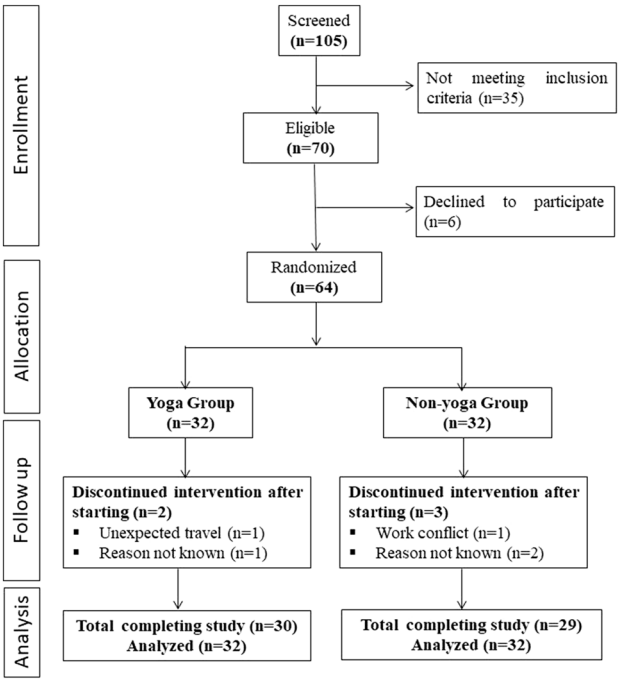

Figure 1. A consort flow diagram of the study.

Variable	Group (RA patients)		*p* value
	Yoga (n = 32)	Non-yoga (n = 32)	
Demographic characteristics			
Age (years)	46.0 ± 9.4	41.8 ± 9.7	0.0886
Sex			
Male	6	9	0.5561
Female	26	23	
Disease duration (years)	6.6 ± 4.8	5.6 ± 4.4	0.3923
BMI (kg/m^2)	25.4 ± 4.6	24.0 ± 2.5	0.1303
Presenting symptoms			
Early morning stiffness (minutes)	22.6 ± 22.1	25.5 ± 21.6	0.6092
Tender joint count (TJC)	6.2 ± 4.7	6.7 ± 4.2	0.6557
Swollen joint count (SJC)	4.1 ± 4.3	3.9 ± 2.7	0.7856
Drug therapy			
No. of patients on methotrexate monotherapy	32	32	0.6217
No. of patients on methotrexate plus, other DMARDs	12	9	
No. of patients on biologic response modifiers	0	0	
Disease severity			
Mean DAS28-ESR	4.6 ± 0.9	4.5 ± 1.1	0.4408
Stratification by disease severity			0.0310*
> 2.6–3.2 (low)	1	3	
> 3.2–5.1 (moderate)	14	22	
> 5.1 (high)	17	7	
Co-morbidity			0.9229
DM type 2	8	9	
Hypertension	7	8	
Tuberculosis	6	4	
Hypothyroidism	10	9	
Others	1	2	

Table 1. Baseline characteristics. Data were described as frequency (%) for sex, drug therapy, stratification by disease severity, co-morbidity and mean ± SD for others. One asterisk (*) indicates a p-value ≤ 0.05; two asterisks (**) indicate a p-value ≤ 0.01; three asterisks (***) indicates a p-value ≤ 0.001.

Group × gender interactions. There was no significant difference in mean DAS28-ESR values between males and females at baseline (DAS28-ESR values 4.7 ± 0.9 and 4.6 ± 1.0 mean ± SD, respectively). Separate analyses for males and females were performed to overcome baseline violations in disease activity and to explore further specific gender effects. Interaction effects including group and gender indicated differential responses to yoga for women for DAS28-ESR [$F(1,25) = 3.39$; $p = 0.042$], Th17 cells [$F(1,25) = 4.06$; $p = 0.025$], Treg cells [$F(1,25) = 21.23$; $p < 0.001$], aged Th17 cells [$F(1,245 = 14.5$; $p < 0.001$], aged Treg cells [$F(1,25) = 13.9$; $p < 0.001$], TGF-β [$F(1,25) = 4.62$; $p = 0.015$], 5-mC [$F(1,25) = 7.5$; $p = 0.001$] and HDAC1 [$F(1,25) = 6.49$; $p = 0.003$]. Clinical improvement was more significant for the women in yoga group [mean between-group difference of change [95% confidence interval (CI)]: female = 1.0, 95% CI (0.15 to 1.8) $p = 0.0211$; male = −0.27, 95% CI (−1.6 to 1.06) $p = 0.6629$ (Fig. 2).

Post-intervention differences in disease activity. There was a significant reduction in DAS28-ESR scores among the participants of yoga group [0.49, 95% (0.13 to 0.85)] with a significant interaction of group and time ($\eta p^2 = 4.3$; $p = 0.042$) (Table 2).

Post intervention differences in molecular markers. *T cell subsets.* The representative graphics from flow cytometry for Th17 and Treg cells measurements are depicted in Supplementary Fig. 1 and 2 respectively. Flow cytometry was performed to evaluate the Th17/Treg cell dynamics and aged T cell populations in both the groups. The mean percentage of Th17 cells ($CD3^+CD4^+IL17^+ROR\gamma t^+$ T cells) has shown a significant overall decline in yoga group ($p = 0.004$) from baseline to 8th week [1.7 ± 0.7 vs 0.9 ± 0.4; $p < 0.0001$], whereas a non-significant difference in non-yoga group from baseline to 8th week [1.5 ± 0.8 vs 1.7 ± 1.1; $p = 0.381$] (Fig. 3). Conversely, the mean percentage of Treg cells ($CD3^+CD4^+CD25^+CD127^-Foxp3^+$ T cells) has shown a significant overall elevation in yoga group ($p < 0.0001$) from baseline to 8th week [1.1 ± 0.7 vs 2.1 ± 0.6; $p < 0.0001$], whereas a non-significant decline in non-yoga group from baseline to 8th week [1.4 ± 0.4 vs 1.1 ± 0.7; $p = 0.093$] (Fig. 3).

Markers of immune aging. A significant overall decline in the mean percentage of aged Th17 cells ($CD3^+CD4^+IL17^+ROR\gamma t^+CD28^-$ T cells) was observed in the yoga group ($p < 0.0001$), from baseline to 8th week [58.9 ± 18.7 vs. 28.1 ± 18.8; $p < 0.0001$], whereas a non-significant difference in the non-yoga group from baseline to 8th week [55.0 ± 19.9 vs. 51.1 ± 20.3; $p = 0.406$] (Fig. 3). Similarly, a significant overall decline in the mean percentage of aged Treg cells ($CD3^+CD4^+CD25^+CD127^-Foxp3^+CD28^-$ T cells) was seen in the yoga group ($p < 0.0001$) from baseline to 8th week [76.1 ± 14.3 vs. 56.8 ± 17.1; $p < 0.0001$], with no significant alterations observed in the non-yoga group from baseline to 8th week [76.9 ± 13.0 vs. 79.3 ± 13.2; $p = 0.329$] (Fig. 3).

Inflammatory markers. There were significant changes observed in various inflammatory markers after 8-weeks of intervention in yoga group as compared to non-yoga group. Pro-inflammatory cytokines like IL-6 [0.54,

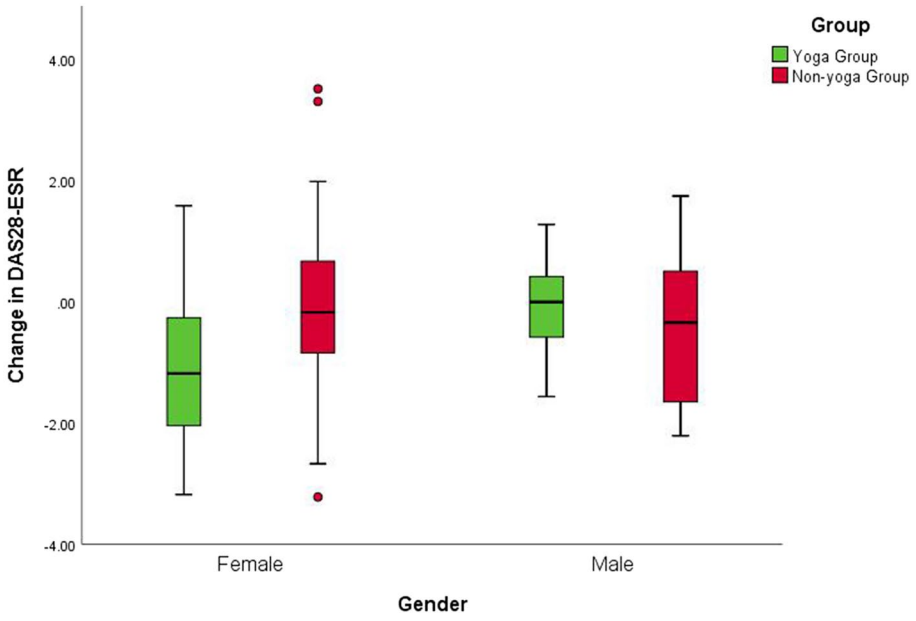

Figure 2. Gender interactions for change in disease activity after the intervention. Mean change of DAS28-ESR score with 95% CI for males in the yoga and the control groups; $p = 0.6629$ for between-group differences of change in the study, adjusted for baseline value. Mean change of DAS28-ESR score with 95% CI for females in the yoga and the control groups; $p = 0.0211$* for the between-group difference of change on the study, adjusted for baseline value.

Outcome	Yoga group (n = 32)			Non-yoga group (n = 32)			Between groups	Variance analysis/effects			
								Time		Group × time	
	Pre	Post	Δ Mean within-group	Pre	Post	Δ Mean within-group	Mean difference (95% CI)[b]	p^b value	η_p^2	p^b value	η_p^2
Disease activity score											
DAS28-ESR	4.7 ± 0.9	3.8 ± 0.9	0.8 ± 1.2	4.5 ± 1.1	4.3 ± 1.3	0.11 ± 1.6	0.49 [0.13 to 0.85]	0.008**	7.4	0.042*	4.3
Inflammatory markers											
IL-6 (pg/ml)	3.4 ± 1.2	2.4 ± 1.6	1.04 ± 1.1	3.7 ± 1.1	3.7 ± 1.4	0.03 ± 1.4	0.54 [0.2 to 0.8]	0.001***	11.9	0.002**	10.4
IL-17 (pg/ml)	191.4 ± 25.8	174.9 ± 25.4	16.4 ± 26.7	187.5 ± 38.9	206.0 ± 41.9	−18.4 ± 21.2	−0.96 [−7.0 to 5.0]	0.750	0.1	< 0.001***	33.4
TGF-β (pg/ml)	40.5 ± 16.9	50.2 ± 16.2	−0.9 ± 13.7	44.8 ± 14.5	43.2 ± 14.5	0.16 ± 11.9	−4.0 [−7.2 to −0.7]	0.015*	6.2	0.001***	12.3
IL-10 (ng/ml)	71.1 ± 12.1	100.9 ± 11.0	−29.7 ± 16.3	66.7 ± 23.4	64.1 ± 24.0	2.5 ± 21.5	−13.5 [−18.3 to −8.8]	< 0.001***	32.2	< 0.001***	45.7
Epigenetic markers											
5-mC (%)	2.2 ± 1.04	3.8 ± 2.9	−1.7 ± 2.8	2.9 ± 1.6	2.6 ± 1.0	0.2 ± 1.4	−0.72 [−1.3 to −0.16]	0.012*	6.6	0.001***	12.8
5-hmC (%)	0.02 ± 0.01	0.007 ± 0.007	0.01 ± 0.02	0.02 ± 0.02	0.01 ± 0.01	0.002 ± 0.02	0.008 [0.003 to 0.014]	0.002**	10.4	0.040*	4.4
HDAC1 (ng/ml)	10.8 ± 7.6	8.3 ± 6.4	2.5 ± 2.9	11.02 ± 6.8	12.2 ± 10.3	−1.1 ± 4.7	0.668 [−0.32 to 1.6]	0.181	1.8	< 0.001***	13.9

Table 2. Intent-to-treat analysis: means (SD) and results of within-group and between-group analysis of primary outcomes ($n = 64$; yoga, 32; non-yoga, 32). One asterisk (*) indicates a p-value ≤ 0.05; two asterisks (**) indicate a p-value ≤ 0.01; three asterisks (***) indicates a p-value ≤ 0.001.

95% CI (0.22 to 0.85); $\eta p^2 = 10.4$; $p = 0.002$], IL-17 [−0.96, 95% CI (−7.0 to 5.06); $\eta p^2 = 33.4$; $p < 0.001$] showed a significant decline with respect to interaction of group and time; whereas anti-inflammatory cytokines like TGF-β [−0.4, 95% CI (−0.7 to −0.07); $\eta p^2 = 12.3$; $p = 0.001$] and IL-10 [−13.5, 95% CI (−18.3 to −8.8); $\eta p^2 = 45.7$; $p < 0.001$] showed a significant increase in yoga group as compared to control group with respect to interaction of group and time (Table 2). Also, the change in mean within non-yoga group showed significantly increased levels of IL-17 [−18.4 ± 21.2; $p < 0.001$] compared to baseline levels (Table 2).

Epigenetic alterations. The percentage of global 5-mC was significantly higher in the yoga group as compared to the non-yoga group [−0.72, 95% CI (−1.3 to −0.16); $\eta p^2 = 12.8$; $p = 0.001$] (Table 2). Conversely, the percentage of global 5-hmC was significantly reduction in the yoga group after 8-weeks of intervention with a significant mean difference observed by group analysis [0.008, 95% CI (0.003 to 0.014); $\eta p^2 = 4.4$; $p = 0.04$)] (Table 2). Also, the HDAC1 levels were found to be significantly reduced after 8-weeks of intervention in the yoga group as compared to the non-yoga group [0.668, 95% CI (−0.32 to 1.6); $\eta p^2 = 13.9$; $p < 0.001$)] (Table 2).

Gene expression levels. The results for expression analysis showed significant downregulation in relative mRNA expression levels of *RORγt* ($p = 0.0002$), *IL-17* ($p = 0.0219$), *IL-6* ($p = 0.0003$), *CXCL2* ($p = 0.0065$), and *CXCR2* ($p = 0.0284$) in the yoga group as compared to the non-yoga group. The mean axis fold change of these transcripts was as follows in the yoga vs. non-yoga group: *RORγt* (−1.64 vs. 1.74), *IL-17* (−3.42 vs. 3.15), *IL-6* (−2.34 vs. 0.72), *CXCL2* (−2.50 vs. 0.19), and *CXCR2* (−4.90 vs. 1.32) respectively. The mRNA expression levels of *JUN* were not found to be different statistically ($p = 0.7237$) with a mean axis fold change of 1.05 vs. 1.38 in the yoga vs. non-yoga group. In the yoga group, the mRNA expression levels were significantly upregulated with the mean axis fold change of *FoxP3* (1.93 vs. −0.65; $p = 0.0169$) and *TGF-β* (3.32 vs. 0.72; $p = 0.0001$) in the yoga vs. non-yoga group respectively (Fig. 4).

Discussion

Our study is the first to highlight the positive impact of yoga on modulation of the T cell subsets, T cell aging markers, epigenetic alterations and associated transcription factors in RA. We found that 8 weeks of yoga practice significantly reduced disease activity, normalized the biomarkers associated with inflammation, and maintained Th17/Treg cell homeostasis. Further, yoga reduced the rate of immunological aging as seen by the reduction in the aged Th17 cell population (CD3+ CD4+ IL17+ RORγt+ CD28-T cells) and aged Treg cell population (CD3+ CD4+ CD25+ CD127-Foxp3+ CD28-T cells). Our findings suggest that yoga positively modified epigenetic changes such as global methylation levels, global hydroxyl methylation levels, and HDAC1 levels which may regulate gene expression patterns. The yoga group showed the downregulation of *RORγt, IL-17, IL-6, CXCL2, CXCR2,* and upregulation of *FoxP3* and *TGF-β*. These findings suggest that yoga possesses an immune-modulatory potential which induces molecular remission in RA by influencing its pathobiology at both cellular and molecular level.

In the present study, the impact of regular practice of yoga was beneficial as there was a significant reduction in the systemic levels of pro-inflammatory markers (IL-6 and IL-17) and various transcripts associated with pro-inflammatory cytokines. IL-6 is essential for the development of RA's systemic(lung, heart skin, brain) and joint inflammation, immune system abnormalities, and joint swelling[30]. The systemic inflammatory signs and symptoms of RA, which are mediated by IL-6, include fever, malaise, sleep disturbances, muscular weakness, and anemia[31]. In order to promote the production of adhesion molecules and draw leukocytes to the affected joints, IL-6 induces endothelial cells to secrete IL-8 and monocyte chemoattractant protein-1 (MCP-1) locally at joint level[32]. IL-6 can promote osteoclast differentiation and synoviocyte proliferation by activation of the NF-kappa

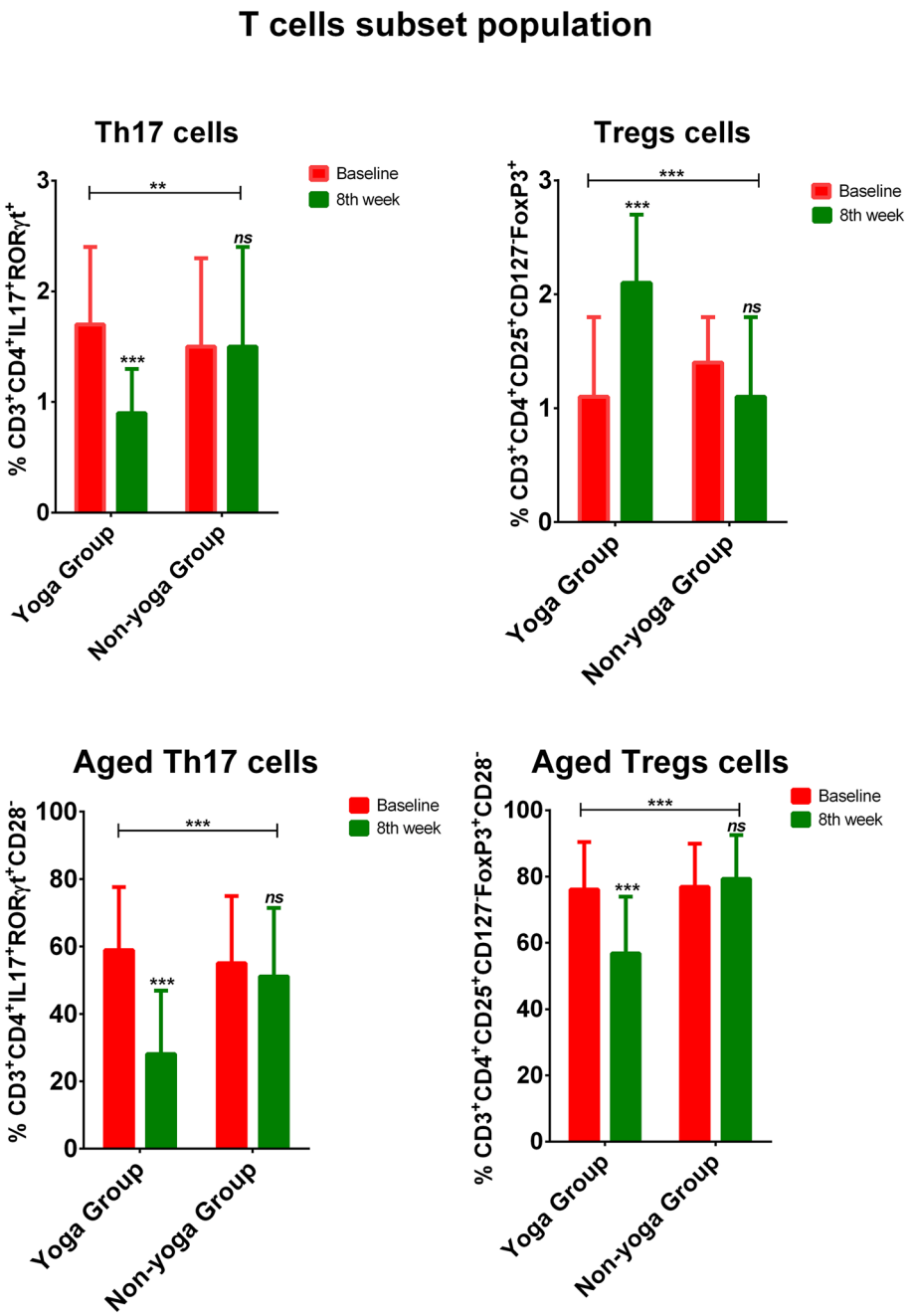

Figure 3. Frequency of Th17, Treg, aged Th17, and aged Treg cells in the yoga group and non-yoga group [p value (ns = p > 0.05; *p ≤ 0.05; **p ≤ 0.01;***p ≤ 0.001)].

B receptor activator ligand (RANKL). Through STAT3-mediated activation of the RORγt in the presence of TGF-β, IL-6 stimulates the differentiation of Th17 cells while inhibiting TGF-induced Treg cell differentiation[33]. Thus, IL-6 encourages Th17 over Treg dominance in the effector CD4+ T cell subsets, which is regarded to be a key factor in the emergence of RA and other immune-mediated illnesses[30]. Another important inflammatory marker, IL-17 affects RA joints by promoting the development of matrix metalloproteases and pro-inflammatory cytokines, which contribute to tissue inflammation and destruction[34]. Th17 cells play a unique role in immune activity through the generation of effector cytokines such as IL-17A, IL-17F, IL-22, etc. Th17 cells influence the development of osteoclasts and bone resorption by the release of IL-17, an activate monocytes to create pro-inflammatory cytokines, accelerating the inflammatory cascade[35,36]. Expression of CXCL2 was significantly increased in RA patients and was associated with bony erosions[37]. CXCL2 is a pro-inflammatory factor which is associated with biological signs of progress, such as angiogenesis, inflammation and cancer. CXCL2 stimulated osteoclastogenesis via extracellular receptor kinase (ERK) mitogen-activated protein kinase (MAPK) and nuclear factor kappa B pathways[37]. Leukocyte trafficking is regulated by chemokines both during homeostasis and immunological responses. CXCR2 plays a cell-autonomous function in the migration of neutrophils to inflamed

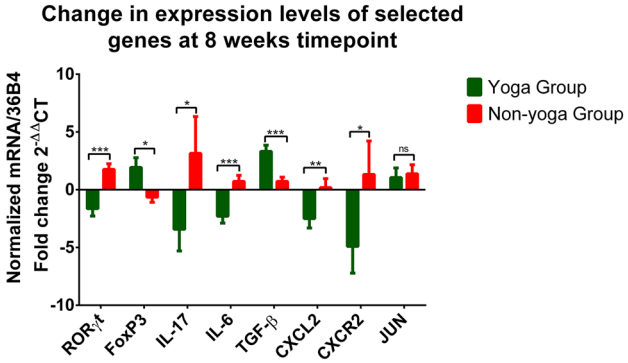

Figure 4. The relative mRNA expression levels of dysregulated transcripts in the yoga group and non-yoga group [p value (ns = p > 0.05; *p ≤ 0.05; **p ≤ 0.01;***p ≤ 0.001)].

joints, which is essential for the emergence of auto-immune arthritis[38]. Furthermore. our study demonstrates that yoga practice down-regulates the mRNA transcript levels of pro-inflammatory genes (*RORγt, IL-6, IL-17, CXCL2, CXCR2*), hence reducing systemic and local inflammation in RA, thus overall providing a clear clinical and molecular evidence of the impact of yoga on RA. Yoga, is mind body energy medicine, comprises of both psychological and physical components and is thus ideal as an adjunct management system of this severe painful disabling autoimmune arthritis like RA and has been documented from previous studies from our group for its role as a powerful adjunct to modern medicine in disease management, rehabilitation and promotion of health.

Yoga is a centuries-old method of unifying the mind, body, and soul. The Patanjali's ashtanga (eight limb) Yoga includes yama (abstinences), niyama (observances), asana (yoga postures), pranayama (breath control), pratyahara (withdrawal of the senses), dharana (concentration), dhyana (meditation) and samadhi (absorption)[18]. Dharna, dhyana and samadhi are *antaranga* yoga. Yoga originated from the belief that stress is the cause of all illnesses, which gives the practice advantages for both physical and mental health[39]. Stress impacts every cell of the body and every organ system and yoga thus targets both the mind and body reducing stress by building emotional resilience by promoting neuroplasticity. Not only is there increase in several neurochemicals like brain derived neurotrophic factor (BDNF), dehydroepiandrosterone (DHEA), melatonin, serotonin but also actual anatomical changes in the brain in the hippocampus, prefrontal cortex which show increase in gray matter and concomitant decrease in size of amygdala. IL-10 possesses anti-inflammatory and immunoregulatory properties. Yoga has the potential to mediate the inflammatory pathways by increasing the levels of anti-inflammatory mediators and reducing the pro-inflammatory markers[19,40]. IL-10 prevents T-cell responses to specified antigens and inhibits the synthesis of proinflammatory cytokines and chemokines[41]. The main mechanism by which IL-10 exerts its effects is by inhibiting the costimulatory capabilities of macrophages and promoting the proliferation and differentiation of antibody-forming B cells. The effectiveness of IL-10 in reducing inflammation and autoreactivity has been demonstrated in preclinical research using a range of animal models, including collagen-induced arthritis[42]. TGF-β is a regulatory cytokine which promotes the growth of Treg cells and controls CD4+ T cell polarization. Depending on the cytokine environment, TGF- β stimulates the differentiation of Th17 and Treg cells[43]. The transcription factor RORγ*t*, which is the principal regulator of Th17 cells, is activated and controlled in its expression by TGF- signaling and STAT3[44]. TGF-β can induce the differentiation of CD4+ T cells into Th17 cells in the presence of IL-6 or IL-21. Our results have shown that the yoga group showed significant upregulation of mRNA expression levels of *FoxP3* and *TGF*-β as compared to the non-yoga group, further confirming the immune-modulatory role of yoga. The dimers of members of the Jun, Fos and activating transcription factor protein families make up the transcription factor activator protein 1 (AP-1)[45]. Jun mostly acts as a proliferating growth regulator of cells[46].In the present study, the mRNA expression levels of *JUN* had shown a declining trend in the yoga group; however, the difference was not statistically significant as compared to the non-yoga group.

The immune dysregulation in RA is attributed to increased secretion of inflammatory cytokines by effector Th17 cells and a loss of Treg cells suppressor function. Yoga's anti-inflammatory properties work to restore immune homeostasis to its ideal state and promote natural immunological tolerance to treat autoimmune diseases[20,21]. Our results also showed that regular practice of yoga was associated with increased Treg cell population and decreased Th17 cell population. Our findings imply that yoga-induced variations in serum cytokine levels stimulate changes in Treg and Th17 cell populations, which may shift the delicate immune system balance to reestablish tolerance. A study on the effect of a 12-week program of regular tai chi chuan exercise showed beneficial effects on functional mobility, beliefs about the benefits of exercise on physical and psychological health and maintained immune regulation in middle-aged volunteers by increase in their Treg cells[47,48]. Our results were in concordance with a study conducted on the ischemic cardiomyopathy rat model in which the Th17/Treg ratio was much lower in the rats trained on treadmill (Slope 0°, 12 m/min, 30 min/time) five times per week, for 12 weeks than non-training group rats[49].Few more studies focused on the impact of endurance training and physical exercise on athletes where a diversion in the Th17/Treg cell balance was seen[49,50]. Our study has documented a post-yoga reduction in the mean percentage of Th17 cells (CD3+ CD4+ IL17+ RORγt+ T cells) in yoga group from baseline to 8th week whereas the mean percentage of Treg cells (CD3+ CD4+ CD25+ CD127− Foxp3+ T cells) has shown a significant elevation in yoga group. RA patients experience the signs of accelerated ageing like reduced

thymic functioning, expansion of late-differentiated effector T cells, increased telomeric attrition, and excessive production of cytokines (senescence-associated secretory phenotype)[12]. Early onset of age-related co-morbidities like osteoporosis, cardiovascular issues, and cognitive decline have all been linked to the progression of RA[51]. The crucial co-stimulatory protein CD28 is expressed on undifferentiated CD4+ and CD8+ T lymphocytes. Since the MHC-I-bound peptide antigen has a low affinity, activating T cells using antigen-presenting cells (APCs) alone is not enough to fully activate and sustain T cells[52]. To extend T cell responses, the co-stimulatory signal from the CD28 cell surface receptor that binds with CD86 or CD80 on antigen presenting cells is required. Yoga possesses the potential to reduce the pace of immunological aging which can be attributed to the reduced mean percentage of aged Th17 cells (CD3+ CD4+ IL17+ RORγt+ CD28-T cells) as well as aged Treg cells (CD3+ CD4+ CD25+ CD127− Foxp3+ CD28-T cells) after 8 weeks of practice.

Inflammatory changes may be influenced by epigenetic mechanisms that subsequently lead to gene expression alterations and, eventually, protein expression[53]. The epigenome controls gene expression and is susceptible to changes brought on by stress, lifestyle changes and other environmental variables[54]. The most extensively researched epigenetic modification is DNA methylation, which is increasingly recognized as a meaningful biomarker in the pathogenesis of RA[55]. High levels of inflammation and poor physical health have both been linked to changes in DNA methylation[56]. Since epigenetic modifications have the capacity to be reversed, they can be used to gauge how well clinical treatments are working. Recent studies have reported a global DNA hypomethylation in immune cells of RA patients as compared to healthy individuals[57]. Global DNA hypomethylation is implicated in various inflammatory and autoimmune disorders and leads to aberrant gene expression[58]. In RA, the low levels of methylation at specific CpG sites in fibroblast-like synoviocytes is correlated with overexpression of genes which are important for the disease pathogenesis such as growth factors/ receptors, extracellular matrix proteins, adhesion molecules, and matrix degrading enzymes, etc[59,60]. In our study, we have seen an overall increase in the percentage of global 5-mC DNA in yoga group over non-yoga group after 8-weeks of yoga intervention, which might lead to the downregulation of pro-inflammatory genes like *RORγt, IL-6, IL-17, CXCL2, CXCR2,* etc. DNA demethylation also occurs via oxidative modification followed by removal of the base[61]. Active DNA demethylation occurs due to the presence of 5-hmC. In order to study the effect of yoga on the status of DNA demethylation in RA patients, the global 5hmC percentage was estimated. This is the first study to document an overall decrease in the percentage of global 5-hmC DNA in yoga group over non-yoga group after 8- weeks of yoga intervention. Modifications of histones are major epigenetic markers that regulate gene expression and establish various cell phenotypes[62]. The open structure of chromatin makes the chromatin available to transcription factors and can increase gene expression dramatically. Histone acetylation is important for gene expression regulation, while histone deacetylation contributes to chromatin condensation and gene transcription repression[63]. Inhibition of HDAC function by epigenetic or non-epigenetic mechanisms can lead to the development of RA and other autoimmune inflammatory diseases, affecting the complex modulation of intracellular signaling pathways[64]. HDAC inhibitors exhibit anti-arthritic activities through modulation of only a small percentage of gene expression involved in chronic inflammation and apoptosis[65]. HDAC inhibitors act via epigenetic and non-epigenetic processes to generate immunomodulatory effects. HDAC inhibitors demonstrated anti-inflammatory effects in animal models of arthritis and synovial tissues in RA patients[66]. In our study, we have seen a reduction in the levels of HDAC1 in yoga group as compared to non-yoga group after 8-weeks of yoga. The effects of HDAC inhibitors on cellular activation have been attributed to epigenetic regulation, signal transduction modifications, and gene expression modulation via regulation of mRNA stability.

Lack of an active control group was one of the study's shortcomings because the non-yoga group had no equal attention control intervention and only received medication therapy in comparison to the active yoga intervention group. Therefore, including such a group would further rule out the therapeutic results that were specifically linked to the yoga intervention. In both the yoga and non-yoga groups, there were fewer men, which was explained by the fact that women had a higher prevalence of RA than men (3:1). It is challenging to maintain a regular schedule for a long-term RA management or home practice regimen because each session of yoga lasted for 120 min every day while being supervised by a certified yoga instructor. Also, the lack of long-term follow-up of the participants made it difficult to predict how quickly participants returned to their baseline levels. In order to investigate the long-term advantages of the yoga practice, we intend to conduct additional research with a large sample size and long-term follow-ups and practice of yoga for shorter duration.

In conclusion, our study findings highlight that yoga possesses an immune-modulatory potential which induces molecular remission and reestablishes immunological tolerance in RA by influencing its pathobiology by optimizing inflammatory markers, maintaining immune-homeostasis, reducing the rate of immune-aging and improving RA health outcome. The 8 weeks of yoga practice significantly reduces disease activity, maintains Th17/Treg cell homeostasis and reduces inflammatory processes by optimizing the levels of various pro-inflammatory cytokines, and anti-inflammatory cytokines with changes in gene expression patterns. Yoga positively modifies the epigenome by elevating global methylation levels, reducing global hydroxyl methylation levels, and HDAC levels which may cause the normalization of dysregulated gene expression. Hence, yoga can be used as an adjuvant therapy in RA as it boosts physical functioning, enhances psychological wellbeing and reestablishes immunological tolerance.

Methods

Ethics declarations and study design. This study was a prospective, single-blinded, randomized controlled trial with active RA patients, aimed at analyzing the effects of an 8-week yoga practice in RA patients on standard drug therapy. The study was initiated after obtaining ethical clearance (IECPG-211/24.02.2016) from the Institute Ethics Committee of AIIMS, New Delhi, India, and registration under the clinical trials registry, India (CTRI/2017/05/008589, Registered on 17.05.2017). All methods were performed in accordance

with the relevant guidelines and regulations. All the participants gave written informed consent before the study protocol's commencement.

Participants and eligibility criteria. The study participants were recruited from the outpatient unit of Rheumatology department of AIIMS, New Delhi. RA patients, 18–60 years old, diagnosed as per 2010 ACR/EULAR RA classification criteria[26], whose DAS28ESR was > 2.6 and who were on standard medical treatment for at least 6 months were recruited after obtaining written informed consent. Patients with any other overlapping autoimmune diseases, chronic systemic diseases, history of administration of oral or intra-articular steroids in the previous six months, medical treatment for any other illnesses, intake of any form of herbo-mineral, antioxidant, homeopathic, or ayurvedic supplementation (*Boswellia serrata*, *Ricinus communis,* dry ginger powder, fenugreek seeds, curcumin, *ashwagandha* etc.) or already practicing yoga and meditation in any way were excluded from the study. Also, during the execution of the study, the events which resulted in the exclusion were the inability to comply with regular yoga and deviating from their usual lifestyle habit.

Sample size calculation. The sample size calculation for the study assumed to detect a standardized effect size [difference in mean change in DAS28-ESR between the two groups/pooled standard deviation (SD)] of 0.8 with a 95% confidence level and 80% power, considering the mean and SD of a previous study by Evans et al. (2011)[27]. Considering some loss to follow-up, we enrolled a total of 64 patients in the study and randomized into two groups—yoga group (32 patients) and non-yoga group (32 patients).

Randomization. For this investigator blinded study, sequentially labeled sealed opaque envelopes were used to conceal random numbers as described earlier[20]. As each patient was enrolled, they were assigned to the next numbered envelope and the associated group, either yoga group or non-yoga group. The sequence of random numbers was generated by permuted block randomization of variable block size with the assistance of the web tool research randomizer (https://www.randomizer.org/). The participants were not blinded to the study, whereas investigators who interviewed patients, conducted experiments, and performed statistical analyses blinded to the group status of the patients.

Intervention. The participants were randomized into two groups- the yoga group and non-yoga group. All the study participants were asked to undergo a clinical evaluation and provide a blood sample on day 0 (baseline) and the end of 8th week of intervention.

Yoga program (yoga group). As described previously[19], the participants of the yoga group were administered a standardized yoga program for eight weeks, which was suitable for active RA patients, so that it did not cause any further irritation to already inflamed joints. The patients with deformed joints and limitations were advised to undergo customized physical postures, relaxation exercises, and practiced breathing forming a slow and deep breathing pattern with exhalation being longer than inhalation. The comprehensive yoga program incorporated the components of Patanjali's ashtanga yoga. Briefly, the intervention comprised of yogic practices including asanas (physical postures), pranayama (regulated breathing techniques), dhyana (meditation), and savasana (relaxation techniques), followed by interactive counseling sessions on yoga, stress management, nutrition, as well as personal lifestyle management (Supplementary Fig. 3). Yoga program was administered five times a week for 120 min duration per session for 8 weeks[19,25]. The sessions were conducted by the registered and well-qualified yoga instructor at the Laboratory for Molecular Reproduction & Genetics, Department of Anatomy, AIIMS, New Delhi. Adherence was monitored with participant diary and yoga teacher's remarks at each visit. As such, there was no home regimen to be followed for the yoga practice due to the extensive time commitment of each session. The patients were encouraged to incorporate yoga into their lifestyle after the end of the 8 weeks of intervention. The patients of this group continued with their standard disease-modifying anti-rheumatic drugs (DMARDs) as per the prescription of rheumatologists.

Usual care control (non-yoga group). As described previously[19], the patients assigned to the non-yoga group continued with their ongoing medical care, which included DMARDs prescribed by the rheumatologists. The patients followed their normal daily physical activities with no change in their daily lifestyle for eight weeks.

Outcome measures. *Primary outcome.* The disease activity of the patients was assessed by DAS28-ESR[28]. The DAS28-ESR consisted of four components: tender joint count, swollen joint count, visual analog scale (VAS) score of the patient's global health, and ESR. In DAS28-ESR, a rating of ≤ 2.6 represents remission, > 2.6 to 3.2 represents low disease activity, > 3.2 to 5.1 represents moderate disease activity, and ≥ 5.1 represents high disease activity.

Change in disease severity was measured by disease activity score—erythrocyte sedimentation rate (DAS28-ESR) from baseline (day 0) to 8-weeks and recorded as primary outcome.

Secondary outcome. All parameters were evaluated on day 0 (baseline) and 8th week (follow-up) of the intervention and the fasting blood samples were obtained at 8 am in the morning.

Alterations in cellular and molecular markers including: (a) T cell subset population: Th17 (CD3+ CD4+ IL17+ RORγt+) cells and Treg (CD3+ CD4+ CD25+ CD127− Foxp3+) cells, (b) markers of immune aging: aged Th17 (CD3+ CD4+ IL17+ RORγt+ CD28−) cells and aged Treg (CD3+ CD4+ CD25+ CD127− Foxp3+ CD28−) cells, (c) inflammatory markers: IL-6, IL-17, TGF-β, and IL-10

(d) epigenetic alterations: 5-methyl cytosine, 5-hydroxymethyl cytosine and HDAC1, and (e) gene expression levels: *RORγt, FoxP3, IL-17, IL-6, TGF-β,CXCL2,CXCR2,* and *JUN* were documented.

Measurement of molecular markers. Following techniques were employed for the measurement of molecular markers:

Phenotyping of T cell subsets by flow cytometry. The isolated PBMCs (1×10^6 cells /ml) were stained with a panel of fluorochrome-conjugated monoclonal antibodies (Thermo Fisher Scientific, USA) for the surface markers, namely CD3, CD4, CD28, CD25, and CD127 and intra-cellular cytokines/transcription factors, namely IL-17, RORγt, and FoxP3. Alexa Fluor 488-labeled anti-human CD3, PerCP Cy5.5-labeled anti-human CD4, APC-labeled anti-human IL-17, PE-labeled anti-human RORγt were used to examine $CD3^+CD4^+IL17^+RORγt^+$ T cells. Alexa Fluor 488-labeled anti-human CD3, PerCP Cy5.5-labeled anti-human CD4, PE-labeled anti-human CD25, APC-eFluor 780-labeled anti-human CD127, and APC-labeled anti-human FoxP3 were used to detect $CD3^+CD4^+CD25^+CD127^-Foxp3^+$ T cells. PE-Cyanine7-labeled anti-human CD28 was used for aged T cell population i.e. aged Th17 cells($CD3^+CD4^+IL17^+RORγt^+CD28^-$ T cells) and aged Treg cells ($CD3^+CD4^+CD25^+CD127^-Foxp3^+CD28^-$ T cells).

The isolated PBMCs (1×10^6 cells /ml) were taken in FACS tubes for immuno-staining. The recommended value of monoclonal antibodies (for surface markers as mentioned above) were added, mixed thoroughly, and incubated on ice or 4 °C for 45 min in the dark. Cells were washed with staining buffer (1× PBS with 1% FBS) and pelleted at 1200 rpm for 10 min. For intracellular staining, cells were permeabilized and added with permeabilization buffer (Thermo Fisher Scientific, USA). The cell pellet was resuspended in 100 µl of transcription factor staining buffer (Thermo Fisher Scientific, USA), and with the recommended value of monoclonal antibodies (for transcription factors & intracellular cytokines) and incubated in the dark at room temperature for 1 h. After two steps of washing with PBS, the cells were resuspended in 100 µl of with permeabilization buffer (Thermo Fisher Scientific, USA) and fixed by adding 20 µl of 4% paraformaldehyde (PFA) and stored at 4 °C. Fixed cells were flow- cytometrically acquired & analyzed by BD Fortessa X20 flow cytometer (BD Biosciences, San Jose, CA) equipped with FACSDIVA™ software. Fifty thousand events were acquired per sample within a typical forward, and side scatter gate set to exclude dead cells and debris. Data were analyzed using FlowJo 7.22 (Tree Star Ashland, Orlando, FLA) software.

Detection of inflammatory and epigenetic markers. Serum levels of IL-6 (Gen-Probe, Diaclone Diagnostic, France), IL-17 (Gen-Asia Biotech, China), IL-10 (Bioassay Tech Laboratory, China), and HDAC1 (Qayee Bio-Technology) were estimated by ELISA using commercially available kits. Briefly, the workflow of the HDAC1 ELISA kit utilizes the sandwich ELISA methodology where the plate was pre-coated with human HDAC1 antibody. The serum samples were then added onto the pre-coated wells. And, then biotinylated human HDAC1 antibody was added, which binded to HDAC1 in the sample. After the addition of Streptavidin-HRP developer followed by substrate and stop solution, the well absorbance for HDAC1 was measured at 450 nm. The 5-methylcytosine DNA ELISA kit (Enzo Life Sciences, Inc., USA) and 5-hydroxymethyl cytosine DNA ELISA kit (Enzo Life Sciences, Inc., USA) was used to quantify the percent 5-mC DNA and 5-hmC DNA respectively. Briefly, the workflow for the 5-mC DNA ELISA kits utilize the indirect ELISA methodology where 100 ng denatured, single-stranded DNA (ssDNA) samples per well were coated on the plate wells and a 5-mC mAb and conjugate HRP-Ab were then added to the wells. The detection of 5-mC was done after the addition of the HRP developer by measuring well absorbance at 405–450 nm. Briefly, the workflow of the 5-hmC DNA ELISA kit utilizes the sandwich ELISA methodology where a 5-hmC pAb was coated to the bottom of plate well surfaces. The ssDNA (100 ng/well) sample was then added onto the well surface which binded to 5-hmC pAb's and was then recognized by a conjugate DNA HRP-Ab. After the addition of HRP developer, the well absorbance for 5-hmC DNA was measured at 405–450 nm. Serum TGF-β levels were estimated by a magnetic bead-based multiplex assay using Bio-Plex Pro TGF-β Assays (Bio-Rad Laboratories Inc., USA) according to the manufacturer's guidelines. Quality-control assays for biomarkers and validation were performed.

Detection of gene expression patterns. As described earlier[20], total RNA was isolated from 1 ml of freshly obtained EDTA blood by TRIzol manual method followed by complementary DNA (cDNA) synthesis by reverse transcribing 1000 ng of RNA by using the iScript cDNA synthesis kit (BioRad). The CFX96 realtime system (BioRad, CA, United States) quantified the relative gene expression using Brilliant III UltraFast SYBR Green qPCR Master Mix. The protocol for gene amplification was standardized at 35 cycles. Normalization of the amount of expressed mRNA used two internal housekeeping genes *36B4* and *β-actin*. The relative fold of gene expression was done by the $2^{-\Delta\Delta Ct}$ method[29]. The primer sequences for the genes used in the study are shown in Table 3.

Statistical analysis. All statistical analyses were carried out on an intent-to-treat basis with the baseline observation carried forward approach using IBM SPSS Statistics for Macintosh, Version 25.0. (IBM Corp. Armonk, NY, United States) and GraphPad Prism Version 6.01. (GraphPad Software, Inc., San Diego, CA). Chi-square test and Fisher's exact test compared the baseline characteristics between the two groups. The assessment of interaction effects among baseline parameters was carried out by mixed factorial design ANOVA. For within-group analysis, paired t-test was used to study the difference between pre- to post-intervention for normally distributed data, or Wilcoxon signed-rank tests for continuous variables without normal distribution. For between-group analysis, the repeated measure ANOVA was used to study the intervention effects along with the interaction of time and group. A p-value of < 0.05 was considered to be statistically significant.

S. no.	Gene	Primer sequence (5′ to 3′)
1	*RORγt*	Forward: CCTGGGCTCCTCGCCTGACC Reverse: TCTCTCTGCCCTCAGCCTTGCC
2	*FoxP3*	Forward: GTGGCCCGGATGTGAGAAG Reverse: GGAGCCCTTGTCGGATGATG
3	*IL-17*	Forward: CGGCTGGAGAAGATACTGGT Reverse: TTAGTCCGAAATGAGGCTGTC
4	*IL-6*	Forward: GGCACTGGCAGAAAACAACC Reverse: GCAAGTCTCCTCATTGAATCC
5	*TGF-β*	Forward: GAAGGGAGACAATCGCTTTAGC Reverse: TGTAGACTCCTTCCCGGTTGAG
6	*CXCL2*	Forward: TGCCAGTGCTTGCAGAC Reverse: TCTTAACCATGGGCGATGC
7	*CXCR2*	Forward: TGGCTTGATCAGCAAGGACTC Reverse: GCCCTGAAGAAGAGCCAACA
8	*JUN*	Forward: CAGCTTCATGCCTTTGTA Reverse: CTCAGAGTGCTCCAAATCTC
9	*36B4*	Forward: AACATGCTCAACATCTCCCC Reverse: CCGACTCCTCCGACTCTTC
10	*β-actin*	Forward: TGAGAGGGAAATCGTGCGTG Reverse: TGCTTGCTGATCCACATCTGC

Table 3. List of primer sequences.

Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

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SYSTEMATIC REVIEW

Barriers and facilitators to yoga practice among people living with arthritis: a qualitative systematic review

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Abstract

The global burden of arthritis is high and increasing. Systematic reviews suggest that yoga, an ancient mind-body discipline, may help in arthritis treatment. This systematic review aimed to synthesise the barriers and facilitators to yoga practice in people with arthritis. JBI methodological guidance for qualitative systematic reviews was followed. MEDLINE, Embase, CINAHL Plus, PsycInfo, AMED, and Web of Science were searched to identify published studies, and ProQuest Dissertations and Theses for unpublished studies. Databases were searched until 07 November 2024, with no language restrictions. Study screening, assessment of methodological quality, and data extraction were completed independently by two reviewers. Data were synthesised using a meta-aggregative approach. Of 1330 identified records, nine articles, representing eight studies, were included in the review. All studies were conducted in high-income countries (the USA, UK, and New Zealand), with a majority of female participants. Methodological quality ranged from moderate to high; six of the eight studies met at least seven of the ten quality assessment criteria. 112 findings were extracted from the articles and grouped into 20 categories based on similarity in meaning. These were formulated into five synthesised findings: (i) Yoga, arthritis, and the body: the anticipated and experienced impacts of yoga on physical well-being influenced yoga practice; (ii) Yoga, arthritis, and the mind: levels of motivation and perceived impact on mental well-being influenced yoga practice; (iii) Yoga, arthritis, and the mind-body impact: yoga's mind-body benefits supported coping with arthritis and encouraged continued practice; (iv) Yoga, arthritis, and session accessibility and structure: factors related to session accessibility and structure influenced engagement with yoga; and (v) Yoga, arthritis, and the session environment: a supportive social environment in yoga sessions impacted yoga practice. Each synthesised finding revealed a range of barriers and facilitators to yoga practice in people with arthritis. Within the included studies, there appeared to be more facilitators than barriers, suggesting that yoga could be a valuable addition to arthritis treatment. Future interventions to support yoga practice in this group should promote these facilitators and address the barriers to ensure successful implementation. *PROSPERO registration number*: CRD42023483350.

Keywords Arthritis · Qualitative research · Systematic review · Yoga

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Introduction

Arthritis is a set of chronic musculoskeletal conditions affecting the joints [1]. It is generally characterised by joint pain, stiffness, inflammation, and deformity, and can lead to impaired joint function [1, 2]. Arthritis has significant physical and mental health impacts and limits participation in social activities [3–6]. It also leads to a considerable economic burden, such as costs for medical treatments, and indirect costs due to absenteeism from work and loss of work productivity [7, 8]. Eventually, the individual's health-related quality of life is affected [8, 9]. Osteoarthritis and rheumatoid arthritis are two major contributors to the global burden of musculoskeletal conditions, affecting nearly 528 million and 18 million people, respectively [1, 10].

Western medical treatment typically includes the use of non-steroidal anti-inflammatory drugs (NSAIDs) for osteoarthritis and disease-modifying anti-rheumatic drugs (DMARDs) for rheumatoid arthritis [11, 12]. However, long-term medication use may have side effects (e.g., gastrointestinal toxicity) [12, 13]. In addition, non-pharmacological approaches to treatment (e.g., physical exercises) are also recommended for symptom relief [2, 11, 12]. Though beneficial, these approaches can be challenging due to high costs, inability to meet individualised needs, difficulty level, and injury concerns [14–17].

Yoga, an ancient mind-body practice originating in the Indian subcontinent, imparts a sense of well-being of the body and mind, and offers an alternative that may address these concerns [18, 19]. Its global popularity continues to rise, with nearly 300 million people practising it [20–22]. Yoga typically involves a gentle approach, requires minimal equipment, and can be practised with a low to moderate level of guidance, in indoor and outdoor settings [19, 23]. Systematic reviews and meta-analyses have shown that yoga is safe and can be beneficial in osteoarthritis and rheumatoid arthritis treatment [24–28]. Further, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) guidelines conditionally recommend yoga as a complementary approach for the treatment of knee osteoarthritis and rheumatoid arthritis [29, 30].

Qualitative research can provide insights into why people with arthritis may, or may not, practice yoga. Such studies have explored the factors that impede (barriers) and encourage (facilitators) yoga practice among people with arthritis [31–33]. However, no systematic review on this topic has been conducted to date. Therefore, this systematic review aimed to synthesise the barriers and facilitators to yoga practice in people with arthritis. It is hoped that the review findings could be used to address the barriers through appropriate actions and promote the facilitators of yoga practice in people with arthritis.

Methods

The review adhered to JBI methodological guidance on systematic reviews of qualitative evidence [34]. It was reported according to the 'Enhancing Transparency in Reporting the Synthesis of Qualitative Research' (ENTREQ) statement and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline [35, 36]. This review protocol was registered with PROSPERO (CRD42023483350).

Inclusion criteria

Participant: This review included studies conducted among adults (aged ≥ 18 years) diagnosed with arthritis of any type. No restrictions on diagnostic criteria were applied.

Phenomena of interest: This review included studies that explored the knowledge, experiences, attitudes, understandings, perceptions, or perspectives that may act as barriers and facilitators to yoga practice.

Context: This review considered studies undertaken in any global context and setting (e.g., community, primary care, secondary care, or tertiary care).

Study design: This review considered studies that had qualitative data, including, but not limited to, designs such as phenomenology, ethnography, action research, case studies, grounded theory, and feminist research. Other study designs, such as mixed methods, quasi-experimental, and cross-sectional descriptive studies, reporting relevant qualitative data, were also included.

Databases and search strategy

Six electronic databases were searched from their inception dates until 07 November 2024 to locate published studies: (i) MEDLINE (Ovid; from 1946), (ii) Embase (Ovid; from 1974), (iii) CINAHL Plus (EBSCOhost; from 1937), (iv) PsycInfo (Ovid; from 1806), (v) AMED (Ovid; from 1985), and (vi) Web of Science (from 1900). In addition, ProQuest Dissertations and Theses were searched for unpublished studies. The search strategies were developed for all the databases in consultation with an experienced research librarian at the University of Nottingham (UK). The search strategy was initially developed for MEDLINE and then adapted as necessary across other databases. "Yoga" and "arthritis" search concepts were based on the search strategies used in previous relevant systematic reviews [25, 26]. Predesigned database-specific search filters were used for the "qualitative study design" concept, where possible [37]. No language restrictions were applied. The search strategies are detailed in Appendix 1. The reference lists of all the included studies were screened for additional studies.

Study screening and selection

Following the searches, all identified citations were collated and uploaded into EndNote X9 [38] and de-duplicated. The remaining records were then imported into Rayyan [39] to facilitate the title and abstract screening process, undertaken by two independent reviewers (IB and PE). Studies identified as potentially eligible or those without an abstract were retrieved in full text, and their details were imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) [40]. The full text of the studies was then assessed in detail against the inclusion criteria by the two independent reviewers. Any disagreements between the two reviewers at each stage of the study selection process were resolved through discussion or by involving a senior reviewer (SL/KC) if a consensus was not reached.

Assessment of methodological quality

The two independent reviewers assessed all eligible studies using the standardised critical appraisal checklist for qualitative research incorporated within JBI SUMARI [40]. The checklist uses a series of criteria that can be scored as being met (yes), not met (no), unclear, or, where appropriate, not applicable (n/a) to the particular study. They went through each criterion and commented on it. Any disagreements between reviewers were resolved through discussion or by involving a senior reviewer. All studies, regardless of their methodological quality, underwent data extraction and synthesis where possible.

Data extraction

The two independent reviewers extracted data using the standardised data extraction tool incorporated within JBI SUMARI [40]. Any disagreements were resolved through discussion or involving the third reviewer. The following details were extracted: author and year of publication, country, phenomena of interest, yoga delivery setting, participant recruitment setting, qualitative research methodology, study design, sample size and participant characteristics (type of arthritis, age, sex, and disease duration), data collection methods, and data analysis technique. Next, findings (i.e., extracted themes from included studies), with relevant illustrations (i.e., quotes or supportive data cited in the included studies for each finding), were extracted. The findings and illustrations were the actual verbatim words of the study authors and participants, respectively. Each finding was then assigned a level of credibility: unequivocal (U) (i.e., evidence beyond a reasonable doubt), credible (C) (i.e., evidence that was open to challenge), or not supported (NS) (i.e., findings were not supported by the data) [40].

Data synthesis

All authors were involved in data synthesis. The extracted study details were first narratively synthesised. Then, study findings were pooled using JBI SUMARI, following a meta-aggregation approach [41]. Initially, the lead reviewer (IB) grouped findings assigned as either unequivocal or credible into categories based on similarity in meaning and concept through discussions with another reviewer (PE). Each finding was labelled, and the related or similar ones were grouped under a representative name. This iterative process continued until all authors (IB, PE, CE, SL, and KC) reached consensus to ensure that the findings were placed under appropriate categories. To interpret the categories as barriers or facilitators, patterns in the data and their relevance to the review objective were analysed. This process helped identify factors influencing yoga practice in people with arthritis, providing a clearer understanding of both barriers and facilitators. The lead reviewer refined the categories and aggregated them into synthesised findings through repeated discussions with other senior reviewers (CE, SL, and KC), formulating statements to represent each.

Results

Study inclusion

The study selection process is detailed in the PRISMA flowchart as shown in Fig. 1. 1330 records were identified through the literature search. After removing duplicate records and title and abstract screening, 15 articles were retrieved for full-text screening. A total of six articles were excluded after full-text screening. The most common reasons were ineligible phenomena of interest (n = 3), conference abstract (n = 2), and study protocol (n = 1). Nine articles, representing eight studies, were included in the review [31–33, 42–47]. Appendix 2 provides information on excluded studies and the reasons for exclusion. No additional articles were identified from citation searching.

Characteristics of included studies

Table 1 describes the characteristics of the eight included studies [31–33, 42–47]. Two articles originated from the same study [33, 42]. Each had different aims and data analysis techniques but were based on the same set of qualitative interview data; hence, they were considered a single study in this review [33, 42]. The included studies were published

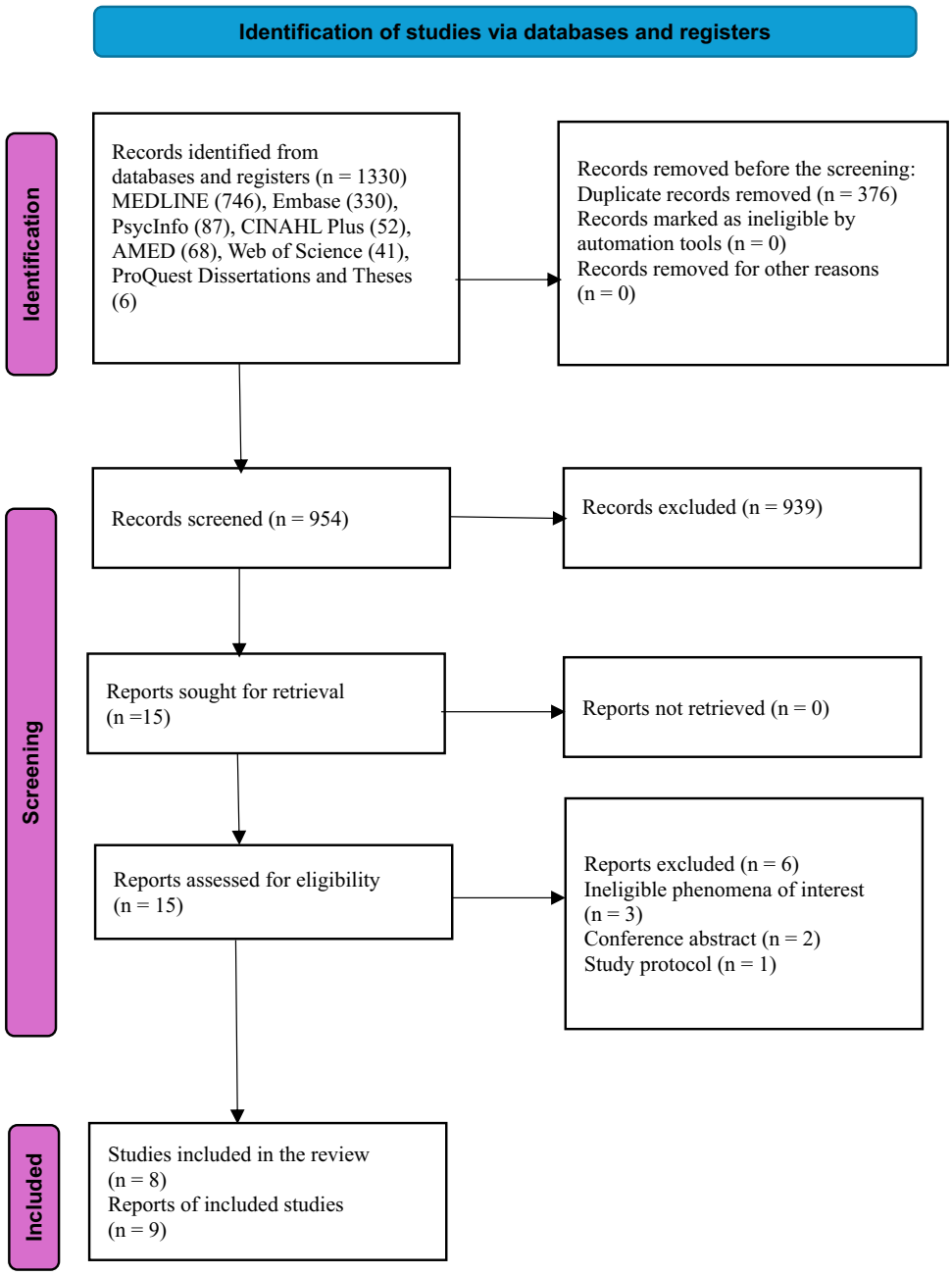

Fig. 1 PRISMA flow diagram for included studies from searches of databases and registers only

over 12 years from 2010 to 2022 [31–33, 42–47]. All studies were conducted in high-income countries, specifically, New Zealand [47], the UK [44], and the USA [31–33, 42, 43, 45, 46]. All studies explored views, experiences, perceptions, or perspectives of people with arthritis regarding yoga practice. Participants were recruited solely from community settings in three studies [31, 43, 46], presumed secondary care settings in three studies [44, 45, 47], and tertiary care settings in one study [32]. Additionally, in one study, participants were recruited from both presumed secondary care and community settings [33, 42]. In six studies, yoga interventions were delivered as group sessions in community settings [31–33, 42, 43, 45, 46], including two studies where participants also practised individually at home [31, 43]. In one study, the yoga intervention was delivered in one-on-one sessions, presumably in a secondary care setting and also practised individually at home [44]. Another study explored insights regarding a potential yoga intervention but did not include its actual delivery [47]. Regarding qualitative research methodology, seven studies employed descriptive methodologies [31, 32, 43–47]. One study used both ethnographic [42] and phenomenological [33] methodologies (reported in two separate articles). Four studies solely used a qualitative study design [31, 32, 45, 47], two used mixed

Table 1 Characteristics of included studies

Author and year of publication	Country	Phenomena of interest	Participant recruitment setting	Yoga delivery setting	Qualitative research methodology	Study design	Sample size and participant characteristics (type of arthritis, age in years [mean (SD or range)], sex, disease duration in years [mean (SD or range)])	Data collection methods	Data analysis technique
Evans, 2010 [42]	USA	Exploring the range and depth of experiences regarding an IY programme	Secondary care? and community	Group sessions in community	Ethnography	Mixed methods	5 participants with RA Age: 28 (3) 4 females and 1 male Disease duration: 16 (8.5)	Face-to-face semi-structured interviews	Ethnographic content analysis
Evans, 2011 [33]	USA	Exploring potential mechanisms of change as a result of participating in an IY programme	Secondary care? and community	Group sessions in community	Phenomenology	Mixed methods	5 participants with RA Age: 28 (24–31) 4 females and 1 male Disease duration: 16 (8–28)	Face-to-face semi-structured interviews	Phenomenological analysis
Park, 2011 [46]	USA	Exploring the pain reduction, well-being, mood, and functional benefits after participation in a chair yoga programme	Community	Group sessions in community	Qualitative descriptive approach	Quasi-experimental (included qualitative approach)	7 participants with OA Age: NR Females and males: NR Disease duration: NR	Face-to-face focus group discussions	Thematic analysis
Ward, 2011 [47]	New Zealand	Exploring views regarding the suitability of yoga as a non-pharmacological option in the management of RA	Secondary care?	N/A	Qualitative descriptive approach	Qualitative	22 participants with RA Age range: 26–73 19 females and 3 males Disease duration: 16	Face-to-face focus group discussions	Thematic analysis
Cheung, 2015 [43]	USA	Identifying the barriers and motivations to yoga practice and exploring the experiences of home-based yoga practice	Community	Group sessions in community and individual practice at home	Qualitative descriptive approach	Cross-sectional descriptive (included qualitative approach)	31 participants with knee OA Age: 72 (6) All females Disease duration: NR	Face-to-face interviews and videotapes of home practice	Content analysis
Greysen, 2017 [45]	USA	Exploring community yoga practice characteristics and perceptions of how and why yoga is practised and factors influencing yoga participation as a symptom management strategy in RA	Secondary care?	Group sessions in community	Qualitative descriptive approach	Qualitative	17 participants with RA Age: 56 (11) 16 females and 1 male Disease duration: 21 (11)	Telephonic structured interviews	Thematic analysis
Middleton, 2017 [32]	USA	Identifying the barriers and facilitators to an adapted HY programme among adults from minority groups (English or Spanish speaking)	Tertiary care	Group sessions in community	Qualitative descriptive approach	Qualitative	12 participants with either OA or RA Age: 64 (33–65) All females Disease duration: NR	Face-to-face semi-structured interviews	Content analysis

Table 1 (continued)

Author and year of publication	Country	Phenomena of interest	Participant recruitment setting	Yoga delivery setting	Qualitative research methodology	Study design	Sample size and participant characteristics (type of arthritis, age in years [mean (SD or range)], sex, disease duration in years [mean (SD or range)])	Data collection methods	Data analysis technique
Cartwright, 2020 [44]	UK	Exploring experiences and perspectives of an adapted YT intervention based on principles of Viniyoga	Secondary care?	One-on-one sessions in secondary care? and individual practice at home	Qualitative descriptive approach	Mixed methods	10 participants with RA Age: 54 (13) 9 females and 1 male Disease duration: 8 (6)	Face-to-face semi-structured interviews	Thematic analysis
Cheung, 2022 [31]	USA	Uncovering the experience and perspectives of long-term practice of a structured HY programme and identifying the barriers to and facilitators of adherence to the programme	Community	Group sessions in community and individual practice at home	Qualitative descriptive approach	Qualitative	28 participants with knee OA Age: 71 (8) All females Disease duration: NR	Face-to-face semi-structured interviews and focus group discussions	Inductive content analysis

? Unclear, *HY* Hatha yoga, *IY* Iyengar yoga, *N/A* Not applicable, *NR* Not reported, *OA* Osteoarthritis, *RA* Rheumatoid arthritis, *SD* Standard deviation, *UK* United Kingdom, *USA* United States of America, *YT* Yoga therapy

methods study designs [33, 42, 44], one used quasi-experimental [46], and one used a cross-sectional descriptive study design [43], allowing extraction of relevant qualitative data. The number of study participants ranged from 5 [33, 42] to 31 participants [43]. Where reported, the mean age of the participants ranged from 28 years [33, 42] to 72 years [43]. Five studies included both male and female participants [33, 42, 44–47], and three included only females [31, 32, 43]. The mean disease duration ranged from eight years [44] to 21 years [45]. Data collection methods primarily included interviews [31–33, 42–45], one of which used telephone interviews [45]. The remaining studies used focus group discussions for collecting data [46, 47]. Data analysis techniques included thematic analysis [44–47], content analysis [31, 32, 43], and phenomenological [33] and ethnographic content analysis [42] (the latter two were applied in one study, reported as two distinct articles).

Methodological quality of included studies

The critical appraisal results of the eight included studies are presented in Table 2. Overall, the methodological quality ranged from moderate to high. None of the studies met al.l of the appraisal criteria. Six studies had "yes" responses to 7 or more questions on the checklist [31, 32, 44, 45, 47, 48]. All studies met the criteria for Q2, Q3, Q4, Q5, Q8, and Q10. However, three questions consistently yielded lower ratings (most often rated as "unclear"): inadequate reporting of congruity between the stated philosophical perspective and the research methodology (Q1); inadequate reporting of cultural or theoretical positioning of the researcher (Q6; and limited reporting of the influence of the researcher on the study and vice-versa (Q7). Ratings of "unclear" reflect gaps in reporting in the original papers, which prevented a definitive judgment.

JBI critical appraisal checklist for qualitative research: Q1 Is there congruity between the stated philosophical perspective and the research methodology? Q2 Is there congruity between the research methodology and the research question or objectives? Q3 Is there congruity between the research methodology and the methods used to collect data? Q4 Is there congruity between the research methodology and the representation and analysis of data? Q5 Is there congruity between the research methodology and the interpretation of results? Q6 Is there a statement locating the researcher culturally or theoretically? Q7 Is the influence of the researcher on the research, and vice-versa, addressed? Q8 Are participants, and their voices, adequately represented? Q9 Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body? Q10 Do the conclusions

Table 2 Critical appraisal of included studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10
Evans, 2010, 2011 [33, 42]	U	Y	Y	Y	Y	U	U	Y	Y	Y
Park, 2011 [46]	Y	Y	Y	Y	Y	U	U	Y	Y	Y
Ward, 2011 [47]	U	Y	Y	Y	Y	N	U	Y	U	Y
Cheung, 2015 [43]	U	Y	Y	Y	Y	U	U	Y	Y	Y
Greysen, 2017 [45]	U	Y	Y	Y	Y	U	U	Y	Y	Y
Middleton, 2017 [32]	U	Y	Y	Y	Y	Y	Y	Y	Y	Y
Cartwright, 2020 [44]	U	Y	Y	Y	Y	N	Y	Y	Y	Y
Cheung, 2022 [31]	U	Y	Y	Y	Y	U	U	Y	Y	Y
Total % of "Y"	13	100	100	100	100	13	25	100	88	100

Y = yes; N = no; U = unclear. For example, Q1 was rated "U" for Evans (2010, 2011) due to insufficient detail on philosophical perspective, making it difficult to determine if the research methodology aligned with the stated philosophical perspective. Q7 was rated "U" for Park (2011) because the study did not clearly discuss how researchers' interactions with participants may have influenced the research process. Note: similar issues apply to other studies with U ratings

drawn in the research report flow from the analysis, or interpretation, of the data?

Review findings

Table 3 depicts the meta-aggregation of findings. A total of 112 findings were extracted from nine articles, of which 111 were assessed as unequivocal and one as credible. There were no unsupported findings. These were grouped into 20 categories and further interpreted into five synthesised findings. Each synthesised finding, along with its categories, findings, and illustrations, is detailed in Appendices 3, 4, 5, 6, and 7. Table 4 shows the categories and their representative illustration(s).

1. Yoga, arthritis, and the body: The anticipated and experienced impacts of yoga on physical well-being influenced yoga practice in people with arthritis

This synthesised finding was derived from 30 findings that were interpreted into five categories, which addressed the perceived impacts of yoga on the "body", i.e., physical well-being in arthritis. It highlighted how yoga affects physical symptoms of arthritis, thereby either hindering or facilitating yoga practice. Limited awareness of yoga's benefits led to a fear of worsening symptoms, discouraging participation. However, noticeable improvements, including relief from arthritis symptoms, increased body awareness, and energy levels, motivated yoga practice. Many reported that these physical benefits encouraged them to maintain an active lifestyle by practising yoga, and some also mentioned reduced reliance on arthritis medication.

Barriers

1a. Yoga practice seemed "an unknown territory" that might aggravate arthritis symptoms

In this category, six findings (U) were aggregated, which showed that people with arthritis were apprehensive about practising yoga due to their limited awareness of yoga and thought that some yoga poses might be beyond their physical capabilities. Some described attempting yoga but giving up eventually as they felt it might add to their existing symptom burden in arthritis, e.g., worsening pain, flare-ups, and even effects on comorbidities (e.g., heart problems) or cause injuries.

1b. Uncertainty about yoga's benefits on arthritis symptoms discouraged yoga practice

Two findings (U) were aggregated to create this category, which described how some people with arthritis were unsure and, at times, uncertain about yoga's benefits on their symptoms. One of them described that on some days, they would feel yoga alleviated their symptoms; on other days, they would not perceive any noticeable difference in their symptoms.

Facilitators

1c. Experiencing relief from arthritis symptoms as a result of yoga practice

Thirteen findings (U) were combined to form this category. People with arthritis mentioned improvement in arthritis symptoms, including pain relief, improved flexibility and mobility, stronger muscles, and reduced swelling, ultimately making them feel at ease with their bodies.

1d. Yoga seemed to elevate body awareness and physical vitality, translating into people's daily lives

This category consisted of seven findings (U). It captured accounts of people with arthritis, suggesting that yoga may

Table 3 Meta-aggregation of findings

Synthesised finding	Category	Findings
Yoga, arthritis, and the body: The anticipated and experienced impacts of yoga on physical well-being influenced yoga practice in people with arthritis.	*Barriers* 1a. Yoga practice seemed "an unknown territory" that might aggravate arthritis symptoms. 1b. Uncertainty about yoga's benefits on arthritis symptoms discouraged yoga practice. *Facilitators* 1c. Experiencing relief from arthritis symptoms as a result of yoga practice. 1d. Yoga seemed to elevate body awareness and physical vitality, translating into people's daily lives. 1e. Yoga practice was perceived to reduce reliance on arthritis medication for pain relief.	30
Yoga, arthritis, and the mind: Levels of motivation and perceived impact on mental well-being influenced yoga practice in people with arthritis.	*Barriers* 2a. Wavering intrinsic motivations (concentration, self-efficacy, and self-assurance) negatively influenced yoga practice. *Facilitators* 2b. High levels of intrinsic motivations (personal interest in yoga, prioritising health, self-efficacy, self-assurance, and self-confidence) facilitated yoga practice. 2c. Extrinsic motivations (doctor's advice, reduced price of yoga sessions, improvement in other health conditions, exposure to yoga, and peer/family support) positively influenced yoga practice in arthritis. 2d. Perception of improvements in mental well-being could encourage yoga practice.	29
Yoga, arthritis, and the mind-body impact: The experience of mind-body benefits of yoga fostered a positive outlook on coping with arthritis and encouraged ongoing engagement with yoga practice in people with arthritis.	*Facilitators* 3a. Practising yoga gave people with arthritis a sense of empowerment, i.e., the ability to take control of their condition. 3b. Yoga was appreciated as a beneficial coping strategy for arthritis. 3c. Practising yoga changed the way people with arthritis viewed their condition, allowing them to rediscover themselves and regain a sense of normalcy in their lives. 3d. Consistent yoga practice was perceived as essential for achieving long-term holistic benefits for arthritis.	23
Yoga, arthritis, and session accessibility and structure: Engagement with yoga practice was influenced by individually determined factors affecting access to sessions, as well as by the structural characteristics of the sessions.	*Barriers* 4a. Juggling with logistical challenges to attending yoga sessions discouraged yoga practice. 4b. Unsatisfactory yoga experiences, including the difficulty level of the practices and discomfort, hindered yoga practice. *Facilitators* 4c. Yoga's adaptability and well-paced sessions to suit people's needs and preferences in arthritis were perceived to be helpful. 4d. Availability of a yoga provider with positive qualities, knowledge, and professional training facilitated yoga practice. 4e. The provision of props and resources was perceived to offer confidence and security for yoga practice.	22
Yoga, arthritis, and the session environment: A supportive social environment in yoga sessions, characterised by a welcoming space and meaningful connections, encouraged yoga practice in people with arthritis.	*Facilitators* 5a. Safe and supportive space (in group sessions) and a "therapeutic" space (in one-to-one sessions) were considered important for yoga practice. 5b. Social connectedness in a group setting was perceived as a strong motivation for yoga practice.	8
Total synthesised findings = 5	Total categories = 20	Total findings = 112

have elevated their energy levels and helped cultivate physical awareness, i.e., alertness on body posture, alignment, and flexibility. One of them appreciated that practising yoga made them internally aware of how stress can sway them towards the structural misalignment of the body (e.g., bad posture) and expanded their body consciousness. They expressed that these physical health benefits translated to their daily lives, as they generally felt stronger and motivated to maintain a healthy and physically active lifestyle despite their symptoms.

1e. Yoga practice was perceived to reduce reliance on arthritis medication for pain relief

Table 4 Categories and their representative illustration(s)

Category	Representative illustration(s), study author, and page number
1a	"I saw people at gym doing it (yoga) and you're like 'yeah right' I'm never going to be able to do that I'm not even gonna try… at first, I didn't even consider it. You hear yoga and arthritis and you just don't think the two mix." (Evans, 2011, p4)
	''I had to stop doing yoga because of my RA. I actually tried yoga again recently, but it caused a flare, so, I've got to stop doing that." (Greysen, 2017, p490)
1b	"And in terms of the pain, I think some days I thought ''Oh wow, it's really working'' and some days I don't know. It's hard to really tell." (Evans, 2010, p910)
1c	"I am very happy because I have learned yoga…it is helping me feel better, sleep better, to stretch and that helps me in my arthritis and I forget that I have it/suffer from it." (Middleton, 2017, p86)
	"Some of those poses, like opening the legs up or even stretching them, helped a little bit with my range of motion and it relaxed around my joints, especially the ones that hurt the most." (Evans, 2011, p6)
1d	"I can see how yoga can correct your body position if you keep on doing that…I'm more aware of how I can do that with my muscles too; lifting up your leg to make it straighter instead of letting your legs do whatever they want." (Evans, 2011, p6)
	"It made me feel better…overall it helped, just in general helped my energy level so that helped across the board with life." (Evans, 2010, p910)
1e	"Halfway through this we reduced my dose from 15 to 7.5mgs so I'm on half the dose of methotrexate and I'm doing fine on it." (Cartwright, 2020, p3)
2a	"I tried to do the exercise on Wednesday but I don't think I did very well. I need to keep my mind only on what I am doing…I tried to do a ten minute meditation. I was concentrating on just one sentence. It was hard to stay focus. I tried just seeing it in my head like a tie on tape but was hard. I don't know if I am doing this correctly." (Middleton, 2017, p86)
2b	''I'm older now and I needed to do something about balance and posture.'' (Greysen, 2017, p490)
	"I try to do it when I exercise I can and I want to learn them and that way I won't depend on the instructors, soon she will leave us alone and we will have to do it ourselves." (Middleton, 2017, p86)
	''I was pretty proud of myself for getting through it. when I do certain moves, I can feel pretty good about myself.'' (Greysen, 2017, p491)
2c	"…God what a great thing to learn at a young age, because sometimes pain can be worsened because we're thinking about it too much so if you are in a position to learn how to quiet that, it will help anything. If you can learn to do that when you are young, how much damage would you have in the long run?" (Evans, 2010, p910)
	''A group of friends here at work had talked about doing Bikram yoga, and there was a deal, so I tried it.'' (Greysen, 2017, p490)
2d	"I am very grateful for doing yoga. I am more tranquil and I can sleep more because I practice breathing and letting go of everything in my mind." (Middleton, 2017, p86)
	"The strength you have within yourself to make a difference." (Cartwright, 2020, p10)
3a	"It tuned me into coping, it tuned into my mind in how I deal with situations…I had to help myself which she taught me to do." (Cartwright, 2020, p24)
3b	"My pain is still there…but now the difference is that I could reduce the pain by relaxing and just learning to be stress-free and just to be more peaceful. I've learned that if I'm peaceful and more stress free my pain eases away a little. So I'm doing better now." (Evans, 2010, p910)
3c	"I felt like I found this inner peace within me. I found a side of myself that I didn't know I had before…You let go of everything when you're there doing yoga…I forgot about the pain sometimes." (Evans, 2011, p7)
3d	"I think I need to stick with practicing yoga on a regular basis to improve symptoms long-term." (Evans, 2010, p911)
4a	"I don't do a lot of yoga because of time restraints." (Cheung, 2022, p7)
	"My disabled daughter continues to [need]a great deal…my husband got prostate cancer…" (Cheung, 2022, p7)
4b	"It was really hard to bend my joints, I felt like it wasn't for me or people with arthritis.'' (Greysen, 2017, p490)
	"It gave me so much stress…[The therapist] was trying to find out, like you know like something like, something in my life which has caused this thing" (Cartwright, 2020, p10)
4c	"I wasn't overwhelmed, so I wasn't like, 'oh my gosh, this is too hard for me, I can't go back,' so, it was just my right pace." (Greysen, 2017, p490)
	"Tailored the routine to suit me and how my health was at that time. If I couldn't do something because of a certain movement then we'd take that bit out." (Cartwright, 2020, p23)
4d	"But for the person to have an understanding and knowledge…and empathy and to know, gosh, this person's got a problem with that joint; this is the alternative way of getting the same effect with this exercise." (Ward, 2011, p218)
	"…the fear can be a problem. But as long as you trust the person that's actually teaching you, that, you know, they've got your well-being, best interests." (Ward, 2011, p218)
4e	"I don't think I could do the yoga unless I had something beside me to help me. The chair yoga offers security for me." (Park, 2011, p323)
	"Standing on the toes holding the wall, it is pretty good. I did the warm up looking at the book." (Middleton, 2017, p86)

Table 4 (continued)

Category	Representative illustration(s), study author, and page number
5a	"I feel like it'll be more of a safe environment being that it's a study for arthritis and everyone in the class may have some issues." (Evans, 2011, p4)
	"…they're not going to go [laugh], you know, what's wrong with you? You know, they already know what's wrong with ya…" (Ward, 2011, p218)
	"It was a bit like a counselling session…where we would find triggers as to what is going on in my life, in my mind that would have a negative impact on my health, so pinpointing those areas and working on that, I feel has had a massive difference." (Cartwright, 2020, p23)
5b	"I just would be more motivated if it was with other people I knew, sort of understood how I felt, or, you know, like, yeah, I just want, wanna feel more comfortable with, even if they are strangers that they've got the same illness and stuff." (Ward, 2011, p215)

Two findings (U) were combined to create this category. A few individuals with arthritis shared that regularly practising yoga helped them manage their pain and allowed them to reduce their prescribed medication dosage slightly.

2. Yoga, arthritis, and the mind: Levels of motivation and perceived impact on mental well-being influenced yoga practice in people with arthritis

This finding was synthesised from four categories comprising 29 findings. It described the interconnection between mental well-being and intrinsic and extrinsic motivations, which work together to influence yoga practice in people with arthritis. Low levels of intrinsic motivation, such as low self-efficacy, self-assurance, and concentration, discouraged yoga practice in arthritis. High levels of intrinsic motivation, including personal interest, prioritising health, and a sense of accomplishment, encouraged participation in yoga. External motivations, including physicians' recommendations, discounted sessions, improved comorbidities, and support from family and friends, also positively influenced yoga practice in people with arthritis. Staying mentally motivated to practise yoga and consequently practising it led to perceived improvements in mental well-being, which, in turn, further reinforced the motivation to continue practising yoga.

Barriers

2a. Wavering intrinsic motivations (concentration, self-efficacy, and self-assurance) negatively influenced yoga practice

Three findings (U) were merged to form this category, reflecting how the lack of intrinsic motivations among people with arthritis may hinder yoga practice. Those new to yoga practice described struggling with keeping their minds focused at the moment and were unsure about their yoga practice due to low levels of self-efficacy and self-assurance.

Facilitators

2b. High levels of intrinsic motivations (personal interest in yoga, prioritising health, self-efficacy, self-assurance, and self-confidence) facilitated yoga practice

Eleven findings (U) were combined to create this category, illustrating how being intrinsically motivated might encourage yoga practice in people with arthritis. In this category, some people described that they were motivated to practice yoga due to their rising concerns towards health as they grew older, and some were enthusiastic to practice yoga out of personal interest. The ease with which yoga could be practised (minimal equipment and supervision) was perceived to increase self-efficacy and self-assurance in people with arthritis to practice yoga. They added that the high levels of intrinsic motivations provided a sense of accomplishment and bolstered their self-confidence in coping with their condition through continued yoga practice.

2c. Extrinsic motivations (doctor's advice, reduced price of yoga sessions, improvement in other health conditions, exposure to yoga, and peer/family support) positively influenced yoga practice in arthritis

This category included seven findings (1 C, 6U) describing the external influences that may motivate people with arthritis to practice yoga. These included yoga recommended by physicians to deal with pain, the provision of yoga at discounted prices, and perceived improvements in comorbidities (e.g., diabetes) were reported to encourage yoga practice in people with arthritis. Many expressed that awareness of, and exposure to, yoga and its benefits earlier in their lives would have equipped them mentally to deal with their pain in the long run. Support from friends and/

or family was also cited as a motivation to practise yoga for arthritis.

2d. Perception of improvements in mental well-being could encourage yoga practice

This category included eight findings (U), which reflected on several perceived improvements in mental health due to yoga practice. They mentioned being able to "let go" of their worries, pain, and discomfort in arthritis and feeling calm and relaxed. Further, perceptions of improvements in their anxiety and depression symptoms were also generally reported. Many expressed feeling "happy" and experienced evident positive changes in their mood, which gave them the mental strength to deal with their condition.

3. Yoga, arthritis, and the mind-body impact: The experience of mind-body benefits of yoga fostered a positive outlook on coping with arthritis and encouraged ongoing engagement with yoga practice in people with arthritis

This synthesised finding aggregated 23 findings into four categories. It explored the perceptions of people with arthritis regarding how practising yoga deepened their understanding of the link between their body and mind and imparted a sense of overall well-being. These perceived intertwined mind-body benefits of yoga provided a sense of empowerment and enabled people to take charge of their condition by positively shifting their perspective towards coping with the physical and mental aspects of their condition.

Facilitators

3a. Practising yoga gave people with arthritis a sense of empowerment, i.e., the ability to take control of their condition

Five findings (U) were merged to create this category, which showed how people with arthritis perceived that yoga practice gave them a sense of agency to deal with their physical and mental health in arthritis. They mentioned that yoga strengthened their mind-body connection and the mind-body benefits were influenced by each other, i.e., improved physical health (reduced pain) led to improved mental health (stress relief and feeling calm) and vice versa.

3b. Yoga was appreciated as a beneficial coping strategy for arthritis

Twelve findings (U) were merged to form this category, which described the perceptions of people with arthritis on how yoga practice offers skill-based coping strategies to deal with the physical and mental aspects of the condition.

3c. Practising yoga changed the way people with arthritis viewed their condition, allowing them to rediscover themselves and regain a sense of normalcy in their lives

This category included three findings (U) illustrating how people with arthritis perceive yoga as a way to reconnect with themselves. They mentioned feeling a sense of calm and being able to distract their minds from the physical discomfort of arthritis. They added that the mind-body benefits enabled reconnection with their "self" (bodies and minds), making them more physically and mentally aware of their arthritis and changing their negative outlook towards dealing with the condition.

3d. Consistent yoga practice was perceived as essential for achieving long-term holistic benefits for arthritis

Three findings (U) constituted this category, which showed how people with arthritis felt that to experience long-term holistic benefits of yoga, it was important to practise yoga regularly and incorporate it into daily routines, including practice at home.

4. Yoga, arthritis, and session accessibility and structure: Engagement with yoga practice was influenced by individually determined factors affecting access to sessions, as well as by the structural characteristics of the sessions

This synthesised finding was generated from five categories developed from 22 findings. It described factors determining an individual's access to yoga sessions (e.g., logistical considerations) and the structural characteristics of a yoga session (e.g., yoga poses delivered and their difficulty level, suitable modifications offered in the sessions, pace of the sessions, qualities and professional training of the yoga providers, and availability of props and resources) that influenced yoga practice in people with arthritis.

Barriers

4a. Juggling with logistical challenges to attending yoga sessions discouraged yoga practice

Five findings (U) were combined to create this category. Time constraints (e.g., difficulty prioritising yoga over other

activities) and financial limitations (e.g., inability to afford yoga sessions) were cited as common barriers to yoga practice among people with arthritis. Other responsibilities, such as caregiver or family commitments, were also perceived to hinder yoga practice in people with arthritis.

4b. Unsatisfactory yoga experiences, including the difficulty level of the practices and discomfort, hindered yoga practice

This category consisted of two findings (U), which showed how the delivery of yoga sessions affected yoga practice. There was some description of yoga delivered in the sessions that was not modified adequately according to people's specific needs in arthritis, which made it physically challenging for them to practice yoga. The intrusive nature of the yoga therapist in a yoga therapy session, leading to stress and discomfort, was also highlighted as a barrier to yoga practice.

Facilitators

4c. Yoga's adaptability and well-paced sessions to suit people's needs and preferences in arthritis were perceived to be helpful

Six findings (U) were aggregated to create this category. Many people expressed their satisfaction about yoga being adapted and paced according to their needs, preferences, and capabilities in the sessions and its added advantage as a non-invasive and non-pharmacological option in arthritis treatment. They described how practising yoga tailored to their needs enabled them to accept their physical limitations and be more compassionate towards themselves, instead of feeling pressurised to achieve a certain yogic pose that might not suit their bodies.

4d. Availability of a yoga provider with positive qualities, knowledge, and professional training facilitated yoga practice

Four findings (U) were grouped to create this category, highlighting the positive qualities of a yoga provider that drew people with arthritis towards yoga practice. People with arthritis emphasised the importance of yoga providers being empathetic and receptive towards individual needs and having adequate professional training to meet those needs safely.

4e. The provision of props and resources was perceived to offer confidence and security for yoga practice

Five findings (U) were combined to create this category, highlighting how the availability of props and resources served as facilitators to yoga practice in people with arthritis. Using props, such as a chair, to perform yoga poses provided support and safety, instilling confidence and a sense of security in their practice. In addition, guidance from resources such as DVDs and yoga instruction manuals made it easy for them to continue yoga practice, even outside the yoga sessions, at their convenience.

5. Yoga, arthritis, and the session environment: A supportive social environment in yoga sessions, characterised by a welcoming space and meaningful connections, encouraged yoga practice in people with arthritis

This synthesised finding was created from eight findings merged into two categories. It encompassed the positive impact of the social environment of yoga sessions, including safe, empathetic, non-judgmental, and supportive spaces that enabled people to form social connections, ultimately enhancing yoga practice in people with arthritis.

Facilitators

5a. Safe and supportive space (in group sessions) and a "therapeutic" space (in one-to-one sessions) were considered important for yoga practice

Three findings (U) were combined to form this category, which highlighted the perceptions of people with arthritis regarding the positive influence of the environment of a yoga session. The availability of a safe, non-judgmental, supportive, and inclusive space in the yoga sessions was commonly cited as a major motivation to practice yoga for arthritis. One of them went for yoga therapy sessions and appreciated the "therapeutic" element in a one-to-one setting where the yoga therapist would pay close attention to individual needs and provide tailored modifications.

5b. Social connectedness in a group setting was perceived as a strong motivation for yoga practice

Five findings (U) comprised this category. People with arthritis expressed that practising yoga in groups helped them connect with others having arthritis, strengthened their social bonds and fostered a sense of community, which reduced feelings of isolation.

Discussion

This systematic review synthesised qualitative evidence on factors influencing yoga practice, with the categories within each synthesised finding offering insight into the barriers and facilitators to yoga practice in people living with arthritis. Six of the eight included studies met at least seven of the ten quality criteria, indicating moderate to high methodological quality. These factors related to (i) the anticipated and experienced impacts of yoga on physical well-being influenced yoga practice in people with arthritis; (ii) the levels of motivation and perceived impact on mental well-being influenced yoga practice in people with arthritis; (iii) the experience of mind-body benefits of yoga fostered a positive outlook on coping with arthritis and encouraged ongoing engagement with yoga practice in people with arthritis; (iv) engagement with yoga practice was influenced by individually determined factors affecting access to sessions, as well as by the structural characteristics of the sessions; and (v) a supportive social environment in yoga sessions, characterised by a welcoming space and meaningful connections, encouraged yoga practice in people with arthritis.

Overall, this review suggested that yoga can be a positive and empowering experience, articulating a range of facilitators to regular yoga practice, and therefore highlighting its potential as a complementary approach to arthritis treatment. Nevertheless, several important barriers were also identified in this review. A key concern was the apprehension among people with arthritis about yoga practice, as they thought yoga might be beyond their physical capabilities and could worsen their condition. Media portrayals often depict yoga as a physically intensive practice with a risk of injury, potentially discouraging yoga practice [48]. This review highlighted the need for future efforts to reduce fears surrounding yoga practice in people with arthritis.

Our review found that intrinsic motivations, e.g., self-efficacy, self-assurance, and self-confidence, can act as both barriers and facilitators to yoga practice in people living with arthritis. Low levels of intrinsic motivation were perceived as obstacles to yoga practice, whilst higher levels were perceived to facilitate it. Yoga practice was also perceived to enhance mental well-being, which in turn boosted intrinsic motivation, creating a positive self-sustaining cycle. This interconnected relationship highlighted the link between mental well-being and an individual's motivation to practice yoga for arthritis. This aligned with findings from a systematic review on physical activity (including a wide range of physical activity interventions, including yoga, suggesting that self-driven intrinsic motivations (e.g., self-compassion) could significantly enhance well-being and further encourage physical activity [49]. This review highlighted improvement in arthritis symptoms, particularly pain relief, as a key motivator for practising yoga in arthritis. A narrative review suggested that yoga may improve pain tolerance and alleviate pain perception [50]. Further, systematic reviews have shown that yoga may help reduce joint stiffness and pain and improve function in osteoarthritis [25–28, 51]. In our own previous systematic reviews and meta-analysis of yoga interventions for osteoarthritis and rheumatoid arthritis, we found quantitative evidence for improvements in outcomes including pain, function, and disease activity score [25, 26]. The present review builds on this by synthesising qualitative insights into how people with arthritis themselves experience and perceive yoga, thus complementing the clinical outcomes literature with patient-centred perspectives. Our review supported these findings, also noting that reduced feelings of anxiety and depression as a result of yoga practice were perceived to make it easier for people with arthritis to cope with the mental burden of the condition. This reinforced evidence that yoga positively impacts mental health in rheumatic diseases, including arthritis [52]. A novel insight from this review was the perceived interplay between mind and body in yoga practice, leading to a sense of mind-body (holistic) benefits. The findings suggest that yoga was not viewed as merely a physical activity but as a practice also contributing to emotional and mental well-being. These synergistic, interconnected, and holistic benefits were a key facilitator underpinning yoga practice in people with arthritis. Accordingly, people with arthritis reported a changed outlook on their condition, a restored sense of normalcy, and a feeling of empowerment to take control of their condition. This resonated with findings from a qualitative study on patients' perceptions of practising yoga to manage chronic pain, in which participants felt that yoga reframed their perceptions of living with it [53]. Therefore, the review emphasised the importance of recognising and promoting yoga as a holistic practice, encompassing physical poses, breathing practices, and meditation and relaxation practices to obtain overall benefits in arthritis.

In addition to health-related benefits, individually determined factors influencing access to yoga sessions, and several structural characteristics of the sessions were also perceived to influence yoga practice in people with arthritis. These included common barriers such as lack of time, financial constraints, and other responsibilities, similar to challenges reported in the general adult population [54]. While physical activity is essential for alleviating arthritis symptoms, people with arthritis can face particular barriers to staying active, poor adherence to exercise, limited guidance on injury prevention, and fears about exacerbating their condition [15, 55, 56]. These concerns can make it difficult to find a suitable form of physical activity [57]. Yoga may offer a valuable alternative, as it emphasises stretching,

strength, posture, balance, and allows for adjustable pace and intensity, ensuring both health benefits and safety [58].

This review found that the adaptability of yoga (e.g., using props) and the flexible pacing of sessions to accommodate arthritis-related needs and capabilities were key facilitators for yoga practice. This finding aligned with qualitative studies emphasising yoga's ability to be tailored to meet the evolving physical and mental health needs in specific health conditions, including arthritis [59–61]. Beyond the practice itself, our review also underscored the important characteristics of the yoga provider. People with arthritis valued empathetic yoga providers who encouraged acceptance of physical limitations, a finding echoed by qualitative studies exploring UK-based yoga providers' insights on arthritis treatment [60]. While our earlier qualitative study focused on yoga provider insights [60], the present review focuses on the voices of people with arthritis, offering a complementary view that can inform the design of more acceptable and sustainable yoga programmes. Additionally, yoga sessions delivered by knowledgeable and professionally trained yoga providers capable of adapting practices to meet arthritis-specific needs were considered essential for ensuring safety and encouraging participation [60].

The social environment of yoga sessions was another key facilitator of yoga practice, synthesised in this review. A safe, supportive, and inclusive space where people did not feel judged due to their physical limitations was perceived as crucial to encourage yoga practice. People with arthritis often desire social interaction but withdraw from social activities due to their symptoms, leading to isolation [62, 63]. Group-based yoga sessions were perceived to engender social support and reduce feelings of loneliness in people with arthritis, thus facilitating yoga practice. These review findings were consistent with prior research suggesting that the sense of community and connection fostered in group yoga settings reduces isolation and offers social support [60, 64].

Overall, our findings suggest that future research should consider clear patient education strategies that highlight the adaptability of yoga, emphasise its physical, mental, and social benefits, and include practical guidance for safe home practice. Tailored handouts, using arthritis-specific modifications, could help reassure patients and increase accessibility across sociodemographic groups. Yoga providers delivering yoga to people living with arthritis should receive training on safety considerations, including yoga practices that may be contraindicated for individuals with arthritis, strategies to modify poses for varying levels of severity and comorbidities, and communication tips to boost people's confidence in sustaining long-term practice. In addition, structured group support mechanisms, such as small class sizes and opportunities for people to share progress, may help sustain yoga practice and reduce isolation.

To our knowledge, this is the first systematic review to synthesise the barriers and facilitators to yoga practice in people with arthritis. The review followed JBI and PRISMA guidelines to ensure the methodology was robust. At least two independent reviewers were involved at each step to enhance credibility and minimise researcher and selection biases, and a record of decisions regarding how the synthesised findings and categories were created was maintained to further strengthen reliability. In line with JBI guidance, we adopted a reflexive approach by openly considering how our professional and social backgrounds and theoretical perspectives might shape the interpretive process. This reflexive stance was maintained throughout study selection, data extraction, and synthesis, to enhance transparency and minimise the influence of assumptions on the findings. Although our search strategy did not apply date or language restrictions and included grey literature sources (e.g., theses, dissertations, conference abstracts), it is possible that relevant unpublished studies or qualitative research published in other languages could have been missed. Consequently, the risk of publication and language bias cannot be completely eliminated. Such bias may have influenced the range of studies identified and the balance of qualitative insights represented in this review. Also, access to the EThOS database was not possible due to an ongoing cyber-attack, limiting the ability to retrieve relevant UK doctoral theses for this review. Only eight studies met our inclusion criteria, reflecting the limited availability of qualitative evidence in the evolving area of yoga and arthritis research. The lack of detail in the included studies limited the ability to fully assess their methodological quality, which may reduce the trustworthiness of the findings. Most studies had small sample sizes, involved predominantly women, and focused on osteoarthritis or rheumatoid arthritis, but not on other types of arthritis. This limits the generalisability of findings, particularly to male participants, people with other types of arthritis, different age groups, and people with comorbidities. All included studies were conducted in high-income Western countries (USA, UK, and New Zealand). This may not capture cultural and socio-economic insights on yoga, which is particularly important given its origins in South Asia, where it is formally recognised and widely practised, and the growing interest in yoga within low- and middle-income countries. Gender differences are also noteworthy, as existing evidence suggests women are more likely than men to practise yoga, underscoring the need to explore barriers and facilitators to yoga in more diverse cultural settings, socio-economic contexts, and gender groups to ensure that interventions are inclusive and globally relevant. At the same time, the concentration of studies

in comparable high-income contexts may be viewed as a strength, as it enhances the transferability of our findings across these settings. This reflects what has been described as a multi-context qualitative review design, in contrast to context-specific syntheses [65]. In addition, reporting standards varied across studies. Few addressed reflexivity (i.e., how researchers' own positions and assumptions may have influenced the research process) or used strategies such as member checking to verify participants' accounts. These gaps raise questions about the credibility and transparency of findings. Furthermore, the included studies were short-term interventions, which restricts understanding of long-term adherence to yoga and the balance of its benefits and harms over time. Future research should therefore recruit more diverse populations, ensure clear reporting of reflexivity and verification, and explore yoga practice across cultural, socio-economic, and gender groups. Future studies should also explore the long-term sustainability of yoga practice for arthritis treatment, given the chronic nature of the condition.

Conclusion

This review synthesised both barriers and facilitators to yoga practice in people with arthritis. Within the included studies, facilitators were somewhat more frequently reported than barriers, in line with the possibility that yoga could be a valuable addition to arthritis treatment. Key barriers included fear of injury, lack of motivation, and limited accessibility to yoga sessions. Physical, mental, and mind-body benefits of yoga were prominent facilitators. Further, yoga's adaptability, availability of professionally trained and empathetic yoga providers, and supportive group environments also encouraged yoga practice in people with arthritis. Addressing these barriers and enhancing the facilitators can support the successful implementation of future yoga interventions in arthritis treatment.

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Author contributions IB conceptualised and designed the systematic review with inputs from SL and KC. IB and PE conducted study screening, assessed the methodological quality of the included studies, and performed data extraction. All authors were involved in data synthesis. IB wrote the first draft of the manuscript, and all the authors contributed significantly to its revision. All authors read and approved the final manuscript and take full responsibility for the integrity and accuracy of all aspects of the work.

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Data availability The data underlying this article are available in the article and its online supplementary material.

Declarations

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.

Disclaimer Neither commercial agencies were involved nor artificial intelligence (AI) was used in the drafting, writing, editing, or revision of the manuscript. The authors confirm that all content was prepared, reviewed, and approved by the authors themselves. No part of this manuscript is copied or published elsewhere, in whole or in part.

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