Evidence-Based Complementary and Alternative Medicine

Mind-Body Interventions and the Management of Chronic Non-Malignant Pain

Lead Guest Editor: Shirley Telles
Guest Editors: Rima Dada and Karen Sherman

Mind-Body Interventions and the Management of Chronic Non-Malignant Pain

Evidence-Based Complementary and Alternative Medicine

Mind-Body Interventions and the Management of Chronic Non-Malignant Pain

Lead Guest Editor: Shirley Telles
Guest Editors: Rima Dada and Karen Sherman

Contents

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 9467002, 10 pages
https://doi.org/10.1155/2022/9467002

Review Article

Effects of Acupuncture, Moxibustion, Cupping, and Massage on Sports Injuries: A Narrative Review

Haoyu Zhang,[1,2] **Mengya Zhao**,[3] **Zugui Wu**,[2] **Xinna Wang**,[4] **Yong Jiang**,[1,2] **Jiabin Liang**,[1,2] **and Hanwei Chen**[1]

[1]*Guangzhou Panyu Central Hospital, Guangzhou 511400, China*
[2]*Guangzhou University of Chinese Medicine, Guangzhou 510405, China*
[3]*Guizhou University of Traditional Chinese Medicine, Guiyang 550000, China*
[4]*Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun 130000, China*

Correspondence should be addressed to Hanwei Chen; docterwei@sina.com

Received 12 October 2021; Revised 17 March 2022; Accepted 14 May 2022; Published 28 May 2022

Academic Editor: Shirley Telles

With the evolution of society, an increasing number of people have realized the importance of sports on human health. However, participation in sports is a double-edged sword as improperly exercising can lead to injury. Many athletes and patients with sports injuries choose traditional Chinese medicine (TCM) when modern medicine fails to relieve their musculoskeletal symptoms. TCM is a splendid legacy of Chinese civilization whose therapies are effective, economical, and convenient, with some administration by trained patients at home. This review analyzes the literature on the application of acupuncture, moxibustion, massage, and cupping in sports injuries to provide novel ideas for the application of TCM in sports medicine.

1. Introduction

Traditional Chinese medicine (TCM) is the accumulation of experience and theoretical sublimation of the toiler in ancient China in the fight against diseases. It is a diagnosis and treatment technology that has been gradually developed through long-term medical practice under ancient dialectical materialism. Ancient doctors integrated *Taichi*, *Baduanjin*, *Wuqinxi*, and other forms of exercise into sports medicine which became a part of TCM health preservation [1]. Acupuncture, moxibustion, cupping, and massage also have unique effects on sports and sports injuries. In addition to treating diseases, they can prevent diseases and maintain health. Moreover, these therapies are part of complementary and alternative medicine.

Sports injuries usually occur during competitions, training courses, or fitness sports [2]. In TCM, a sports injury is known as an "injury of the muscle and tendon," and its pathogenesis includes damaged meridians and blocked blood vessels, resulting in sudden spasms, swelling, and pain. The goal of treatment is "relieving spasm and pain, dispersing stasis, and removing blood stasis." The *Lingshu Jing* has long proposed that treatment of sports injuries should "take pain as acupoints." Many kinds of TCM external therapies are implemented in accordance with this principle [3]. The impact of sports injuries is profound; these injuries prevent athletes from participating in regular training and competitions, hinder sports performance, and even shorten or damage professional careers. For ordinary sports lovers, sports injuries can affect health, studies, and work and can cause adverse psychologic effects, hindering the normal development of a sport [4]. Moreover, sports medicine diseases occur frequently, causing a severe economic burden in regard to not only medical expenses but also one's personal life. Therefore, the exploration of low-cost, high-efficiency, and cost-effective treatments is very important for both individuals and society, and TCM therapies have a wide range of applications in the treatment of sports medicine diseases due to their unique advantages.

Many active patients and athletes use TCM therapies when modern medicine fails to relieve their musculoskeletal symptoms. Athletes often lead the charge in exploring these

alternative treatments. For example, C.T. Moorman III, MD, director of sports medicine at the University of Maryland School of Medicine in Baltimore, says athletes at the university have been "seeking out everything from hyperbaric oxygen treatment to acupuncture to manual medicine, all of which we would consider outside the realm of traditional allopathic medicine." In addition, patients may seek alternative therapies when experiencing conditions such as fibromyalgia, back pain, and lateral epicondylitis because they feel frustrated with modern medicine's inability to relieve their symptoms [5]. The following are several popular TCM external therapies used on athletes: acupuncture, moxibustion, cupping, and massage.

2. Acupuncture

Acupuncture is an ancient therapy based on the theory of meridians and acupoints of TCM. Recently, it has been increasingly used in sports injuries worldwide. It involves placing thin needles at specific anatomic points to redirect the body's energy flow, known as Qi (pronounced "chee"), to cure diseases [5]. It includes acupuncture, electroacupuncture (EA), needle knife, acupoint injection, ear acupuncture, and skin acupuncture. From the TCM perspective, it balances Yin and Yang, regulates Qi and blood, dredges the meridians, promotes blood circulation, and relieves pain. From the modern medicine perspective, it eliminates inflammatory tissue adhesion and relieves swelling and pain to cure sports injuries [6]. Furthermore, acupuncture can mobilize positive factors in the body to strengthen anti-inflammation, increase analgesic and anti-shock effects, and relieve spasms, thereby enhancing the body's defense mechanisms and disease resistance [4]. The World Health Organization's latest global traditional medicine survey results show that acupuncture therapy is recognized by 113 countries worldwide, ranking first in traditional medical treatment methods. Electroacupuncture is a treatment system based on the theory of TCM meridians, combining acupuncture and massage with contemporary technology. As a common treatment method for muscle strains, it has been affirmed and written in sports medicine monographs. It treats the pain at the site of injury, mainly through the neurohumoral mechanism to stimulate the brain to produce more analgesic substances such as 5-tryptamine, endogenous opioid (OLS) kephalin, and enkephalin, so as to relieve the pain caused by the muscle strain [7].

Multiple studies show that acupuncture is used to treat a variety of sports injuries (Table 1). It can be used for acute injury, chronic impairment, and convalescence. For example, acupuncture at the Xiaojie point combined with tendon-regulation manipulation achieves an apparent analgesic effect and detumescence on ankle sprains [8]. During the postoperative rehabilitation of acute closed Achilles tendon rupture, contralateral acupuncture combined with rehabilitation training can improve ankle plantar flexor function [9]. Acupuncture combined with massage therapy for nonfractured ankle injuries can promote the recovery of ankle joint function [10, 11]. Achilles tendinopathy, characterized by pain, swelling, and impaired performance, is one of the most common overuse injuries in elite and recreational athletes. Acupuncture intervention decreases pain and improves activity in patients compared with eccentric exercises [12]. In addition, acupuncture might be a therapeutic alternative for shoulder impingement syndrome, chronic shoulder pain, chronic plantar fasciitis, chronic temporomandibular disorder, low back pain in athletes, tennis elbow, and supraspinatus tendinitis under proper treatment control [13–21].

Many experiments have proven the effectiveness of acupuncture in sports injuries (Table 2). Inoue et al. examined the effect of EA on early postrupture tendon repair in a rat model of Achilles tendon rupture using histological and mechanical evaluations. They found that the application of EA increased total cell counts, transforming growth factor-β1 (TGF-β1), and basic fibroblast growth factor (b-FGF) positive cell counts, as well as the mechanical strength of the repaired tendon. These results suggest that EA promotes Achilles tendon repair and could be an effective complementary treatment for tendon rupture [22]. Yu et al. used a rat model of myofascial pain syndrome and found that transcutaneous EA point stimulation treatment produces an analgesic effect by inhibiting the expression of phosphorylated c-Jun N-terminal kinase [23]. Li et al. found that EA inhibited osteoarthritis-induced pain by enhancing spinal 5-HT2A/2C receptor activity [24].

In summary, for sports injuries, acupuncture alleviates fatigue, relieves pain, promotes recovery of tissue function, reduces the use of drugs, and has almost no side effects providing a viable option for patients and athletes. However, acupuncture should be performed by a qualified acupuncturist according to the condition; otherwise, it is prone to undesirable consequences such as needle dizziness.

3. Moxibustion

Moxibustion is a traditional Chinese method that utilizes heat generated by burning moxa to stimulate acupoints. The technique consists of lighting a moxa stick and bringing it close to the skin. The intensity of moxibustion will be just below the individual tolerability threshold [29]. Unlike drug treatment, moxibustion rarely causes side effects but can effectively relieve a patient's pain symptoms and improve overall function [30]. Moxibustion conducts heat from the moxa local skin surface to deep tissues, and the heat sensation spreads around the moxa point [29]. From the TCM perspective, moxibustion is thought to regulate Qi and blood, tonifying healthy Qi to eliminate pathogenesis by means of warming [31]. It can also dispel wind and cold, activate meridians, and relieve swelling and pain. Moxibustion relies on the medicinal power of wormwood. Because wormwood is a rare medicine in TCM that can pass through twelve meridians, the ancients, after years of exploration, finally set wormwood as the main raw material for moxibustion [32]. From the modern medicine perspective, moxibustion produces a warming effect. The volatile oil produced after ignition combined with infrared radiation provides energy for cell regeneration, accelerates wound healing and repair, and promotes the proliferation of blood

Table 1: The application of acupuncture for various diseases.

Condition	Intervention	Acupoints	Comparison	Primary outcomes measure	Effective rate/ result/conclusion	Reference
Ankle sprain	Acupuncture plus tendon-regulation manipulation	Xiaojie	Tendon-regulation manipulation	Symptom score such as swelling, motor dysfunction, and total score	100%	[8]
Acute closed Achilles tendon rupture	Contralateral acupuncture plus rehabilitation training	ST36, GB34, BL57, and KI3	Rehabilitation training	PFPT, PT/BW, and TW	94.6%	[9]
Nonfracture ankle injury	Acupuncture and massage plus routine therapy	ST41, GB40, GB39, SP5, and KI3	Routine therapy: anti-infection and pain relief	Motor dysfunction score	96.08%	[10]
Nonfracture ankle injury	Acupuncture and massage plus routine therapy	PC7, GB40, Ashi points, GB34, and GB39	Routine therapy: eat painkillers or undergo surgery	Symptom score: swelling and pain	96.7%	[11]
Chronic Achilles tendinopathy	Acupuncture	Ashi points	Eccentric exercises	VISA-A and VAS	Acupuncture improved pain and activity compared with eccentric exercises	[12]
Shoulder impingement syndrome	Acupuncture	LI15, LI16, SJ14, and SI9	Acupuncture at sham points	VAS and UCLA questionnaire	Acupuncture is a safe, reliable technique to achieve significant results	[13]
Chronic shoulder pain	Acupuncture (verum)	Ashi points; local and distal points according to the channel and the pain	Sham acupuncture (sham); conventional conservative orthopaedic treatment (COT)	The 50% responder rate for pain was measured on a VAS	Results were significant for verum over sham and verum over COT	[14]
Chronic shoulder pain	Trigger point acupuncture (TrP)	Myofascial trigger point in neck and superior limb	Sham (SH) acupuncture	Pain intensity (VAS) and shoulder function (constant-Murley score: CMS)	Compared with SH, TrP appears more effective	[15]
Chronic shoulder pain	Contralateral manual acupuncture (MA)	SJ3, SI3, LI11, and ST38	Conventional orthopaedic therapy	VAS	Contralateral acupuncture is beneficial	[16]
Chronic plantar fasciitis	EA plus conventional treatments	Ashi points	Conventional treatments: stretching exercise, shoe modification, and rescue analgesics	VAS and foot function index (FFI)	Patients in the EA group obtained higher success rates than those in the control group (80%,13.3%, resp.)	[17]
Chronic temporomandibular disorder (TMD)	Laser acupuncture plus reversible occlusal splint therapy (EG)	ST6, SI19, GB20, GB43, LI4, and LR3	Placebo laser associated with occlusal splint therapy (CG)	VAS	Laser acupuncture is effective, secure, and noninvasive	[18]
Low back pain in athletes	EA	ST36, BL25, GB30, BL40, and GB34	Sham EA; pharmacological treatment (diclofenac sodium)	Pain score (VAS) and a serum level of catecholamines quantified by enzyme-linked immunosorbent assay	EA relieves pain, ameliorates inflammation, and protects muscle tissue	[19]

Table 1: Continued.

Condition	Intervention	Acupoints	Comparison	Primary outcomes measure	Effective rate/ result/conclusion	Reference
Tennis elbow	Needle knife (A)	Ashi points	Trigger point injection (B); A plus B (C)	MPQ and VAS	Group A has the same curative effect as group C, both better than group B	[20]
Supraspinatus tendinitis	EA plus extracorporeal shock wave	GB21, SI12, LI14, SI10, LI15, SJ14, SI9, and Ashi points	Extracorporeal shock wave	VAS	94.74%	[21]

Note. BW: body weight; EA: electroacupuncture; PFPT: affected-side plantar flexion peak torque; MPQ: McGill Pain Questionnaire; PT: peak torque; TW: total work; VAS: visual analogue scale; VISA-A: the validated Victorian Institute of Sports Assessment-Achilles; ST: yangming stomach channel of foot; GB: shaoyang gallbladder channel of foot; BL: taiyang bladder channel of foot; KI: shaoyin kidney channel of foot; SP: taiyin spleen channel of foot; PC: jueyin pericardium channel of hand; LI: yangming large intestine channel of hand; SJ: shaoyang sanjiao channel of hand; SI: taiyang small intestine channel of hand; LR: jueyin liver channel of foot.

Table 2: The experimental research published on acupuncture, moxibustion, and massage.

Condition	Intervention	Animals	Models	Results	Conclusion	Reference
Achilles tendon rupture	EA	Wistar rats	Achilles tendon rupture	TGF-β1↑ b-FGF ↑	EA may be a useful therapy for promoting tendon repair	[22]
Myofascial pain syndrome	TEAS	Rats	Myofascial pain syndrome	p-JNK↓	TEAS therapy may produce an analgesic effect by inhibiting the expression of p-JNK	[23]
Osteoarthritis	EA	Rats	Osteoarthritis pain	5-HT2A/C receptor activity↑	EA inhibits osteoarthritis-induced pain by enhancing activity of spinal 5-HT2A/2C receptor	[24]
Osteoarthritis	Moxibustion	Rats	Inflammatory joint disease	TNF-α↓ IL-1b↓ Bcl-2↑	The protective effect of antiapoptotic is one of the key mechanisms for an ambient moxa smoking environment	[25]
Arthritis	Moxibustion	Dilute brown nonagouti mice	Collagen-induced arthritis (CIA)	Phospho-Erk1/2↓ Myostatin↓ GF-1↑	Moxibustion influences muscle regeneration in the CIA mouse model	[26]
Muscle damage	Massage plus acupuncture	Rats	Exercise-induced muscle damage (EIMD)	CK↓	Massage combined with acupuncture may reduce CK and have a protective effect on EIMD	[27]
Sciatic nerve injury	Massage	Rats	Neurons of sciatic nerve injury	NF-M↑	Massage therapy improved the motor function by the expression of spinal proteins NF-M	[28]

Note. 5-HT2A/C: 5-hydroxytryptamine 2 A/C; b-FGF: basic fibroblast growth factor; Bcl-2: B-cell lymphoma-2; CK: creatine phosphokinase; EA: electroacupuncture; IGF-1: insulin-like growth factor 1; IL-1b: interleukin 1 beta; NF-M: neurofilament proteins-M p-JNK: phosphorylated c-Jun N-terminal kinase; TEAS: transcutaneous electrical acupuncture point stimulation; TGF-β1: transforming growth factor-β1; TNF-α: tissue necrosis factor-alpha.

vessels and vascular endothelial cells in tissues [33]. Studies show that the radiation energy spectrum produced by moxibustion during combustion is infrared, while near-infrared is the main component. The penetration depth of near-infrared rays through the skin is deeper than that of far-infrared rays, up to 10 mm, and is absorbed by the body. Near-infrared rays can stimulate hydrogen bonds at human acupuncture points, produce stimulated coherent resonance absorption effects, and transmit the energy required by human cells through the neurohumoral system. The infrared radiation generated during moxibustion can provide the necessary energy for cell metabolic activities and immune function and can also provide activation energy to injured cells [32].

Moxibustion is used to treat various sports injuries (Table 3). It is most often used in chronic impairment and convalescence. For instance, moxibustion is safe and effective for chronic knee osteoarthritis (KOA) [34]. Mild moxibustion relieves pain and swelling degree of obsolete collateral ligament injury of the interphalangeal joints [35]. Heat-sensitive moxibustion reduces pain and improves physical activity in patients with KOA [36]. Furthermore, moxibustion is effective for acute tennis elbow and injured medial collateral ligaments [37, 38]. Zhang et al. found that moxa smoke suppresses the inflammatory effects of TNF-α and IL-1b and enhances the antiapoptotic effects of Bcl-2 [25]. Kim et al. confirmed that direct administration of moxibustion at BL 23 and ST 36 influences muscle

Table 3: The application of moxibustion for various diseases.

Condition	Intervention	Acupoints	Comparison	Primary outcome measure	Effective rate/results/ conclusion	References
Chronic knee osteoarthritis pain	Moxibustion	ST35 and Ashi point	Sham moxibustion	Osteoarthritis index (WOMAC VA 3.1) criteria	Moxibustion could relieve pain effectively and improve function	[34]
Collateral ligament injury of interphalangeal joints	Mild moxibustion	Affected digital joints	Specific electromagnetic spectrum	VAS for pain	83.4%	[35]
Osteoarthritis	Heat-sensitive moxibustion (HSM)	SP9, GB34, ST34, and SP10	CM and CI with sodium hyaluronate	GPCRND-KOA	It provided some evidence for the superiority of HSM	[36]
Acute tennis elbow	Ginger moxibustion and painkiller	Ashi points	Painkiller	VAS for pain	94.59%	[37]
Collateral ligament injury of knee joint	Heat-sensitive moxibustion	SP10, ST34, and ST35	Surgery	VAS for pain	VAS scores of two groups had statistical significance ($P < 0.01$)	[38]

Note. CM: conventional moxibustion; CI: conventional injection; GB: shaoyang gallbladder channel of foot.; GPCRND-KOA: guiding principle of clinical research on new drugs in the treatment of KOA; KOA: knee osteoarthritis; SP: taiyin spleen channel of foot; ST: yangming stomach channel of foot; VAS: visual analogue scale.

regeneration in the collagen-induced arthritic mouse model [26]. Many studies show that moxibustion promotes recovery from fractures, skeletal muscle injuries, and ligament and tendon injuries [38–41].

In addition, moxibustion is economical and easy to operate; patients can operate it themselves after professional training. The moxa sticks are inserted into the moxibustion box, and the patients can complete the operation of moxibustion alone. However, patients must strictly follow the doctor's advice with regard to body parts and the duration of moxibustion. Otherwise, it is easy to produce undesirable consequences such as burns. In China, moxibustion is also a part of health maintenance, and many people use it to prevent diseases and maintain health. In summary, moxibustion has a significant therapeutic effect and is simple to use, low in cost, and has almost no side effects.

4. Massage

Chinese massage (referred to as *Tuina*) is an ancient therapy that has sparked renewed interest, particularly in sports medicine. It involves a wide range of technical manipulations performed by a practitioner's finger, hand, elbow, knee, or foot applied to muscles or soft tissues at specific body locations [42]. Massage manipulation can effectively regulate the body's nervous, endocrine, and immune systems through sensory stimulation such as touch and temperature. It is delivered to the central nervous system through afferent nerve fibers in the form of nerve impulses and complex electrical, chemical, and tissue metabolic changes [43]. Studies confirmed that endorphins, acetylcholine, serotonin, and catecholamine are all related to massage analgesia [44]. From the TCM perspective, massage regulates Qi and blood and dredges the meridians and collaterals. From the modern medicine perspective, massage is indicated in sports therapy when inflammation fails to resolve, healing is delayed, or tissue drainage or perfusion appears inadequate. Massage helps to reduce pain and restore regular muscle activity, promoting the healing of injured muscles, ligaments, and tendons, thus, reestablishing normal function [6, 45, 46]. The use of massage manipulations results in different mechanical effects and generates energy by performing work for a certain period through force. With this, the local damaged tissue gradually recovers from a state of acute spasm to a state of relaxation. This rhythmic contraction of muscle fibers and relief of spasms can effectively treat pain symptoms [47]. At the 1996 Atlanta Olympics, massage was included in official medical services for the first time.

The American Massage Therapy Association of Evanston, Illinois, certifies sports massage therapists through a written and practical exam [5]. As a safe, low-technology therapy, massage is a valuable treatment option for sports injuries (Table 4). Massage is often used for chronic impairment and convalescence. When combined with other therapies, it has better clinical efficacy in patients with KOA [48, 49]. Massage manipulation is an appropriate method to treat intervertebral instability [50]. Moreover, massage therapy is also effective for plantar fasciitis, knee stability, and functional recovery [51, 52]. When combined with acupuncture, it reduced creatine phosphokinase and had a protective effect in rats with exercise-induced muscle damage [27]. Massage therapy also improved the motor function of rats with sciatic nerve injury by increasing the expression of neurofilament protein M in the spinal cord [28].

Massage can also relieve exercise fatigue [53], but timing is an essential factor. Before competitions, gentle massage and language induction can eliminate excessive tension in athletes, thus alleviating fatigue. After competition, massage is best performed after a bath or before going to bed. Because of sweat and salt on the skin after exercise, it is not appropriate to massage at this time [1]. Eliminating tension and relieving muscle fatigue are beneficial for preventing sports injuries. Massage has high safety and low side effects.

Table 4: The application of massage for various diseases.

Condition	Intervention	Area	Comparison	Primary outcomes measure	Effective rate/ results/conclusion	References
KOA	Massage plus CMM footbath fumigation and washing	Around the popliteal fossa and knee	Oral administration of meloxicam	Lysholm knee score scale (LKSS)	Intervention group had better clinical efficacy	[48]
KOA	Aromatherapy massage with lavender essential oil	Knee	Massage with almond oil; control (without massage)	VAS for pain	Intervention group was found effective in relieving pain	[49]
Lumbar intervertebral instability	Massage	Waist	Exercise	JOA score and Oswestry disability score	86.7%	[50]
Knee stability and functional recovery	CMF and massage therapy (A)	Around the knee	Normal rehabilitation therapy group	The change in width of ligament tunnel in femur and tibia	A therapy improved knee function earlier	[51]
Plantar heel pain syndrome (PHPS)	DMS	Posterior calf muscles	USS	Functional status (FS)	DMS therapy was significantly more effective than USS	[52]

Note. CMM: Chinese materia medica; DMS: deep massage therapy and neural mobilization with a self-stretch exercise program; KOA: knee osteoarthritis; JOA: Japanese Orthopaedic Association; CMF: Chinese medicine fumigation; USS: ultrasound therapy to the painful heel area with the same self-stretch exercises; VAS: visual analogue scale.

It is a therapy that patients themselves can perform. Patients can choose specific muscles or acupoints according to the condition and doctor's advice for a simple massage. At the same time, massage too soon after an injury can cause secondary bleeding of the tissue. Gentle manipulation should be used for 5 to 7 days after injury, and medium-intensity manipulation for more than 15 days. The massage should be performed perpendicular to the direction of the injured tissue fibers [54]. However, overmassage can lead to the aggravation of the physical condition, which should be avoided.

5. Cupping

In the 2016 Olympic Games, marks of blood stasis on the back of swimmer Michael Phelps gained attention. This TCM therapeutic modality, cupping, is used by many athletes and coaches. Cupping therapy has been used as a traditional medical technology for more than a thousand years. Cupping therapy is used for sports injuries such as congestion, swelling, and spasms and plays an important role in analgesia and elimination of the cause [55]. In major sports events, cupping is used as an emergency response to acute sports injuries. In injury treatment, cupping speeds up muscle excretion, which is beneficial for emergency treatment of acute injuries.

Cupping is a significant component of complementary and alternative medicine worldwide, as it is prevalent in many countries, especially China, Korea, Japan, Saudi Arabia, and Egypt [56, 57]. It is based on sucking traction of the skin and hypoderm, which is applied to a predefined skin area or acupoint, and negative pressure (compared to atmospheric pressure) is generated mechanically (pumping) or thermally (cooling heated air), withdrawing the trapped air from under the cup [58, 59]. As a result, the cupping area becomes red and warm due to increased perfusion. "Dry cupping" requires application of negative pressure on a specific skin area, while "wet cupping" requires a needle under the cup, which results in slight bleeding. From the TCM perspective, cupping promotes Qi and relieves pain, promotes blood circulation, removes blood stasis, dispels cold, and removes dampness. From the modern medicine perspective, it increases skin blood flow, changes biomechanical properties of the skin, and reduces inflammation [57]. Cupping promotes hemolysis through negative pressure to increase histamine production, which enhances the physiological function of organs [60].

Cupping therapy is helpful in treating many diseases (Table 5). It can be used for acute injury, chronic impairment, and convalescence. There is increasing evidence to suggest that cupping is effective in improving various pain conditions. For example, dry cupping combined with exercises was effective for patients with plantar heel pain, ankle dorsiflexion, range of motion, and plantar flexor strength [61]. Cupping combined with McKenzie therapy improves waist flexion and extension in patients with low back pain [62–65]. Cupping is also useful in myofascial pain syndrome, shoulder pain, and chronic nonspecific neck pain [66–70]. The mechanism of action of cupping therapy only recently became clear. Guo et al. put forward the theory of immunomodulation and believe that the mechanism of action of cupping is the same as that of acupuncture. The theory of immunomodulation suggests that changing the microenvironment through skin stimulation could be converted into biological signals to activate the neuroendocrine-immune system, thereby producing therapeutic effects [71].

From the clinician's perspective, the risks of dry cupping are low. Typical side effects, such as hematoma of the skin under the cupping area, are mild and transient. In addition, the suction cupping method is a modernized technology that fastens a suction cup tightly on the skin while the air in the cup is extracted with the suction device to produce negative

Table 5: The application of cupping for various diseases.

Condition	Intervention	Area	Comparison	Primary outcomes measure	Effective rate/conclusion	References
Plantar heel pain	Dry cupping plus exercises	Calf muscle	Stretching exercises and plantar fascia and ankle dorsiflexion exercises	VAS, PPT, and PSFS	Intervention group was superior to only exercises in pain and plantar flexor strength	[61]
Low back pain	Cupping plus McKenzie therapy	DU2, BL40, and Ashi points	McKenzie therapy	VAS	95.8%	[62]
Low back pain	Moxibustion and cupping plus medium-frequency pulse	Waist	Medium-frequency pulse	The degree of low back pain	97.62%	[63]
Low back pain	Control group plus cupping	Bladder meridian	Oral analgesics and external application of the Chinese medicine	VAS	95%	[64]
Low back pain	Acupuncture and cupping plus microwave	Bladder meridian	Microwave treatment	The degree of low back pain	94%	[65]

Note. PPT: pressure pain threshold; PSFS: patient-specific functional scale; VAS: visual analogue scale.

pressure. Because its operation is simple and safe and has few adverse effects, it is very suitable for home operation. However, cupping has contraindications, which should be avoided when operating at home.

6. Summary and Future Prospects

Combined with the principles of McMurray and Packer in the development of the cardiovascular drug treatment process, the application of a new treatment scheme should have the following characteristics. First, the new scheme should be applied independently to obtain a therapeutic effect. Second, it should be effective in the initial application at a small dose. Third, compared with the original dosage of essential treatment drugs, the new scheme should be more effective than the original. Fourth, the new scheme should improve overall security. Fifth, after a short-term assessment of the disease, it should be added to the initial treatment [72].

TCM therapies have significant advantages in the treatment of sports injuries. Moreover, according to the TCM philosophy of "preventive treatment of disease," it is also important to prevent sports injuries. Acupuncture, moxibustion, massage, and cupping are often used for this purpose. Massage and cupping are commonly used in sporting events such as the Olympics. The Jamaican runner, Usain Bolt, received a massage before every training session, including a 60-minute massage before each Olympic competition, to improve his physical condition. Massage enhances the ligament and joint flexibility, increases muscle strength, improves an athlete's action response and self-control ability, forms a positive psychological state, and improves human body functions to prevent sports injuries. Different massage techniques should be selected based on functional states, sports, climate, and other factors. The American swimmer, Michael Phelps, utilized cupping. Circular marks on his shoulders and back were often seen during Olympic competitions [73].

It has been proven that these therapies are convenient and economical medical means to treat sports injuries with a short course and immediate curative effect. On the one hand, moxibustion, cupping, and massage as self-help strategies administered by trained patients provide an exciting field for future research. This may reduce costs and be easily learned and performed. On the other hand, current evidence provides a scientific rationale to include moxibustion, cupping, acupuncture, and massage as nonpharmacological treatment tools as part of a multimodal treatment strategy for sports injuries, which may help reduce the use of medications. Although most patients will use alternative therapies to treat sports injuries, most of these therapies are not included in the relevant disease guidelines. More high-quality studies are needed to change the current situation.

How to effectively develop and apply the time-honored treasures of TCM to sports medicine is still a problem that many doctors and researchers need to explore more actively. Combining moxibustion, cupping, acupuncture, massage, and other modern therapies in the field of sports medicine to prevent and treat acute and chronic injuries is imperative, thereby promoting TCM in the field of sports medicine.

Data Availability

The data used to support the findings of this study are included within the paper.

Conflicts of Interest

All the authors declare that they do not have any conflicts of interest.

Authors' Contributions

Hanwei Chen contributed to the original draft and took responsibility for the integrity of the final version of the paper. Haoyu Zhang and Mengya Zhao collected the

references and drafted the paper. Zugui Wu, Xinna Wang, Jiabin Liang, and Yong Jiang revised the paper. All authors have read and approved the final version of the paper. Haoyu Zhang and Mengya Zhao contributed equally to this work.

Acknowledgments

This work was supported by the Science and Technology Program of Panyu (Nos. 2019-Z04-07, 2019-Z04-35, 2019-Z04-84, and 2020-Z04-054) and the Science and Technology Project of Guangzhou Health Commission (No. 20211A011114).

References

[1] C. Wang and H. Zhang, "Application of traditional Chinese medicine in sports field," *Asia-Pacific Traditional Medicine*, vol. 13, no. 15, pp. 64–67, 2017.

[2] S. Rahim, F. Rahim, K. Shirbandi, B. B. Haghighi, and B. Arjmand, "Sports injuries: diagnosis, prevention, stem cell therapy, and medical sport strategy," *Advances in Experimental Medicine & Biology*, vol. 1084, pp. 129–144, 2018.

[3] H. Yu, "Advantages of common external therapy in TCM in acute sports injuries," *Hubei Sports Science*, vol. 39, no. 4, pp. 327–330, 2020.

[4] P. Chen, "Research of acupuncture for sports injury," *Sports World (Scholarly)*, vol. 36, no. 5, pp. 60–62, 2007.

[5] J. White, "Alternative sports medicine," *The Physician and Sportsmedicine*, vol. 26, no. 6, pp. 92–105, 1998.

[6] B. Zhang and E. Lei, "Research progress of acupuncture and massage for soft tissue injuries caused by sports," *Journal of Marketing Theory and Practice*, vol. 33, no. 11, pp. 1756–1758, 2020.

[7] X. An, "Electroacupuncture for the treatment of muscle strain in athletes," *Journal of Shanghai University of Sport*, vol. 39, no. 4, pp. 53–55 + 65, 1997.

[8] W. B. Du, G. A. Bao, and R. F. Quan, "Impacts on analgesia and detumescence in ankle sprain treated with acupuncture at Xiaojie point combined with tendon-regulation manipulation," *Zhongguo Zhen Jiu*, vol. 34, no. 7, pp. 647–650, 2014.

[9] D. Zhang, X. Ye, X. Zhang, and W. Zhang, "The application of contralateral acupuncture for rehabilitation after acute closed achilles tendon rupture," *Zhongguo Zhen Jiu*, vol. 37, no. 3, pp. 237–241, 2017.

[10] Y. Li, "Clinical observation on acupuncture and massagethe for non-fracture ankle joint injury," *Inner Mongolia Journal of Traditional Chinese Medicine*, vol. 39, no. 9, p. 144 + 152, 2020.

[11] J. Lai, "Clinical observation on acupuncture and massagethe for non-fracture ankle joint injury," *Guangming Journal of Chinese Medicine*, vol. 34, no. 22, pp. 3470–3472, 2019.

[12] B. M. Zhang, L. Zhong, S. Xu, H. Jiang, and J. Shen, "Acupuncture for chronic Achilles tendnopathy: a randomized controlled study," *Chinese Journal of Integrative Medicine*, vol. 19, no. 12, pp. 900–904, 2013.

[13] J. C. Rueda Garrido, J. Vas, and D. R. Lopez, "Acupuncture treatment of shoulder impingement syndrome: a randomized controlled trial," *Complementary Therapies in Medicine*, vol. 25, pp. 92–97, 2016.

[14] A. F. Molsberger, T. Schneider, H. Gotthardt, and A. Drabik, "German Randomized Acupuncture Trial for chronic shoulder pain (GRASP)—a pragmatic, controlled, patient-blinded, multi-centre trial in an outpatient care environment," *Pain*, vol. 151, no. 1, pp. 146–154, 2010.

[15] K. Itoh, S. Saito, S. Sahara, Y. Naitoh, K. Imai, and H. Kitakoji, "Randomized trial of trigger point acupuncture treatment for chronic shoulder pain: a preliminary study," *Journal of Acupuncture and Meridian Studies*, vol. 7, no. 2, pp. 59–64, 2014.

[16] H. Zhang, J. Sun, C. Wang et al., "Randomised controlled trial of contralateral manual acupuncture for the relief of chronic shoulder pain," *Acupuncture in Medicine*, vol. 34, no. 3, pp. 164–170, 2016.

[17] W. Kumnerddee and N. Pattapong, "Efficacy of electro-acupuncture in chronic plantar fasciitis: a randomized controlled trial," *American Journal of Chinese Medicine*, vol. 40, pp. 1167–1176, 2012.

[18] L. A. Ferreira, R. G. de Oliveira, J. P. Guimaraes, A. C. P. Carvalho, and M. V. Q. De Paula, "Laser acupuncture in patients with temporomandibular dysfunction: a randomized controlled trial," *Lasers in Medical Science*, vol. 28, no. 6, pp. 1549–1558, 2013.

[19] L. Arriaga-Pizano, D. C. Gomez-Jimenez, L. A. Flores-Mejia et al., "Low back pain in athletes can be controlled with acupuncture by a catecholaminergic pathway: clinical trial," *Acupuncture in Medicine*, vol. 38, no. 6, pp. 388–395, 2020.

[20] C. Bi, *Clinical Observation of Small Needle-Knife for the Treatment of Tennis Elbow*, Chengdu University of TCM, Chengdu, China, 2013.

[21] H. Lv, *The Clinical Observation of Electroacupuncture Combined with Extracorporeal Shock Wave in the Treatment of Supraspinatus Tendinitis*, Nanjing University of Chinese Medicine, Nanjing, China, 2019.

[22] M. Inoue, M. Nakajima, Y. Oi, T. Hojo, M. Itoi, and H. Kitakoji, "The effect of electroacupuncture on tendon repair in a rat Achilles tendon rupture model," *Acupuncture in Medicine*, vol. 33, no. 1, pp. 58–64, 2015.

[23] X. Yu, F. Zhang, and J. Zhang, "Effect of transcutaneous electrical acupuncture point stimulation on expression of p-JNK in the dorsal root ganglion in a rat model of myofascial pain syndrome," *Acupuncture in Medicine*, vol. 37, no. 5, pp. 312–318, 2019.

[24] A. Li, Y. Zhang, L. Lao et al., "Serotonin receptor 2A/C is involved in electroacupuncture inhibition of pain in an osteoarthritis rat model," *Evid Based Complement Alternat Med*, vol. 2011, Article ID 619650, 6 pages, 2011.

[25] J. Zhang, Q. Li, and S. Chang, "The effects of particle density in moxa smoke on the ultrastructure of knee cartilage and expressions of TNF-α, IL-1b, BAX, and Bcl-2 mRNA in a rat model for osteoarthritis," *Journal of Cellular Biochemistry*, vol. 120, no. 4, pp. 6589–6595, 2019.

[26] M. J. Kim, U. Namgung, and K. E. Hong, "Regenerative effects of moxibustion on skeletal muscle in collagen-induced arthritic mice," *Journal of Acupuncture and Meridian Studies*, vol. 5, no. 3, pp. 126–135, 2012.

[27] X. Zhan and S. Shi, "Protective effect of massage combined with acupuncture on exercise-induced muscle damage in rats," *Chinese Journal of Gerontology*, vol. 37, no. 2, pp. 311–314, 2017.

[28] Y. Gao, J. Wu, N. Geng, and T. Yu, "Effect of Tuina therapy on motor function and scaffolding protein NF-M in neurons of sciatic nerve injury rat models," *Global Traditional Chinese Medicine*, vol. 6, no. 12, pp. 894–897, 2013.

[29] R. Chen, M. Chen, M. Kang et al., "The design and protocol of heat-sensitive moxibustion for knee osteoarthritis: a multi-center randomized controlled trial on the rules of selecting moxibustion location," *BMC Complementary and Alternative Medicine*, vol. 10, no. 1, p. 32, 2010.

[30] L. Chen, Z. Huang, K. Cheng et al., "The efficacy of jade moxibustion in knee osteoarthritis," *Medicine*, vol. 99, no. 17, Article ID e19845, 2020.
[31] Y. J. Sun, J. M. Yuan, and Z. M. Yang, "Effectiveness and safety of moxibustion for primary insomnia: a systematic review and meta-analysis," *BMC Complementary and Alternative Medicine*, vol. 16, no. 1, p. 217, 2016.
[32] G. Jiang, P. Liu, A. Peng et al., "Application of traditional Chinese medicine health care technology in sports rehabilitation," *Contemporary Sports Technology*, vol. 7, no. 11, p. 17 + 19, 2017.
[33] S. Chen and J. Ge, "Research on moxibustion for sports injuries," *Science & Technology Information*, vol. 17, no. 18, pp. 255-256, 2019.
[34] L. Zhao, K. Cheng, L. Wang et al., "Effectiveness of moxibustion treatment as adjunctive therapy in osteoarthritis of the knee: a randomized, double-blinded, placebo-controlled clinical trial," *Arthritis Research and Therapy*, vol. 16, no. 3, Article ID R133, 2014.
[35] Y. Liang, W. Li, X. Xu et al., "Control observation between mild moxibustion and TDP for obsolete collateral ligament injury of interphalangeal joints," *Zhongguo Zhen Jiu*, vol. 36, no. 1, pp. 21–24, 2016.
[36] R. Chen, M. Chen, T. Su et al., "Heat-sensitive moxibustion in patients with osteoarthritis of the knee: a three-armed multicentre randomised active control trial," *Acupuncture in Medicine*, vol. 33, no. 4, pp. 262–269, 2015.
[37] G. Cao, S. Chen, Q. Liu, and B. Deng, "Clinical effect of ginger moxibustion for acute external humeral epi-condylitis," *International Medicine and Health Guidance News*, vol. 25, no. 13, pp. 2143–2146, 2019.
[38] J. Xiong, H. Xu, H. Li, X. Chang, Z. Zhang, and L. Jiao, "Effect of knee medial collateral ligament sport injury in treatment of heat-sensitive moxibustion therapy: a randomized controlled trial," *Chinese Archives of Traditional Chinese Medicine*, vol. 35, no. 4, pp. 867–869, 2017.
[39] Y. Han, "Sixty-one cases of supraspinatus muscle tendonitis treated by massage and moxibustion," *Liaoning Journal of Traditional Chinese Medicine*, vol. 37, no. S1, pp. 268-269, 2010.
[40] L. Huang, J. Lin, and C. Yan, "Effect of moxibustion KI1 combined with ice compress on postoperative swelling of lower extremity fracture," *Medicine and Pharmacy of Yunnan*, vol. 42, no. 1, pp. 65–67, 2021.
[41] J. Zhou, *A Study on the Dynamic Changes of Inflammation and Heat-Sensitive Moxibustion Intervention Result after Plyometric Induced Muscle Damage*, Beijing Sport University, Beijing, China, 2020.
[42] W. W. Tao, H. Jiang, X. M. Tao, P. Jiang, L. Y. Sha, and X. C. Sun, "Effects of acupuncture, Tuina, Tai Chi, Qigong, and traditional Chinese medicine five-element music therapy on symptom management and quality of life for cancer patients: a meta-analysis," *Journal of Pain and Symptom Management*, vol. 51, no. 4, pp. 728–747, 2016.
[43] Y. Zhang, Y. Sun, and Q. Zhang, "Prognostic value of the systemic immune-inflammation index in patients with breast cancer: a meta-analysis," *Cancer Cell International*, vol. 20, no. 3, pp. 224-225 + 229, 2020.
[44] X. Tan, "Clinical observation of 30 cases of shoulder periarthritis treated by cao's massage," *Guiding Journal of Traditional Chinese Medicine*, vol. 16, no. 12, pp. 55-56, 2010.
[45] G. C. Goats, "Massage—the scientific basis of an ancient art: Part 2. Physiological and therapeutic effects," *British Journal of Sports Medicine*, vol. 28, no. 3, pp. 153–156, 1994.
[46] L. L. Andersen, K. Jay, C. H. Andersen et al., "Acute effects of massage or active exercise in relieving muscle soreness: randomized controlled trial," *The Journal of Strength & Conditioning Research*, vol. 27, no. 12, pp. 3352–3359, 2013.
[47] W. T. Su, P. Y. Lee, H. S. Kuo, and C. L. Kuo, "Research progress of massage combined with other therapies for shoulder injury," *Hu li za zhi*, vol. 68, no. 5, pp. 41–50, 2021.
[48] S. W. Zhou, Q. Shen, and Y. X. Liao, "Clinical study of treating knee osteoarthritis (Bi syndrome of knee) by massage combined Chinese materia medica footbath fumigation and washing," *Zhongguo Zhong Xi Yi Jie He Za Zhi*, vol. 32, no. 8, pp. 1060–1063, 2012.
[49] A. Nasiri, M. A. Mahmodi, and Z. Nobakht, "Effect of aromatherapy massage with lavender essential oil on pain in patients with osteoarthritis of the knee: a randomized controlled clinical trial," *Complementary Therapies in Clinical Practice*, vol. 25, pp. 75–80, 2016.
[50] Z. Zhou, Y. Zhang, W. Chen, and J. Wang, "Massage manipulation vs. low back muscle exercise for lumbar intervertebral instability: a preliminary randomized clinical trial," *Journal of Pakistan Medical Association*, vol. 70, no. 2, pp. 324–336, 2020.
[51] Z. H. Min, Y. Zhou, L. Jing et al., "Case-control study on Chinese medicine fumigation and massage therapy for the treatment of knee stability and functional recovery after anterior cruciate ligament reconstruction operation," *Zhong Guo Gu Shang*, vol. 29, no. 5, pp. 397–403, 2016.
[52] B. Saban, D. Deutscher, and T. Ziv, "Deep massage to posterior calf muscles in combination with neural mobilization exercises as a treatment for heel pain: a pilot randomized clinical trial," *Manual Therapy*, vol. 19, no. 2, pp. 102–108, 2014.
[53] O. Dupuy, W. Douzi, D. Theurot, L. Bosquet, and B. Dugue, "An evidence-based approach for choosing post-exercise recovery techniques to reduce markers of muscle damage, soreness, fatigue, and inflammation: a systematic review with meta-analysis," *Frontiers in Physiology*, vol. 9, p. 403, 2018.
[54] G. Shi, X. Wang, G. Li, G. Yuan, S. Wu, and X. Li, "Morphological study on the repairing effect of massage on muscle injury," *Chinese Journal of Sports Medicine*, vol. 10, no. 4, pp. 201–205 + 253, 1991.
[55] G. Lin and L. Li, "Research progress of cupping therapy for myofascial trigger points," *Chinese Journal of Ethnomedicine and Ethnopharmacy*, vol. 28, no. 22, pp. 83–85, 2019.
[56] N. A. Qureshi, G. I. Ali, T. S. Abushanab et al., "History of cupping (Hijama): a narrative review of literature," *Journal of Integrative Medicine*, vol. 15, no. 3, pp. 172–181, 2017.
[57] B. Chen, M. Y. Li, P. D. Liu, Y. Guo, and Z. L. Chen, "Alternative medicine: an update on cupping therapy," *QJM*, vol. 108, no. 7, pp. 523–525, 2015.
[58] H. Cramer, P. Klose, M. Teut et al., "Cupping for patients with chronic pain: a systematic review and meta-analysis," *The Journal of Pain*, vol. 21, no. 9-10, pp. 943–956, 2020.
[59] P. Mehta and V. Dhapte, "Cupping therapy: a prudent remedy for a plethora of medical ailments," *Journal of Traditional and Complementary Medicine*, vol. 5, no. 3, pp. 127–134, 2015.
[60] S. Cui and J. Cui, "Research progress on the mechanism of negative pressure effect of cupping therapy," *Acupuncture Research*, vol. 37, no. 6, pp. 506–510, 2012.
[61] N. AlKhadhrawi and A. Alshami, "Effects of myofascial trigger point dry cupping on pain and function in patients with plantar heel pain: a randomized controlled trial," *Journal of Bodywork and Movement Therapies*, vol. 23, no. 3, pp. 532–538, 2019.

[62] Y. An, Y. Duan, and J. Chen, "Puncture cupping plus McKenzie therapy in improving lumbar flexion and extension function of patiens suffering low back pain," *Acta Chinese Medicine*, vol. 35, no. 5, pp. 1115–1119 + 1130, 2020.

[63] X. Wu, "Effect of middle frequency pulse therapy, moxibustion combined with cupping for low back pain," *Electronic Journal of Clinical Medical Literature*, vol. 6, no. 88, p. 15, 2019.

[64] B. Xiao, "Clinical observation of balancing cupping for acute discogenic lower back pain," *Journal of Emergency in Traditional Chinese Medicine*, vol. 27, no. 12, pp. 2198–2200, 2018.

[65] F. Tian, "Effect of acupuncture, cupping and microwave on 83 cases of lumbar spinous ligament injury," *Chinese Journal of Clinical Rational Drug Use*, vol. 5, no. 25, p. 105, 2012.

[66] R. Lauche, H. Cramer, K. E. Choi et al., "The influence of a series of five dry cupping treatments on pain and mechanical thresholds in patients with chronic non-specific neck pain—a randomised controlled pilot study," *BMC Complementary and Alternative Medicine*, vol. 11, no. 1, p. 63, 2011.

[67] X. Wang, X. Ren, and G. Zhang, "Effects of acupuncture combined with cupping in the treatment of shoulder joint pain," *The Journal of Medical Theory and Practice*, vol. 31, no. 15, pp. 2283–2285, 2018.

[68] Y. C. Chiu, I. Manousakas, S. M. Kuo, J. W. Shiao, and C. L. Chen, "Influence of quantified dry cupping on soft tissue compliance in athletes with myofascial pain syndrome," *PLoS One*, vol. 15, no. 11, Article ID e0242371, 2020.

[69] R. Lauche, H. Cramer, C. Hohmann et al., "The effect of traditional cupping on pain and mechanical thresholds in patients with chronic nonspecific neck pain: a randomised controlled pilot study," *Evidence-based Complementary and Alternative Medicine*, vol. 2012, p. 10, 2012.

[70] R. Lauche, H. Cramer, J. Langhorst, and G. Dobos, "Cupping for chronic nonspecific neck pain: a 2-year follow-up," *Forsch Komplementmed*, vol. 20, no. 5, pp. 328–333, 2013.

[71] Y. Guo, B. Chen, D. Wang, M. Li, and C. H. Lim, "Cupping regulates local immunomodulation to activate neural-endocrine-immune worknet," *Complementary Therapies in Clinical Practice*, vol. 28, pp. 1–3, 2017.

[72] J. J. V. McMurray and M. Packer, "How should we sequence the treatments for heart failure and a reduced ejection fraction?: a redefinition of evidence-based medicine," *Circulation*, vol. 143, no. 9, pp. 875–877, 2021.

[73] Y. Wang and Y. Ding, "Application of traditional Chinese medicine in the prevention and treatment of football injuries," *Modern Business Trade Industry*, vol. 39, no. 3, pp. 79-80, 2018.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 5448671, 15 pages
https://doi.org/10.1155/2022/5448671

Review Article

Potential Role of Yoga Intervention in the Management of Chronic Non-malignant Pain

Shivani Gupta,[1] **Surabhi Gautam**,[1] **Uma Kumar**,[2] **Taruna Arora**,[3] **and Rima Dada**[1]

[1]*Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India*
[2]*Department of Rheumatology, All India Institute of Medical Sciences, New Delhi, India*
[3]*Division of Reproductive Biology, Maternal & Child Health, Indian Council of Medical Research, New Delhi, India*

Correspondence should be addressed to Rima Dada; rima_dada@rediffmail.com

Received 15 October 2021; Revised 18 March 2022; Accepted 13 May 2022; Published 28 May 2022

Academic Editor: Vijaya Anand

Pain is an unpleasant and upsetting experience. Persistent pain has an impact on an individual's quality of life which causes stress and mood disorders. There are currently no pain-relieving techniques available that can eliminate pain and offer relief without causing any adverse effects. These factors draw attention to traditional treatments like yoga and meditation, which can reduce biological stress and hence increase immunity, as well as alleviate the psychological and emotional suffering produced by pain. Yoga reduces the stress response and the pain cascade via the downregulation of the hypothalamus-pituitary-adrenal (HPA) axis and vagal stimulation. Yoga is a cost-effective growing health practice that, unlike pharmaceuticals, has no side effects and can help patients stay in remission for longer periods of time with fewer relapses. Yoga not only reduces stress and depression severity but also improves functional status and reduces pain perception. This article highlights the impact of yoga on pain management and on a malfunctioning immune system, which leads to improved health, pain reduction, disease management, and improvement in overall quality of life.

1. Introduction

Chronic non-malignant pain is defined as pain that lasts longer than three months or pain that lasts longer than the predicted recovery time. It can be associated with trauma or disease or can occur *de novo* [1]. Pain is a distressing sensory and emotional experience. Chronic pain is commonly thought to be caused by a variety of factors, including physical, sociocultural, and psychological deficits [2]. It is a widespread health problem that has negative consequences for both patients and society, including diminished productivity, lower quality of life, and a higher cost to the healthcare system. Multidisciplinary pain programs appear to be the best therapeutic choice for patients with complicated chronic pain [3]. There is, therefore, a need for a well-designed interdisciplinary pain management program, to address the psychological aspect of pain diseases as well such as low back pain, osteoarthritis (OA), rheumatoid arthritis (RA), headache, neck pain, fibromyalgia, and irritable bowel syndrome.

The literature review in this article was done using the advanced search engine in the PubMed database and used a combination of English keywords, i.e., "chronic pain," "yoga," and "inflammation." Pain management is one of the most challenging tasks for medical practitioners. For better pain management, several pain-relieving medications are available like local anesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids (tramadol), and strong opioids (morphine) which are usually recommended by physicians for the treatment of moderate to severe pain [4, 5]. All these pain-relieving medications provide pain relief but for a short duration with accompanying side effects like gastrointestinal dysfunction, nausea, vomiting, and even respiratory depression in the case of opioids [6, 7]. The

persistence of pain affects the quality of life of an individual simultaneously generating stress and mood disorders. Till now, no such pain-relieving measures are available which can alleviate the pain completely and provide relief without any side effects. These lead to the attention towards traditional therapies such as yoga and meditation which can minimize biological stress and correspondingly improve immunity and can also counter the psychological and emotional suffering caused due to pain.

Pain is an unpleasant experience which carries both sensory and emotional aspects that are linked with potential or actual tissue damage. Pain arises due to tissue injury and repetitive noxious stimuli which leads to unpleasant sensation. This sensation is processed by complex and integrative signaling mechanisms from the periphery to the central nervous system (CNS) where inputs are ultimately integrated and then a reflex response is generated [8]. This mechanism includes ascending pathway and descending pain pathway. This neural pathway consists of three relay stations. At the periphery, the free nerve endings are called nociceptors which belong to unmyelinated C-fibers, responsible for dull pain, and myelinated Aδ fibers which carry acute sharp pain [9, 10]. C-fibers have a slow conduction velocity of 2 μm/second and the diameter of nerves is less than 2 μm. However, Aδ fibers are the smallest myelinated nerves and have a fast conduction velocity of 3 m/sec. The diameter of the nerves is about 2–5 μm [9]. These are primary afferent fibers whose cell bodies are located in the dorsal root ganglion. These nerve endings have specific receptors for different stimuli such as Transient receptor potential vanilloid (TRPV) for temperature, P2X receptors for purinergic receptors for adenosine triphosphate (ATP), acid-sensing ion channels for hydrogen ions, or polymodal receptors that can be activated via different types of stimulus [11].

When tissue damage occurs due to a noxious stimulus, it leads to the production of inflammatory mediators such as prostaglandins which sensitize the nociceptors to accepting the stimulus or directly activate them. Furthermore, other molecules like histamine, bradykinin, nerve growth factor, tumor necrosis factor (TNF), interleukins (ILs), ATP, hydrogen ions, and potassium are released by infiltrating inflammatory cells which directly activate the nociceptors [12]. Activation of nociceptors causes the opening of voltage-gated ion channels accompanied by the influx of ions such as sodium and calcium into the cytoplasm to generate an action potential. These signals are transmitted to the primary sensory neurons of the dorsal root ganglion (DRG) followed by transmission to secondary sensory neurons located in the dorsal horn of the spinal cord (Rexed lamina I, II, and V) [8]. The fibers of spinal neurons decussate and ascend to form a synapse with the tertiary sensory neuron located in the ventroposterolateral nucleus of the thalamus. Finally, the tertiary neuron fibers send signals to the somatosensory cortex where pain signals are perceived. During their course of transmission to the brainstem region, collateral fibers also send signals to the reticular system which is responsible for arousal during pain. The descending pathway includes the periaqueductal grey (PAG) region which receives inputs from the anterior cingulated cortex, hypothalamus, amygdala, and frontal lobe and also receives the ascending input from the spinal dorsal horn. Then, PAG integrates the information and sends it to RVM (including nucleus raphe magnus and nucleus reticularis gigantocellularis) according to which the processing of nociceptive signals is regulated by the spinal dorsal horn neurons [8, 13]. The cannabinoid and opioid systems and the neurotransmitters like norepinephrine and serotonin are involved in regulating the facilitatory and inhibitory mechanism of the pain pathway.

2. Modulation of Pain Signal Transmission via Gate Control Theory

The theory was reported by Melzack and Wall in 1965. The concept suggests that inhibition or decrease in transmission of pain sensation can be possible through activation of non-painful sensation [14]. The process involves peripheral pain-carrying fibers (Aδ & C-fibers) which communicate with the second-order neuron located in substantia gelatinosa (Laminae II) of the dorsal horn in the spinal cord. The large fibers carry non-painful input (such as Aβ fibers) which communicate with inhibitory interneurons of laminae II and also make synapses with primary afferent fibers of pain and second neurons. So, the non-painful input carrying fibers activate the inhibitory interneuron, leading to the release of gamma-aminobutyric acid (GABA), resulting in presynaptic inhibition of noxious stimulus.

Based on gate control theory, some stimuli are used to generate non-noxious signals for closing the gate for pain signals such as transcutaneous electrical nerve stimulation (TENS), massage, heat and cold therapy, and movements of joints [14–16]. The gate control theory mainly suggests that how pain signals are perceived by the brain through the body's nervous system can be inhibited or decreased and enhanced by psychological factors [17]. So, it is suggested that mind-body practice like yoga can inhibit pain signals and it has the potential to change the way an individual experiences pain.

Pain can be classified based on duration, site of origin, or location. Following are few types of pains which can be encountered upon various external and internal noxious stimuli.

2.1. Acute and Chronic Pain. When pain lasts for hours to days or for short period then it is considered acute pain. Acute pain mainly acts as a warning signal for the body towards the harmful stimuli. It is specific, sharp, and usually comes suddenly.

Acute pain disappears when the cause of pain goes away (postoperative pain, fracture of bones, cuts, and wounds). However, chronic pain lasts for more than six months and it persists even after the healing and removal of the cause of pain (arthritis, fibromyalgia, cancer, and neuropathic pain) [18]. Chronic pain also produces emotional stress, anxiety, and depression which adversely affect the quality of life of an individual [19].

Based on mechanism and function, pain can be classified as nociceptive, inflammatory, and neuropathic.

2.2. Nociceptive Pain. Nociceptive pain occurs due to internal tissue damage when expose to noxious stimuli like extreme heat, cold, or trauma. The nerve endings which are activated by such stimuli are nociceptors which are located in the skin, bone, muscles, joint capsules, and other tissues. They sense chemical, mechanical, and thermal sensations. The nociceptors are Aδ myelinated fibers, activated by thermal or mechanical stimuli. However, unmyelinated C-fibers are activated not only by thermal and mechanical but also by chemical stimuli [8].

2.3. Neuropathic Pain. Neuropathic pain is defined as the occurrence of pain due to a lesion or disease of somatosensory nerves. It mainly arises from the pathology of the nervous tissue due to injury, diseases such as diabetes, nerve compression, and autoimmune diseases. This causes inflammation within the nerve tissue that could lead to both peripheral and central sensitization. Peripheral neuropathy showed alteration in electrical properties of sensory nerves, resulting in impairment of excitatory and inhibitory signaling [18]. In turn, sensory signals transmission and disinhibition mechanism are altered at the spinal level which could move to the state of hyper excitability. With time this sequence of changes from the periphery to the CNS contributes to neuropathic pain becoming chronic. Alteration in the ion channels, within the affected nerves for example upregulation of sodium channels lead to increased excitability, signal transduction, and increased release of neurotransmitters at the spinal cord terminus of the primary afferent fibers [20, 21]. Enhanced activation of spinal neurons expands the field of many modalities (low threshold Aβ and Aδ fibers). This causes the increase in excitation of second-order neurons in the spinal cord which generates central sensitization. The increase in signals further increases the excitatory release of pain facilitatory transmitters that phosphorylate the N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, contributing to the state of hypersensitivity [18]. Moreover, the non-neuronal cells such as astrocytes and microglia also contribute either directly or indirectly to the development of hypersensitization [22].

2.4. Inflammatory Pain. Pain caused by activation of nociceptors via the release of inflammatory mediators by damaged cells is known as inflammatory pain. Inflammation occurs as a natural biological response produced by the body tissues as a reaction to noxious stimuli to remove the necrotic cells and initiate the tissue repairing process. During inflammation, neutrophils move through the bloodstream to the injured site followed by the release of chemical mediators. Other responses like the release of platelet-activating factor (PAF) by mast cells followed by the release of serotonin (5-HT), and macrophages augment the inflammatory response [23]. The inflammatory exudate is rich in nerve growth factors, cytokines, protons, and ions. Together, it produces cardinal inflammatory signs such as redness, swelling, hotness, and inflammation at the site due to increased blood flow. These mediators like bradykinin, prostaglandins, and 5-HT can directly activate their receptors and G-protein receptors present at the peripheral nerve ending [8]. This is accompanied by activation of a cascade of signaling mechanisms such as protein kinase A and C signaling pathway which further recruits more receptors and enhanced the sensitivity of primary afferent fibers resulting in peripheral sensitization [24]. As a result, non-noxious stimuli like light touch produce pain sensation (allodynia) or normal painful stimuli produce intense pain sensation (hyperalgesia) [25].

Even inflammatory pain can be categorized into two types: acute and chronic. As a first respondent to the harmful stimuli, accumulation of leukocytes and plasma cells at the site of injury takes place to assist the inflammatory process. This stimulates the activation of primary afferent fibers which are normally mediated by Aδ fibers, resulting in the generation of intense pain which lasts for a short duration called acute inflammatory pain. However, in chronic inflammatory pain, prolonged inflammation is accompanied by the persistence of pain which lasts beyond the healing period. The nociceptive signals are typically mediated by C-fibers and they occur due to the recruitment of mononuclear cells at the inflammatory site as well [8]. Some other mediators are also released from the necrotic tissue during the inflammatory process like 5-HT, kinins, histamine, nerve growth factors (NGF), ATP, glutamate, leukotrienes, nitric oxide (NO), NE, and protons which also contribute to inactivation of nociceptors within the inflamed area [26]. Further, this increases the afferents' input in the dorsal horn of the spinal cord and leads to the development of central sensitization resulting in persistent pain.

2.5. Biomolecules Involved in Induction, Transmission, and Modulation of Pain Signaling. Glutamate is the main neurotransmitter involved in the shaping of transmission of pain signaling. It is also involved in the generation and maintenance of central sensitization [27, 28]. Substance P, calcitonin gene-related peptide (CGRP), and ATP are also released by primary sensory neurons which act as a transmitter and neuromodulators and they are distributed both at the spinal cord and peripheral nerve endings. Stimulation of primary sensory fibers releases these transmitters to bind to neurokinin-1, NMDA, and AMPA, CGRP receptors on the postsynaptic site in the dorsal horn and also bind to the receptors present on the microglia and astrocytes. Microglia release pro-inflammatory mediators which act in a paracrine manner and enhanced the pain input at the dorsal horn level in the spinal cord. The inflammatory mediators like TNF, IL-1, and IL-6 play important role in the induction and maintenance of pain signals. Activation of chemokines receptors, present on the peripheral nociceptors, lowers the threshold of DRG neurons and leads to the state of hypersensitivity. Transient receptor potential vanilloid 1 (TRP) or capsaicin-sensitive receptors are well known in the pain

signaling mechanism [29]. TRPV1 is widely distributed in the unmyelinated C-type sensory nerve fibers and partially in the myelinated Aδ-type sensory nerve fibers CNS. It activates by chemical and noxious heat stimuli in the peripheral and CNS [30–32]. Activation of TRPV1 increases the Ca ion influx and release of pain facilitatory neurotransmitters and neuropeptides into the dorsal horn of the spinal cord [33–35]. TRPV1 also play a role in the activation of spinal glial cells and contributes to the induction and maintenance of pain [36]. Multiple phosphorylation sites are present on TRPV1 through which various intracellular signaling cascade is activated such as protein kinase A (PKA), protein kinase C, Ca^{2+}/calmodulin-dependent kinase II (CaMKII), and Ca^{2+}-dependent phosphatase calcineurin which contribute in hyperalgesia or sensitization of primary afferents to mechanical and thermal stimuli [37]. Besides these, oxidative stress plays role in the induction and maintenance of neuropathic and inflammatory pain [38–40]. Reactive oxygen species contribute to neuropathic pain by triggering the phosphorylation of CAMKII signaling [39].

Pain and inflammation are closely related and integrated, not merely via acute peripheral sensitization at the joint but also derived from the modulation in the processing of pain signals at the central level. RA is an inflammatory joint disease that occurs with a prevalence rate ranging from 0.3–4.2%, based on the studied population [41, 42]. RA pain mainly occurs in small joints such as joints of the hand and foot, wrist, ankle, knee, and hip joints.

For the management of pain symptoms, a variety of treatment options have been explored to help patients manage their symptoms of pain, including pharmacological approaches, physical therapy, exercise, surgery, psychological therapy, and complementary and alternative therapies. Pain medications, such as opioids, are frequently given. The use of opioids in the treatment of chronic non-malignant pain is a contentious topic because of the adverse effects, short-term efficacy, and safety of pain medications, as well as the danger of abuse and addiction [43]. Various adverse effects of opioids have been listed in Table 1 [44]. Patients with chronic non-malignant pain face a complicated interaction of biological, psychological, and social variables, thus therapy must take all of these elements into account [45]. Psychological factors play a significant role in deciding whether or not a patient with chronic non-malignant pain will respond to therapy [46].

3. Role of Tryptophan Metabolites Formed via Kynurenine Pathway in Pain

Tryptophan is an amino acid that metabolizes to form various active biological molecules such as serotonin, NAD^+, and melatonin. The metabolism of TRP involves mainly two routes: the serotonin pathway which includes 5% TRP metabolism and 95% is taken place by the KP pathway resulting in the formation of kynurenines. Kynurenine is involved in the regulation of several biological processes such as host-microbiome signaling, the excitability of neurons, and the response of the immune cells [47]. In the KP pathway, TRP converts to N-formyl-L-kynurenine via three enzymes: indole amine 2,3-dioxygenase 1 and 2 (IDO 1 and (2) and tryptophan 2,3-dioxygenase (TDO) and rapidly converted to L-kyukynurenineYN). The downstream cascade of the L-kynurenine can undergo three transformations, also called kynurenines: 3-hydroxykynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and then quinolinic acid (QUIN) is formed via enzymatic action of kynurenine 3-monooxygenase (KMO) and anthranilic acid (AA). The quinolinic acid (QUIN) acts as a precursor for NAD^+ synthesis.

Glutamate is the predominant excitatory neurotransmitter in the nervous system. Also, KYN is converted into kynurenic acid (KYNA) through irreversible transformation via kynurenine aminotransferase (KAT) enzymes, the end product of its lateral branch. Glutamate binds to AMPA and NMDA receptors which regulate pain transmission and cognitive function. QUIN is an agonist of NMDA receptors leading to a neurotoxic effect. The KYNA acts as an agonist for the NMDA receptor but plays a dual role on AMPA receptors. At lower concentrations, it facilitates AMPA receptor response while at higher concentrations it antagonizes the AMPA receptors' action by allosteric modulation of desensitization of AMPA receptors [48]. In vitro studies suggested that astrocytes are mainly involved in the synthesis of neuroprotective KYNA, and activation of microglia/macrophages during various neuroimmunological diseases leads to the synthesis of neurotoxic QUIN [49, 50]. The link between the development of neuropathic pain and the activity of Kynurenine pathway enzymes was explored in different neuropathic pain models. Several studies reported the upregulation of KP enzymes (IDO 1/2, KMO, and KYNU) in the CNS tissues in various neuropathic pain models [51, 52] (Figure 1). Moreover, inhibition of IDO 2 and KMO enzymes resulted in alleviation of mechanical, tactile, or thermal hypersensitivity in neuropathic pain models [53].

RA is the most common inflammatory arthritis. The role of yoga as an effective adjunct intervention has been documented in the literature to assist in the management of chronic diseases like RA concerning its clinical symptoms like pain perception, stress management, disability outcomes, sleep quality, functional ability, QOL, and psychosocial outcomes [54–56]. RA has a multifactorial etiology, diverse pathogenesis, heterogeneous clinical phenotypes and, this disease comprises a psychosomatic component, hence an integrative approach of yoga might improve clinical outcomes in RA by bringing changes in all interconnected biological components and at various levels-molecular, cellular, organ systems, and the person as a whole. RA serves as a model for chronic inflammatory pain. With this context in mind, this article contains RA as an inflammatory model and the aim is to investigate the effects of yoga and its mechanism of action and analyze their association with the clinical health outcomes including disease activity, functional status, depression severity, and quality of life.

Table 1: Adverse effects of opioids [44].

S.No.	Organ system	Adverse effects
1	Respiratory system	Respiratory depression, obstructive and central sleep apnea, ataxic breathing, respiratory arrest, and death
2	Central nervous system	Increased risk of falls, cognitive impairment, myoclonus, delirium, depression, somnolence, and sleep disorders
3	Cardiovascular system	Orthostatic hypotension, bradycardia, vasodilation, and an increased risk of cardiovascular events, e.g., myocardial infarction
4	Gastrointestinal system	Constipation, nausea and vomiting, gastric reflux, delayed gastric emptying, abdominal cramping, and distension
5	Immune system	Decreased wound healing, pruritus, altered cytokine production, increased histamine release, inhibition of macrophage, neutrophil, and natural killer cell activity and recruitment, increased HIV replication, and cancer progression
6	Endocrine system	Opioid-induced endocrinopathy (usually only with high opioid doses, long-term), resulting in decreased libido, testicular atrophy, early menopause, and sexual dysfunction

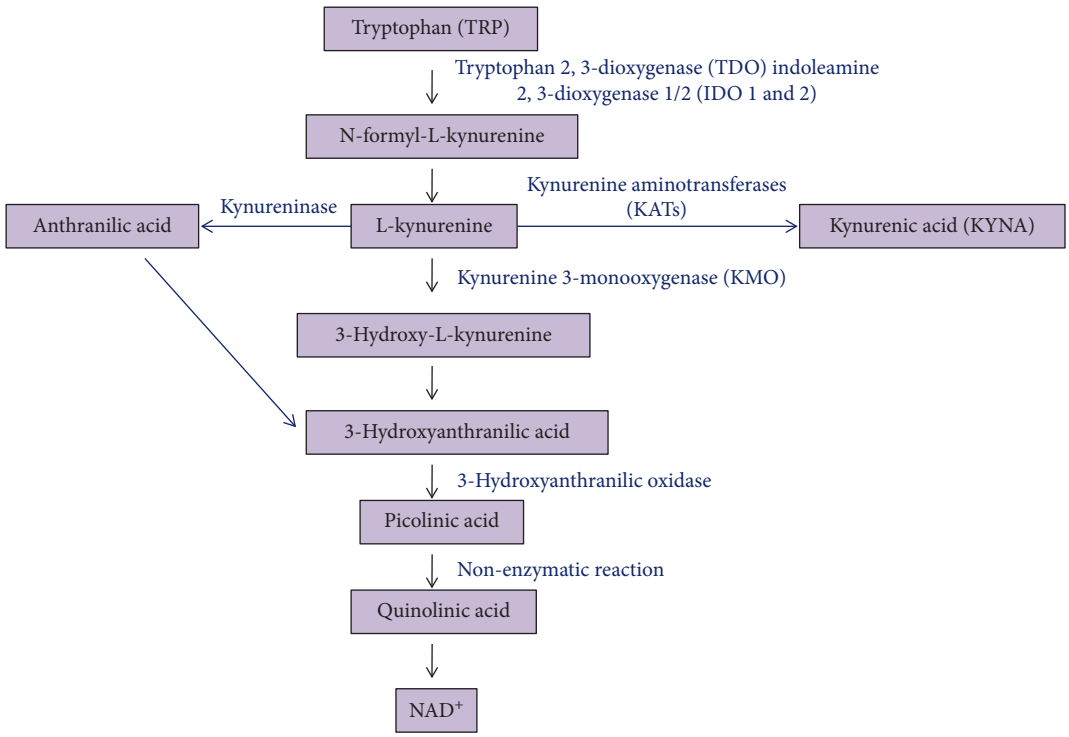

Figure 1: Illustration of the metabolism of tryptophan via the kynurenine pathway.

3.1. Mechanism of Pain in RA. RA is associated with inflammation of the synovial that correlates with the severity of pain in joints. RA pain arises as a result of the combined interaction of joint pathogenesis and modulation in the neuronal sensitivity throughout the nociceptive pathway either at the peripheral or the central level (both spinal cord and brain) [42, 57]. Inflamed synovium is the manifestation of the release of pro-inflammatory mediators by local immune cells. This causes direct activation and sensitization of sensory-free nerve endings called nociceptors, present not only on the synovium but also in the joint capsule, the outer region of menisci, ligaments, muscles, subchondral bone, and tendon sheath [57, 58]. Even during the late phase, the osteochondral junction is disrupted by subchondral erosion and exposes the nerve ending which approaches the degenerative part resulting in an enhancement of inflammatory response. These free nerve endings are the peripheral process of primary sensory neurons located in the dorsal root ganglion and carry pain signals to secondary sensory neurons located in the spinal cord [8, 58]. Direct stimulation induces pain and sensitization; as a consequence normal pain can be felt due to non-noxious stimuli (allodynia) such as pressure, weight-bearing, and movement [57]. The following illustration shows the central and peripheral mechanisms of pain and the various components involved in the process (Figure 2).

3.2. Mechanism of Peripheral Sensitization in RA. Peripheral sensitization leads to the genesis of chronic pain. It constitutes a decrease in the threshold of nociceptors and an increase in their response towards the stimulus which

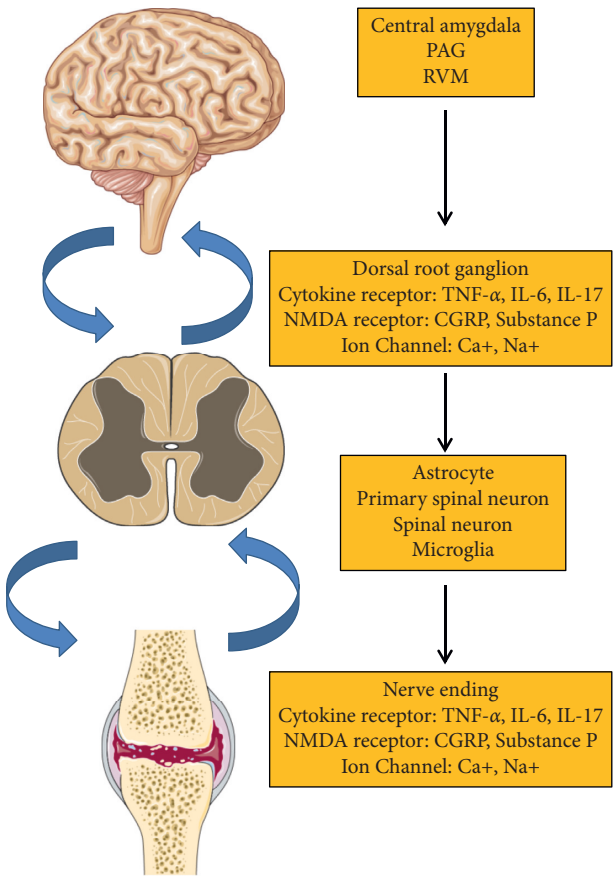

Figure 2: Schematic diagram showing pain mechanism in RA (modified from Cao et al., [59]).

occurs because of post-translational changes in and alteration in the trafficking of ion channels and transducer receptors. This is initiated by the activation of nociceptors by local inflammatory mediators at the inflammation site, resulting in a state of pain hypersensitivity [60, 61]. This is known as primary hyperalgesia. Medications that bind to opioid receptors are increasingly being prescribed for the treatment of multiple and diverse chronic painful conditions. Their use for acute pain or terminal pain is well accepted. Their role in the long-term treatment of chronic non-cancer pain is, however, controversial for many reasons. One of the primary reasons is the well-known phenomenon of psychological addiction that can occur with the use of these medications. Abuse and diversion of these medications is a growing problem as the availability of these medications increases and this public health issue confounds their clinical utility. Also, the extent of their efficacy in the treatment of pain when utilized on a chronic basis has not been definitively proven. Lastly, the role of opioids in the treatment of chronic pain is also influenced by the fact that these potent analgesics are associated with a significant number of side effects and complications. It is these phenomena that are the focus of this review.

Common side effects of opioid administration include sedation, dizziness, nausea, vomiting, constipation, physical dependence, tolerance, and respiratory depression. Physical dependence and addiction are clinical concerns that may prevent proper prescribing and in turn inadequate pain management. Less common side effects may include delayed gastric emptying, hyperalgesia, immunologic and hormonal dysfunction, muscle rigidity, and myoclonus. The most common side effects of opioid usage are constipation (which has a very high incidence) and nausea. These side effects can be difficult to manage and frequent tolerance to them does not develop; this is especially true for constipation. They may be severe enough to require opioid discontinuation and contribute to under-dosing and inadequate analgesia. Several clinical trials are underway to identify adjunct therapies that may mitigate these side effects. Switching opioids and/or routes of administration may also provide benefits for patients. Proper patient screening, education, and preemptive treatment of potential side effects may aid in maximizing effectiveness while reducing the severity of side effects and adverse events. Opioids can be considered broad-spectrum analgesic agents, affecting a wide number of organ systems and influencing a large number of body functions [44]. The signaling molecules are involved in mediating peripheral sensitization such as protons, ATP, prostaglandins (PGE2), leukotrienes, nerve growth factor (NGF), cytokines (IL-6, IL-1β, TNF-α), chemokines, neuropeptides, CGRP, substance P, bradykinin, histamine, lipids, and diverse proteases [62]. Inflamed synovium manifests an increased level of prostaglandins and bradykinin in RA patients that can directly activate unmyelinated sensory nerves [58]. Furthermore, NGF-β and cytokines such as IL-1, IL-6, and TNF-α also increased which can sensitize the peripheral sensory nerves in synovium and subchondral bone of RA patients [60, 63]. The stimulation of these nociceptive fibers activates the intracellular signaling pathway following the activation of the phosphorylation cascade in the neuronal cell. Synovitis is also associated with alteration in the expression of neurotransmitters, neuromodulators, and their receptors at nociceptive neurons located in the DRG and dorsal horn of the spinal cord [60].

3.3. Mechanism of Central Sensitization in RA. Central sensitization is responsible for a variety of chronic pain diseases including RA [64, 65]. Central sensitization is the enhanced response of nociceptive neurons in the CNS towards their normal and subthreshold afferent inputs. This is known as secondary hyperalgesia. Stimulation of nociceptors results in the generation of action potential leading to the release of excitatory neurotransmitters at the spinal level. At the spinal level, central sensitization occurs in the dorsal horn which relieves inputs from an enlarged receptive field leading to pain hypersensitivity. This occurs in two steps: in the acute stage, primary afferent fibers released glutamate which binds to their receptors on postsynaptic neurons and the chronic stage includes activation of spinal microglia and the transcription of pain regulatory molecules [27]. Glutamate is the key transmitter that activates both NMDA and non-NMDA receptors on spinal cord neurons [63]. This leads to the release of various inflammatory mediators and in turn, initiates the central hypersensitivity or central sensitization [57, 66–68]. Synovitis is

accompanied by upregulation of SP, CGRP, and their receptors in the spinal cord [27, 57]. Stimulation of primary sensory fibers releases these transmitters to bind to neurokinin-1, NMDA, AMPA, and CGRP receptors on the postsynaptic site in the dorsal horn and they also bind to the receptors present on the microglia and astrocytes [69]. Microglia release pro-inflammatory mediators which act in a paracrine manner and enhanced the pain input at the dorsal horn level in the spinal cord [70]. The inflammatory mediators like TNF, IL-1, and IL6 play important role in the induction and maintenance of pain signals [12]. Microglia also secrete other pro-inflammatory molecules like nitric oxide and superoxide anion which act in a positive feedback manner and lead to hyperalgesia [57]. On the other side, astrocytes activation further leads to the recruitment of pro-inflammatory mediators like TNF-α which modulates pain signaling in various ways. TNF-α can directly act on neurons and modulate synaptic activity. Activation of astrocytes by TNF-α induces phosphorylation of pJNK1, mitogen-activated protein kinase (MAPK) which regulates the gene transcription. Pain signals from sensory neurons of the dorsal horn in the spinal cord transmit to the sensory neurons of the ventroposterolateral region of the thalamus. Then to the somatosensory cortex where finally pain signals are perceived in the brain. In response, the pain regulatory mechanism of the CNS activates the descending pain pathway. These pathways transmit signals from the brain through the brainstem to the spinal cord. In the brainstem, afferent signals are received by periaqueductal grey (PAG) from the frontal cortex, amygdalae, and hypothalamus related to stress and mood which influence the perception of pain. The signals are integrated by PAG and transmitted to the rostral ventromedial medulla (RVM) in the brainstem. Depending on the activation of specific pathways RVM can transmit or inhibit the pain [42]. Even RA pain is also manifested due to non-inflammatory factors like sleep disturbances, anxiety, and depression which affect the perception of pain [71].

RA has become one of the major public health problems and around 1% of the world population is affected [72]. Among these, it is more common in women than men. The condition of RA is manifested by pain, swelling, stiffness, loss of joint function, and increased acute-phase reactant levels [73]. Management of RA includes Disease-Modifying Anti-rheumatic Drugs (DMARDs), Non-steroidal anti-inflammatory drugs (NSAIDs), Glucocorticoids (GC), and even opioids [74]. However, this provides pain relief but never cures it completely so it is necessary to search for effective therapy which includes better pain management with fewer or no side effects. Individuals suffering from chronic pain may benefit from mindfulness training as a therapy option [75, 76]. The deliberate and nonjudgmental conscious awareness of the current moment is characterized as mindfulness. Psychological factors have been proven to have a significant influence on how patients feel and tolerate pain, yet they are frequently overlooked when chronic non-malignant pain treatment strategies are adopted. Chronic pain is associated with dysregulation of emotional and cognitive functions leading to anxiety, depression, altered attention, fear, etc. [2]. These alterations are also linked to the phenomena of "pain catastrophizing," which is described as the repeated negative thoughts that occur during or before pain [77]. Anxiety, depression, drug use disorders, and sleep problems are just a few of the variables that can make the pain worse. Hence, management of these comorbidities becomes essential to control the overall patient's pain state. A multi-disciplinary treatment approach model which incorporates both pharmacological and non-pharmacological interventions is more effective in managing chronic pain than single treatment modalities [78]. A systematic review reported that there was evidence of better effectiveness of multi-disciplinary treatment groups compared to the single treatment group in the management of musculoskeletal pain [78]. There is a wide range of social, psychological, non-pharmacological, and non-opioid pharmacological treatment options available for patients with chronic non-malignant pain. It may be essential to test several therapies combinations to discover the optimal treatment option for each patient [43]. There are various non-pharmacological treatment options in the management of chronic pain like physical therapy, yoga, tai-chi, massage, acupuncture, and cognitive behavioral therapy.

3.4. Yoga in the Management of Chronic Pain. As chronic pain is multidimensional and affects an individual's different organ systems, hence an integrated mind body medicine approach like yoga is highly beneficial. Pain is divided into five categories based on its mechanism: peripheral neuropathy, central sensitization, sympathetically sustained pain, nociceptive, and cognitive-affective pain. Every occurrence of pain is evaluated from many perspectives, i.e., sensory, emotional, behavioral, and cognitive [19]. The brain is built to anticipate the worst and tends to take caution by eliciting a strong pain response quickly. For the sake of efficiency, the brain creates streamlined neuropathways based on previous experience for coping with comparable dangers and uses them for each episode of pain. The physical body, physiology, mental appraisal, emotional reaction, and general attitude towards life must all be considered while managing chronic pain [79]. Yoga is a collection of physical, mental, and spiritual disciplines that originated in ancient India and are aimed at controlling the mind as well as recognizing the detached consciousness. The five koshas (Panchamaya model) consist of five main layers of our systems: physical structure, physiological processes, the content of minds, ideas, and attitudes towards our surroundings, and our sense of connection to other people, society, and the Universe [80, 81]. Each of those layers includes tools established by the yoga tradition to promote balance and healing (Figure 3). Yoga is a profound science-based health discipline and can be used as a complementary, integrative, and adjunct medical therapy that impacts the body, and mind as a whole and results in promoting physical and mental health and improving quality of life [82]. Yoga is a technique associated with mind-body relaxation and acts as a cushion to the changing cellular immunity related to the stress. Yoga mainly focuses on regulated breathing practices,

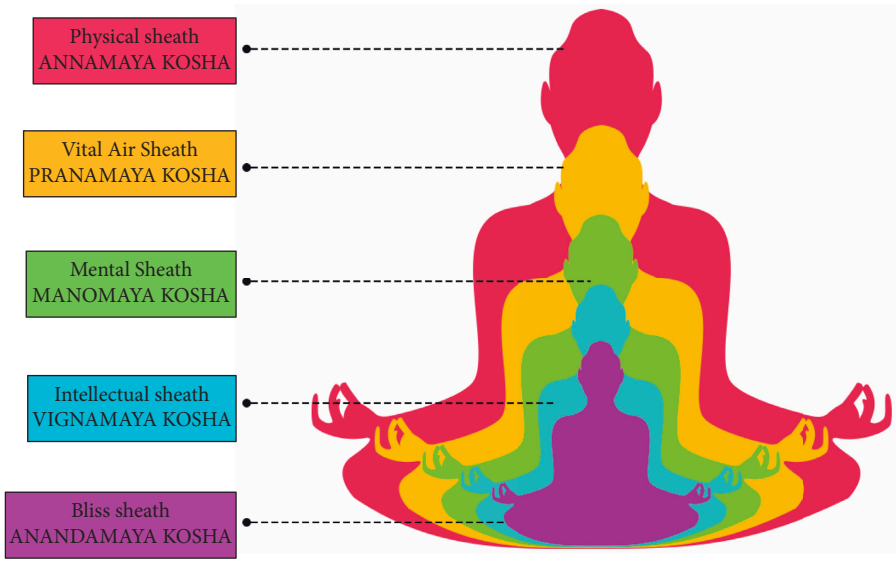

Figure 3: The Panchamaya model (modified from an illustration by Maya Chastain).

mind, and body which includes mild to moderate postural exercises (asana), breathing exercise (pranayama), and meditation (dhyana). Regular practice of yoga is effective in reducing pro-inflammatory biomarkers such as IL-6 and TNF-α from their basal level in healthy yoga practitioners [83]. Chronic elevation in these markers leads dysregulated immune response and sets stage for autoimmune progression of inflammatory diseases like RA.

Yoga decreases systemic and local inflammation in RA by normalizing circulation levels (IL-6, IL-17A, and TNF-α) and mRNA transcript levels of pro-inflammatory cytokines (IL-6, TNF-α) [84]. Yoga also improves autonomic reflex regulation systems and restores the balance between sympathetic and parasympathetic limbs in inflammatory situations [85]. Yoga practice also reduces the level of oxidative stress and improves the anti-oxidant levels [86]. Therefore, one of the possible mechanisms by which yoga could be reducing RA pain is by decreasing the level of inflammatory mediators. This leads to peripheral reduction of inflammatory mediators levels which results in the decrease of stimulation of nociceptors so the transduction and transmission of pain signals are reduced from the periphery to the spinal cord. There is a decrease in the level of oxidative stress at the spinal and brain level due to less activation of spinal neurons and non-neuronal cells. Together, overall it reduces the level of pain hypersensitivity throughout the pain pathway from the periphery to the central level. In addition, the pain pathway is also regulated by GABA, an inhibitory neurotransmitter. In chronic pain, the level of GABA is reduced in the brain and it is also involved in the gate control mechanism of pain signals. This includes the GABAergic interneuron that controls the transmission of signals. Practicing yoga on regular basis also increases the level of GABA which could facilitate the inhibitory action on the transmission of pain signaling.

Yoga is now being used more often to alleviate painful ailments and enhance emotional resilience and enhance threshold to pain. Studies are being conducted to look at probable neuroanatomical changes as a result of yoga practice. A study conducted on North-American yogis analyzed the anatomical alterations in the grey and white matter of the brain which indicated that yogis had more left intrainsular white matter integrity than controls, and they were able to endure more pain than the control group due to their parasympathetic activation and enhanced awareness [87]. Yoga, as an integrated health technique, has both psychological and physical components, making it appropriate as an adjunct management approach for severe, debilitating autoimmune arthritis such as RA [85, 88, 89]. Yoga has a substantial impact on RA because it helps to reduce articular and extra-articular symptoms while also improving systemic indicators of inflammation, oxidative stress, and cellular health [84]. Yoga works through psycho-neuro-immunological systems to attain life's homeostatic equilibrium [90]. Yoga enhanced the quality of life in active RA patients by lowering pain perception, disability quotient, disease activity, and severity of comorbid depression [84, 85, 90–92].

Pranayama is a voluntary breathing regulation that is commonly practiced in conjunction with yoga asanas and meditation. The three phases of pranayama consist of the inhalation "puraka," the breath-holding "kumbhaka," and the exhalation "rechaka." Stepwise breath regulation influences the autonomic nervous system's control, which has additional favorable effects on the body's organ systems. The parasympathetic nervous system is activated when pranayama breathing is done with the extended breath retention [93]. The mode of action of yoga is vagal stimulation, which improves baroreflex sensitivity and lowers inflammatory cytokines, and parasympathetic activation, which is linked to anti-stress processes (Figure 4). Yoga lowers stress perception and hypothalamus pituitary adrenal (HPA) axis activation, resulting in improved metabolic and psychological profiles [94].

Yoga is a profound science-based mind body practice that may be utilized as adjunct to medical therapy that affects the whole body and mind, boosting physical and mental

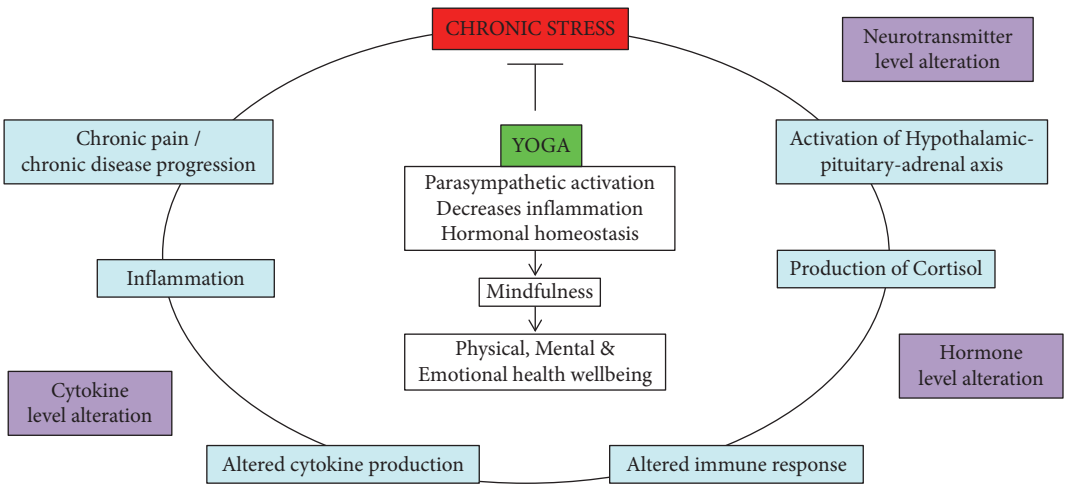

Figure 4: Yoga in reducing chronic stress and its consequences.

health and enhancing the quality of life. It is a low-cost mind-body intervention that, unlike medicines, has no side effects and has a beneficial influence on the entire body, allowing for longer periods of remission with fewer relapses. Yoga has a beneficial influence on the genome and epigenome, resulting in molecular remission and immunological tolerance [85, 95–97]. Various studies from our lab showed that 8 weeks of yoga intervention significantly reduced disease activity, altered methylation patterns, improved mitochondrial integrity and biogenesiss and thus slowed down the rate of functional decline associated with aging, normalized the systemic biomarkers of inflammation, oxidative stress, immune-senescence, aging, and promoted neuroplasticity [90, 91, 98, 99]. This is due to the impact on the genome and epigenome, leading to the normalization of gene expression and epigenetic marks. There was an improvement in various systemic, molecular, epigenetic, and genetic markers associated with RA pathogenesis. Also, there was a favourable clinical outcome of RA with a reduction in disease activity, disability index, pain acuity, depression severity, and improvement in quality of life [90].

3.5. Impact of Yoga on Inflammatory Cytokine Profile. Yoga decreases systemic and local inflammation in RA by normalizing circulation levels (IL-6, IL-17A, and TNF-α) and mRNA transcript levels of pro-inflammatory cytokines (IL-6, TNF-α) [84]. Yoga also improves autonomic reflex regulation systems and restores the balance between sympathetic and parasympathetic limbs in inflammatory situations [85]. Various studies have seen a marked reduction in the levels of inflammatory markers after yoga intervention in various conditions (Table 2).

3.6. IL-6. The *IL-6* gene on chromosome 7 encodes a pleiotropic cytokine that plays a crucial role in the etiology of RA and has a significant positive association with disease activity and joint damage [108]. It has pro-inflammatory effects by attaching to transmembrane or soluble receptors and activating gp130, a transmembrane protein, which then triggers the IL-6 signaling cascade. The JAK-STAT signaling pathway stimulates numerous transcriptional factors in response to IL-6 signaling, resulting in $CD4^+$ *T* cell proliferation, differentiation, and activation [109]. In the presence of transforming growth factor (TGF)-β, IL-6 enhances Th17 cell development, which secretes IL-17A, another strong pro-inflammatory cytokine, while inhibiting TGF-β induced Treg cell differentiation [110]. As a result, IL-6 disrupts immunological homeostasis by boosting Th17 cell numbers over Treg cell populations. By activating B cells, IL-6 is a powerful stimulator of the HPA axis, causing acute phase responses and the generation of autoantibodies [111]. In inflammatory conditions, the HPA axis is triggered by inflammatory cytokines. Stressors/pro-inflammatory cytokines cause the hypothalamus to release the corticotrophin-releasing hormone, which stimulates the adrenal gland to generate and release cortisol by acting on the anterior pituitary and inducing the production of adrenocorticotropic hormone. Cortisol counteracts the stressor and reduces the prevailing inflammation [112]. However, the HPA axis becomes hypersensitive as a result of persistent inflammatory stimulation and negative

Table 2: Reduction of various inflammatory markers in different disease conditions.

Condition	Inflammatory markers	References
Rheumatoid arthritis	IL-6, IL-17A, TNF-α, and ESR,	[84]
	CRP, ROS	[91]
	NFKB	[100]
	IL-10	[101]
Type 2 diabetes	IL-8, IL-6, IL-18, CRP, and IL-6	[102]
Low back pain	TNF-α	[103]
Depression	IL-6, Cortisol	[98]
	IL-6, TNF-α, and CRP	[104]
Multiple sclerosis	IL-1, IL-2, IL-4, IL-6 IL-10, IFN-γ, TGF-β, and TNF-α	[105]
Inflammatory bowel disease	IL-6	[106]
Cancer	NFKB, IL-6, and GP130-JAK pathways	[107]

feedback regulation of cortisol on the hypothalamus and anterior pituitary begins. This condition leads to adrenal insufficiency. Yoga reduces stress and inflammation by inhibiting the hypersensitive HPA axis and regulating cortisol levels [100].

3.7. TNF-α. TNF-α is one of the most important pro-inflammatory cytokines in the pathogenesis of RA [113]. TNF-α functions in increasing vasodilatation and edema formation causing leukocyte adhesion to epithelium through the expression of adhesion molecules and contributing to oxidative stress in sites of inflammation [114]. In the TNF signaling pathway, TNF cytokines interact with its receptor to activate MAPK and NF-κB signaling pathways resulting in the release of leukocyte inflammatory factors. The released inflammatory factors further activate the membrane receptors leading to a vicious circle of inflammatory responses. It is reported that stimulating the NF-κB and TNF signaling pathways could promote cell inflammation in RA [115]. Recent studies from our lab showed that yoga aids in the regression of inflammatory processes by the reduction in the levels of TNF-α and IL-6 cytokines in RA patients [84, 85].

3.8. TGF-β. TGF-β is another key pleiotropic cytokine that helps maintain immunological homeostasis and produces peripheral tolerance through its regulatory activities. TGF-β enhances the differentiation of induced Treg cells using IL-2 and retinoic acid and preserves the survival of naturally existing Treg cells. Treg cells monitor abnormal immune responses and are thought to be protective against an overactive immune system and the onset of autoimmunity [116]. A study from our lab showed that yoga holds the immune-regulatory potential and reduces the severity of RA by elevating *TGF-β* transcript levels and circulating levels of TGF-β hence developing immunological tolerance.

3.9. IL-17A. IL-17A is responsible for articular symptoms as it induces inflammation in synovial tissue. As ROS damage the mitochondrial DNA, this might be a compensatory strategy to ensure appropriate ATP levels. Simultaneously, there is a reduction in OS and overexpression of genes that preserve mitochondrial integrity, resulting in fewer free radicals being produced. Increased ROS levels cause T helper 17 (Th17) cells to differentiate, resulting in increased production of interleukin IL-17, indicating that mitochondrial changes play a significant role in the Th17 cell effector phenotype. The immune system equilibrium between Tregs and effector Th17 cells is disrupted. [117]. Dysfunction of Tregs fails to maintain peripheral tolerance and results in autoimmunity [118]. TGF-β, IL-10, IL-35, and the soluble human leukocyte antigen (HLA)-G molecule are secreted by Tregs, whereas Th17 cells release pro-inflammatory cytokines such as IL-17, TNF-α, IL-22, and IL-26, IFN-γ, and others [119]. Increased production of inflammatory cytokines by effector Th17 cells and a loss of Treg suppressor activity are both linked to immunological dysregulation in RA [117]. In an unpublished study from our lab, the mean proportion of Th17 cells ($CD3^+CD4^+IL17^+RORt^+$ *T* cells) in the yoga group decreased significantly from baseline to the eighth week, but the mean percentage of Treg cells ($CD3^+CD4^+CD25^+CD127$-$Foxp3^+$T cells) increased significantly in the yoga group. The mean percentage of aged Th17 cells ($CD3^+CD4^+IL17^+ROR\gamma t^+CD28^-$ *T* cells), as well as aged Treg cells ($CD3^+CD4^+CD25^+CD127^-Foxp3^+CD28^-$ *T* cells), has shown a significant overall decline in yoga group as compared to non-yoga group. There was an upregulation of soluble HLA-G levels in RA patients followed by yoga intervention. HLA-G, a non-classical HLA class I molecule, has anti-inflammatory and immune-modulatory effects. It is an excellent reference parameter for autoimmune and inflammatory disease prevention, diagnosis, and therapy since higher levels are linked to less severe illness and fewer relapses in RA patients.

3.10. Impact of Yoga on Endogenous Opioids and Neurotransmitters. Encephalin and endorphins are endogenous opioids that are generated largely in the brain and have various effects throughout the body [120]. Opioid antagonists can limit the activity of encephalin and endorphins, which act on opioid receptors. Increased levels of brain-derived neurotrophic factor (BDNF), dehydroepiandrosterone sulfate (DHEAS), and β-endorphins suggest a significant improvement in mind-body communication indicators following yoga practice. Yoga raises the levels of BDNF, a key neuroplasticity biomarker, as well as DHEAS, serotonin, neuregulin, and neurotropin [121, 122]. Multiple neurotransmitters in the brain are altered by regular yoga practice. In a study, yoga practice for one hour boosted GABA levels in the brain [123]. BDNF has neuroprotective and neurotrophic properties [122, 124]. Yoga promotes mind-body communication, which controls neuroplasticity and decreases the stress cascade by increasing BDNF, DHEAS, and β-endorphins. DHEAS is dysregulated in RA and possesses neuroprotective, anti-oxidant, and anti-inflammatory effects. DHEAS levels were shown to be increased in RA patients when given a TNF antagonist, which enhanced adrenal function [125, 126]. This study also discovered a substantial increase in DHEAS levels after yoga, indicating that yoga can help with emotional control, neurocircuits, cognition, emotional resilience, and memory. Upregulated DHEAS levels following a yoga practice have also been shown to lower depression severity in individuals with major depressive disorder and situations of comorbid depression, such as in RA patients [98].

Another study found that doing yoga for one hour every day for three months reduces adrenocorticotropic hormone (ACTH) and cortisol while increasing serotonin, dopamine, and BDNF in healthy active males [127]. β-Endorphins are endogenous morphine produced by the pituitary gland and diffused throughout the body. This neuro-hormone functions as a neuro-regulator and its levels in the blood tend to rise with intense and long-lasting physical exercise [128]. As a result, yoga has the ability to increase β-endorphin levels and generate a good sensation of pleasure, wellbeing, and security in RA patients who are already depressed [98]. Yoga

has the ability to reorganize the structure and function of the nervous system which was manifested by the upregulation of markers of neuroplasticity. Yoga intervention leads to decline in severity of the disease which further influences psychological health via changes in biomarkers at a systemic level. The yoga group was more compliant with the therapy and able to conduct daily activities without any difficulty as their psychological health and depression severity improved [84]. Improvement in the overall quality of life, as well as health assessment questionnaire, was seen after the yoga intervention, with improvement in the physical, psychological, social, and environment domain scores of the WHOQOL-BREF questionnaire [90]. Yoga improved physical and emotional fitness, psychological health, and overall wellbeing in patients who practiced it [85].

4. Conclusion

Yoga, a mind-body medicine and is a profound science and technique for achieving optimal health and well being. It has immune-modulatory properties, lowers pain perception, regulates the psycho-neuro-immune axis, reduces depression severity, reduces disability quotient, and improves the quality of life. Hence, yoga is useful to patients with chronic pain as a complementary treatment that improves physical function and enhances emotional resilience and mental wellbeing.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Shivani Gupta and Surabhi Gautam contributed equally to this article.

References

[1] R. D. Treede, W. Rief, A. Barke et al., "A classification of chronic pain for ICD-11," *Pain*, vol. 156, pp. 1003–1007, 2015.

[2] L. J. Crofford, "Chronic pain: where the body meets the brain," *Transactions of the American Clinical and Climatological Association*, vol. 126, pp. 167–183, 2015.

[3] U. Kaiser, B. Arnold, M. Pfingsten, B. Nagel, J. Lutz, and R. Sabatowski, "Multidisciplinary pain management programs," *Journal of Pain Research*, vol. 6, pp. 355–358, 2013.

[4] A. A. Anekar and M. Cascella, *WHO Analgesic Ladder*, StatPearls Publishing, St.Petersburg, FL, USA, 2021.

[5] R. D. Blondell, M. Azadfard, and A. M. Wisniewski, "Pharmacologic therapy for acute pain," *American Family Physician*, vol. 87, pp. 766–772, 2013.

[6] R. I. Russell, "Non-steroidal anti-inflammatory drugs and gastrointestinal damage-problems and solutions," *Postgraduate Medical Journal*, vol. 77, no. 904, pp. 82–88, 2001.

[7] M. H. Algera, J. Kamp, R. van der Schrier et al., "Opioid-induced respiratory depression in humans: a review of pharmacokinetic-pharmacodynamic modelling of reversal," *British Journal of Anaesthesia*, vol. 122, no. 6, pp. e168–e179, 2019.

[8] M. Yam, Y. Loh, C. Tan, S. Khadijah Adam, N. Abdul Manan, and R. Basir, "General pathways of pain sensation and the major neurotransmitters involved in pain regulation," *International Journal of Molecular Sciences*, vol. 19, no. 8, p. 2164, 2018.

[9] A. E. Dubin and A. Patapoutian, "Nociceptors: the sensors of the pain pathway," *Journal of Clinical Investigation*, vol. 120, no. 11, pp. 3760–3772, 2010.

[10] C. J. Woolf and Q. Ma, "Nociceptors-noxious stimulus detectors," *Neuron*, vol. 55, no. 3, pp. 353–64, 2007.

[11] R. Melzack and P. D. Wall, "Pain mechanisms: a new theory," *Science*, vol. 150, no. 3699, pp. 971–979, 1965.

[12] A. D. Cook, A. D. Christensen, D. Tewari, S. B. McMahon, and J. A. Hamilton, "Immune cytokines and their receptors in inflammatory pain," *Trends in Immunology*, vol. 150, no. 3699, pp. 971–979, 1965.

[13] M. H. Ossipov, G. O. Dussor, and F. Porreca, "Central modulation of pain," *Journal of Clinical Investigation*, vol. 120, no. 11, pp. 3779–3787, 2010.

[14] L. M. Mendell, "Constructing and deconstructing the gate theory of pain," *Pain*, vol. 155, no. 2, pp. 210–216, 2014.

[15] T. Maeda, H. Yoshida, T. Sasaki, and A. Oda, "Does transcutaneous electrical nerve stimulation (TENS) simultaneously combined with local heat and cold applications enhance pain relief compared with TENS alone in patients with knee osteoarthritis?" *Journal of Physical Therapy Science*, vol. 29, no. 10, pp. 1860–1864, 2017.

[16] R. Adams, B. White, and C. Beckett, "The effects of massage therapy on pain management in the acute care setting," *International Journal of Therapeutic Massage and Bodywork*, vol. 3, no. 1, pp. 4–11, 2010.

[17] S. Banth and M. D. Ardebil, "Effectiveness of mindfulness meditation on pain and quality of life of patients with chronic low back pain," *International Journal of Yoga*, vol. 8, pp. 128–133, 2015.

[18] L. Colloca, T. Ludman, D. Bouhassira et al., "Neuropathic pain," *Nature Reviews Disease Primers*, vol. 3, no. 1, Article ID 17002, 2017.

[19] M. A. Lumley, J. L. Cohen, G. S. Borszcz et al., "Pain and emotion: a biopsychosocial review of recent research," *Journal of Clinical Psychology*, vol. 67, no. 9, pp. 942–968, 2011.

[20] S. R. Levinson, S. Luo, and M. A. Henry, "The role OF sodium channels IN chronic pain," *Muscle and Nerve*, vol. 46, no. 2, pp. 155–165, 2012.

[21] P. Boadas-Vaello, S. Castany, J. Homs, B. Álvarez-Pérez, M. Deulofeu, and E. Verdú, "Neuroplasticity of ascending and descending pathways after somatosensory system injury: reviewing knowledge to identify neuropathic pain therapeutic targets," *Spinal Cord*, vol. 54, no. 5, pp. 330–340, 2016.

[22] M. Tsuda, S. Beggs, M. W. Salter, and K. Inoue, "Microglia and intractable chronic pain," *Glia*, vol. 61, no. 1, pp. 55–61, 2013.

[23] F. Marchand, M. Perretti, and S. B. McMahon, "Role of the immune system in chronic pain," *Nature Reviews Neuroscience*, vol. 6, no. 7, pp. 521–532, 2005.

[24] Y. S. Su, W. H. Sun, and C. C. Chen, "Molecular mechanism of inflammatory pain," *World Journal of Anesthesiology*, vol. 3, no. 1, pp. 71–81, 2014.

[25] J. Sandkühler, "Models and mechanisms of hyperalgesia and allodynia," *Physiological Reviews*, vol. 89, pp. 707–758, 2009.

[26] K. B. J. Franklin and F. V. Abbott, "Techniques for assessing the effects of drugs on nociceptive responses," in *Psychopharmacology*, A. A. Boulton, G. B. Baker, and

A. J. Greenshaw, Eds., Humana Press, Totowa, NJ, USA, 2008.

[27] A. Latremoliere and C. J. Woolf, "Central sensitization: a generator of pain hypersensitivity by central neural plasticity," *The Journal of Pain*, vol. 10, no. 9, pp. 895–926, 2009.

[28] V. Pereira and C. Goudet, "Emerging trends in pain modulation by metabotropic glutamate receptors," *Frontiers in Molecular Neuroscience*, vol. 11, p. 464, 2019.

[29] I. Jardín, J. J. López, R. Diez et al., "TRPs in pain sensation," *Frontiers in Physiology*, vol. 8, p. 392, 2017.

[30] M. C. Marrone, A. Morabito, M. Giustizieri et al., "TRPV1 channels are critical brain inflammation detectors and neuropathic pain biomarkers in mice," *Nature Communications*, vol. 8, no. 1, Article ID 15292, 2017.

[31] M. Tominaga, M. J. Caterina, A. B. Malmberg et al., "The cloned capsaicin receptor integrates multiple pain-producing stimuli," *Neuron*, vol. 21, no. 3, pp. 531–543, 1998.

[32] Y. S. Kim, Y. Chu, L. Han et al., "Central terminal sensitization of TRPV1 by descending serotonergic facilitation modulates chronic pain," *Neuron*, vol. 81, no. 4, pp. 873–887, 2014.

[33] K. W. Ho, N. J. Ward, and D. J. Calkins, "TRPV1: a stress response protein in the central nervous system," *American Journal of Neurodegenerative Disease*, vol. 1, pp. 1–14, 2012.

[34] W. Huang, H. Wang, J. J. Galligan, and D. H. Wang, "Transient receptor potential vanilloid subtype 1 channel mediated neuropeptide secretion and depressor effects: role of endoplasmic reticulum associated Ca^{2+} release receptors in rat dorsal root ganglion neurons," *Journal of Hypertension*, vol. 26, no. 10, pp. 1966–1975, 2008.

[35] Y. V. Medvedeva, M.-S. Kim, and Y. M. Usachev, "Mechanisms of prolonged presynaptic Ca^{2+} signaling and glutamate release induced by TRPV1 activation in rat sensory neurons," *Journal of Neuroscience*, vol. 28, no. 20, pp. 5295–5311, 2008.

[36] Y. Chen, H. H. Willcockson, and J. G. Valtschanoff, "Influence of the vanilloid receptor TRPV1 on the activation of spinal cord glia in mouse models of pain," *Experimental Neurology*, vol. 220, no. 2, pp. 383–390, 2009.

[37] Y. M. Shuba, "Beyond neuronal heat sensing: diversity of TRPV1 heat-capsaicin receptor-channel functions," *Frontiers in Cellular Neuroscience*, vol. 14, p. 485, 2021.

[38] P. Basu, R. S. Hornung, C. Maier, and D. L. Averitt, "Reduction of oxidative stress as a potential mechanism underlying Euphorbia bicolor latex extract-induced analgesia in a rat model of orofacial pain," *The FASEB Journal*, vol. 33, 2019.

[39] J. Yowtak, K. Y. Lee, H. Y. Kim et al., "Reactive oxygen species contribute to neuropathic pain by reducing spinal GABA release," *Pain*, vol. 152, no. 4, pp. 844–852, 2011.

[40] S. J. Forrester, D. S. Kikuchi, M. S. Hernandes, Q. Xu, and K. K. Griendling, "Reactive oxygen species in metabolic and inflammatory signaling," *Circulation Research*, vol. 122, pp. 877–902, 2018.

[41] J. Park, A. Mendy, and E. R. Vieira, "Various types of arthritis in the United States: prevalence and age-related trends from 1999 to 2014," *American Journal of Public Health*, vol. 108, no. 2, pp. 256–258, 2018.

[42] A. Zhang and Y. C. Lee, "Mechanisms for joint pain in rheumatoid arthritis (RA): from cytokines to central sensitization," *Current Osteoporosis Reports*, vol. 16, no. 5, pp. 603–610, 2018.

[43] A. Rosenblum, L. A. Marsch, H. Joseph, and R. K. Portenoy, "Opioids and the treatment of chronic pain: controversies, current status, and future directions," *Experimental and Clinical Psychopharmacology*, vol. 16, no. 5, pp. 405–416, 2008.

[44] R. Benyamin, A. M. Trescot, S. Datta et al., "Opioid complications and side effects," *Pain Physician*, vol. 11, pp. S105–S120, 2008.

[45] R. R. Edwards, R. H. Dworkin, M. D. Sullivan, D. C. Turk, and A. D. Wasan, "The role of psychosocial processes in the development and maintenance of chronic pain," *The Journal of Pain*, vol. 17, no. 9, pp. T70–T92, 2016.

[46] J. Sturgeon, "Psychological therapies for the management of chronic pain," *Psychology Research and Behavior Management*, vol. 7, pp. 115–124, 2014.

[47] A. A. Badawy, "Kynurenine pathway of tryptophan metabolism: regulatory and functional aspects," *International Journal of Tryptophan Research: IJTR*, vol. 10, Article ID 1178646917691938, 2017.

[48] C. Prescott, A. M. Weeks, K. J. Staley, and K. M. Partin, "Kynurenic acid has a dual action on AMPA receptor responses," *Neuroscience Letters*, vol. 402, pp. 108–112, 2006.

[49] G. J. Guillemin, S. J. Kerr, G. A. Smythe et al., "Kynurenine pathway metabolism in human astrocytes: a paradox for neuronal protection," *Journal of Neurochemistry*, vol. 78, no. 4, pp. 842–853, 2001.

[50] G. J. Guillemin, D. G. Smith, G. A. Smythe, P. J. Armati, and G. J. Brew, "Expression of the kynurenine pathway enzymes in human microglia and macrophages," *Advances in Experimental Medicine and Biology*, vol. 527, pp. 105–112, 2003.

[51] E. Rojewska, K. Ciapała, A. Piotrowska, W. Makuch, and J. Mika, "Pharmacological inhibition of indoleamine 2,3-dioxygenase-2 and kynurenine 3-monooxygenase, enzymes of the kynurenine pathway, significantly diminishes neuropathic pain in a rat model," *Frontiers in Pharmacology*, vol. 9, p. 724, 2018.

[52] G. Laumet, W. Zhou, R. Dantzer et al., "Upregulation of neuronal kynurenine 3-monooxygenase mediates depression-like behavior in a mouse model of neuropathic pain," *Brain, Behavior, and Immunity*, vol. 66, pp. 94–102, 2017.

[53] K. Ciapała, J. Mika, and E. Rojewska, "The kynurenine pathway as a potential target for neuropathic pain therapy design: from basic research to clinical perspectives," *International Journal of Molecular Sciences*, vol. 22, Article ID 11055, 2021.

[54] S. Evans, L. Cousins, J. C. Tsao, S. Subramanian, B. Sternlieb, and L. K. Zeltzer, "A randomized controlled trial examining Iyengar yoga for young adults with rheumatoid arthritis: a study protocol," *Trials*, vol. 12, no. 1, p. 19, 2011.

[55] K. R. Middleton, M. M. Ward, S. Haaz et al., "A pilot study of yoga as self-care for arthritis in minority communities," *Health and Quality of Life Outcomes*, vol. 11, no. 1, p. 55, 2013.

[56] S. Telles and N. Singh, "Is yoga a suitable treatment for rheumatoid arthritis: current opinion," *Open Access Journal of Sports Medicine*, vol. 3, pp. 81–87, 2012.

[57] D. A. Walsh and D. F. McWilliams, "Pain in rheumatoid arthritis," *Current Pain and Headache Reports*, vol. 16, no. 6, pp. 509–517, 2012.

[58] Y. T. Konttinen, V.-M. Tiainen, E. Gomez-Barrena, M. Hukkanen, and J. Salo, "Innervation of the joint and role of neuropeptides," *Annals of the New York Academy of Sciences*, vol. 1069, no. 1, pp. 149–154, 2006.

[59] Y. Cao, D. Fan, and Y. Yin, "Pain mechanism in rheumatoid arthritis: from cytokines to central sensitization," *Mediators*

of Inflammation, vol. 2020, Article ID 2076328, 11 pages, 2020.

[60] H.-G. Schaible, G. S. von Banchet, M. K. Boettger et al., "The role of proinflammatory cytokines in the generation and maintenance of joint pain," *Annals of the New York Academy of Sciences*, vol. 1193, no. 1, pp. 60–69, 2010.

[61] D. R. Spiegel, A. Pattison, A. Lyons et al., "The role and treatment implications of peripheral and central processing of pain, pruritus, and nausea in heightened somatic awareness: a review," *Innovations in Clinical Neuroscience*, vol. 14, pp. 11–20, 2017.

[62] V. Gangadharan and R. Kuner, "Pain hypersensitivity mechanisms at a glance," *Disease Models & Mechanisms*, vol. 6, no. 4, pp. 889–895, 2013.

[63] H.-G. Schaible, A. Ebersberger, and G. S. Banchet, "Mechanisms of pain in arthritis," *Annals of the New York Academy of Sciences*, vol. 966, no. 1, pp. 343–354, 2002.

[64] L. Meert, R. J. E. M. Smeets, I. Baert, M. Mertens, A. Boonen, and M. Meeus, "Treatment of central sensitization in patients with rheumatoid arthritis: a narrative overview," *Current Treatment Options in Rheumatology*, vol. 5, no. 3, pp. 179–189, 2019.

[65] M. Meeus, S. Vervisch, L. S. De Clerck, G. Moorkens, G. Hans, and J. Nijs, "Central sensitization in patients with rheumatoid arthritis: a systematic literature review," *Seminars in Arthritis and Rheumatism*, vol. 41, no. 4, pp. 556–567, 2012.

[66] D. Brenn, F. Richter, and H.-G. Schaible, "Sensitization of unmyelinated sensory fibers of the joint nerve to mechanical stimuli by interleukin-6 in the rat: an inflammatory mechanism of joint pain," *Arthritis & Rheumatism*, vol. 56, no. 1, pp. 351–359, 2007.

[67] L. Zhang, T. Berta, Z. Z. Xu, T. Liu, J. Y. Park, and R. R. Ji, "TNF-α contributes to spinal cord synaptic plasticity and inflammatory pain: distinct role of TNF receptor subtypes 1 and 2," *Pain*, vol. 152, pp. 419–427, 2011.

[68] L. R. Watkins and S. F. Maier, "Beyond neurons: evidence that immune and glial cells contribute to pathological pain states," *Physiological Reviews*, vol. 82, no. 4, pp. 981–1011, 2002.

[69] M. B. Johnson, A. D. Young, and I. Marriott, "The therapeutic potential of targeting substance P/NK-1R interactions in inflammatory CNS disorders," *Frontiers in Cellular Neuroscience*, vol. 10, p. 296, 2017.

[70] G. Chen, Y.-Q. Zhang, Y. J. Qadri, C. N. Serhan, and R.-R. Ji, "Microglia in Pain: detrimental and protective roles in pathogenesis and resolution of pain," *Neuron*, vol. 100, no. 6, pp. 1292–1311, 2018.

[71] S. D. Boyden, I. N. Hossain, A. Wohlfahrt, and Y. C. Lee, "Non-inflammatory causes of pain in patients with rheumatoid arthritis," *Current Rheumatology Reports*, vol. 18, no. 6, p. 30, 2016.

[72] E. Myasoedova, J. Davis, E. L. Matteson, and C. S. Crowson, "Is the epidemiology of rheumatoid arthritis changing? Results from a population-based incidence study, 1985—2014," *Annals of the Rheumatic Diseases*, vol. 79, no. 4, pp. 440–444, 2020.

[73] J. A. Sparks, "Rheumatoid arthritis," *Annals of Internal Medicine*, vol. 170, no. 1, 2019.

[74] Y. Lu, L. Li, Z. Lin et al., "A new treatment modality for rheumatoid arthritis: combined photothermal and photodynamic therapy using Cu7.2 S4 nanoparticles," *Advanced Healthcare Materials*, vol. 7, Article ID e1800013, 2018.

[75] F. Zeidan and D. R. Vago, "Mindfulness meditation-based pain relief: a mechanistic account," *Annals of the New York Academy of Sciences*, vol. 1373, no. 1, pp. 114–127, 2016.

[76] L. E. Carlson, "Mindfulness-based interventions for physical conditions: a narrative review evaluating levels of evidence," *ISRN Psychiatry*, vol. 2012, Article ID 651583, 21 pages, 2012.

[77] P. J. Quartana, C. M. Campbell, and R. R. Edwards, "Pain catastrophizing: a critical review," *Expert Review of Neurotherapeutics*, vol. 9, no. 5, pp. 745–758, 2009.

[78] L. Scascighini, V. Toma, S. Dober-Spielmann, and H. Sprott, "Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes," *Rheumatology*, vol. 47, no. 5, pp. 670–678, 2008.

[79] S. J. Linton and W. S. Shaw, "Impact of psychological factors in the experience of pain," *Physical Therapy*, vol. 91, no. 5, pp. 700–711, 2011.

[80] A. J. Motilal, "Self—realization through through vedanta and yoga," *Ancient Science of Life*, vol. 3, pp. 31–36, 1983.

[81] C. Woodyard, "Exploring the therapeutic effects of yoga and its ability to increase quality of life," *International Journal of Yoga*, vol. 4, no. 2, pp. 49–54, 2011.

[82] A. Büssing, A. Michalsen, S. B. Khalsa, S. Telles, and K. J. Sherman, "Effects of yoga on mental and physical health: a short summary of reviews," *Evidence-Based Complementary and Alternative Medicine: eCAM*, vol. 2012, Article ID 165410, 7 pages, 2012.

[83] A. Vijayaraghava, V. Doreswamy, O. S. Narasipur, R. Kunnavil, and N. Srinivasamurthy, "Effect of yoga practice on levels of inflammatory markers after moderate and strenuous exercise," *Journal of Clinical and Diagnostic Research*, vol. 9, 2015.

[84] S. Gautam, M. Tolahunase, U. Kumar, and R. Dada, "Impact of yoga based mind-body intervention on systemic inflammatory markers and co-morbid depression in active Rheumatoid arthritis patients: a randomized controlled trial," *Restorative Neurology and Neuroscience*, vol. 37, no. 1, pp. 41–59, 2019.

[85] S. Gautam, U. Kumar, and R. Dada, "Yoga and its impact on chronic inflammatory autoimmune arthritis," *Frontiers in Bioscience*, vol. 13, pp. 77–116, 2021.

[86] S. Telles, N. Sayal, C. Nacht et al., "Yoga: can it Be integrated with treatment of neuropathic pain," *Integrative Medicine International*, vol. 4, pp. 69–84, 2017.

[87] C. Villemure, M. Ceko, V. A. Cotton, and M. C. Bushnell, "Insular cortex mediates increased pain tolerance in yoga practitioners," *Cerebral Cortex*, vol. 24, no. 10, pp. 2732–2740, 2014.

[88] S. H. Moonaz, C. O. Bingham, L. Wissow, and S. J. Bartlett, "Yoga in sedentary adults with arthritis: effects of a randomized controlled pragmatic trial," *Journal of Rheumatology*, vol. 42, no. 7, pp. 1194–1202, 2015.

[89] S. J. Bartlett, S. H. Moonaz, C. Mill, S. Bernatsky, and C. O. Bingham, "Yoga in rheumatic diseases," *Current Rheumatology Reports*, vol. 15, no. 12, p. 387, 2013.

[90] S. Gautam, M. Kumar, U. Kumar, and R. Dada, "Effect of an 8-week yoga-based lifestyle intervention on psycho-neuro-immune Axis, disease activity, and perceived quality of life in rheumatoid arthritis patients: a randomized controlled trial," *Frontiers in Psychology*, vol. 11, p. 2259, 2020.

[91] S. Gautam, U. Kumar, M. Kumar, D. Rana, and R. Dada, "Yoga improves mitochondrial health and reduces severity of autoimmune inflammatory arthritis: a randomized controlled trial," *Mitochondrion*, vol. 58, pp. 147–159, 2021.

[92] S. Gautam, R. Saxena, T. Dada, and R. Dada, "Yoga—impact on mitochondrial health: clinical consequences," *Annals of Neurosciences*, vol. 28, no. 3-4, pp. 114–116, 2021.

[93] S. Telles, N. Sayal, C. Nacht et al., "Yoga: can it be integrated with treatment of neuropathic pain?" *Annals of Neurosciences*, vol. 26, no. 2, pp. 82–91, 2019.

[94] H. N. Venkatesh, H. Ravish, C. R. Wilma Delphine Silvia, and H. Srinivas, "Molecular signature of the immune response to yoga therapy in stress-related chronic disease conditions: an insight," *International Journal of Yoga*, vol. 13, pp. 9–17, 2020.

[95] S. Bisht, S. Banu, S. Srivastava et al., "Sperm methylome alterations following yoga-based lifestyle intervention in patients of primary male infertility: a pilot study," *Andrologia*, vol. 52, Article ID e13551, 2020.

[96] S. Bisht, B. Chawla, M. Tolahunase, R. Mishra, and R. Dada, "Impact of yoga based lifestyle intervention on psychological stress and quality of life in the parents of children with retinoblastoma," *Annals of Neurosciences*, vol. 26, no. 2, pp. 66–74, 2019.

[97] V. Dhawan, M. Kumar, D. Deka et al., "Meditation & yoga: impact on oxidative DNA damage & dysregulated sperm transcripts in male partners of couples with recurrent pregnancy loss," *Indian Journal of Medical Research*, vol. 148, pp. S134–S139, 2018.

[98] M. R. Tolahunase, R. Sagar, M. Faiq, and R. Dada, "Yoga- and meditation-based lifestyle intervention increases neuroplasticity and reduces severity of major depressive disorder: a randomized controlled trial," *Restorative Neurology and Neuroscience*, vol. 36, no. 3, pp. 423–442, 2018.

[99] M. Tolahunase, R. Sagar, and R. Dada, "Impact of yoga and meditation on cellular aging in apparently healthy individuals: a prospective, open-label single-arm exploratory study," *Oxidative Medicine and Cellular Longevity*, vol. 2017, Article ID 7928981, 9 pages, 2017.

[100] S. Arora and J. Bhattacharjee, "Modulation of immune responses in stress by Yoga," *International Journal of Yoga*, vol. 1, no. 2, pp. 45–55, 2008.

[101] J. E. Bower and M. R. Irwin, "Mind-body therapies and control of inflammatory biology: a descriptive review," *Brain, Behavior, and Immunity*, vol. 51, pp. 1–11, 2016.

[102] M. L. Kohut, D. A. McCann, D. W. Russell et al., "Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of β-blockers, BMI, and psychosocial factors in older adults," *Brain, Behavior, and Immunity*, vol. 20, no. 3, pp. 201–209, 2006.

[103] Y. Colgrove, N. Gravino-Dunn, S. Dinyer, E. Sis, A. Heier, and N. Sharma, "Physical and physiological effects of yoga for an underserved population with chronic low back pain," *International Journal of Yoga*, vol. 12, no. 3, pp. 252–264, 2019.

[104] J. K. Kiecolt-Glaser, L. Christian, H. Preston et al., "Stress, inflammation, and yoga practice," *Psychosomatic Medicine*, vol. 72, no. 2, pp. 113–121, 2010.

[105] S. M. Gold, K.-H. Schulz, S. Hartmann et al., "Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls," *Journal of Neuroimmunology*, vol. 138, pp. 99–105, 2003.

[106] B. Kuo, M. Bhasin, J. Jacquart et al., "Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease," *PLoS One*, vol. 10, no. 4, Article ID e0123861, 2015.

[107] J. E. Bower, G. Greendale, A. D. Crosswell et al., "Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial," *Psychoneuroendocrinology*, vol. 43, pp. 20–29, 2014.

[108] S. Srirangan and E. H. Choy, "The role of interleukin 6 in the pathophysiology of rheumatoid arthritis," *Therapeutic Advances in Musculoskeletal Disease*, vol. 2, no. 5, pp. 247–256, 2010.

[109] H. Su, C.-T. Lei, and C. Zhang, "Interleukin-6 signaling pathway and its role in kidney disease: an update," *Frontiers in Immunology*, vol. 8, p. 405, 2017.

[110] G. J. Martinez, R. I. Nurieva, X. O. Yang, and C. Dong, "Regulation and function of proinflammatory TH17 cells," *Annals of the New York Academy of Sciences*, vol. 1143, no. 1, pp. 188–211, 2008.

[111] M. Venihaki, P. Dikkes, A. Carrigan, and K. P. Karalis, "Corticotropin-releasing hormone regulates IL-6 expression during inflammation," *Journal of Clinical Investigation*, vol. 108, no. 8, pp. 1159–1166, 2001.

[112] M. N. Silverman, B. D. Pearce, C. A. Biron, and A. H. Miller, "Immune modulation of the hypothalamic-pituitary-adrenal (HPA) Axis during viral infection," *Viral Immunology*, vol. 18, no. 1, pp. 41–78, 2005.

[113] S. L. Hider, W. Tanveer, A. Brownfield, D. L. Mattey, and J. C. Packham, "Depression in RA patients treated with anti-TNF is common and under-recognized in the rheumatology clinic," *Rheumatology*, vol. 48, no. 9, pp. 1152–1154, 2009.

[114] M. Farrugia and B. Baron, "The role of TNF-α in rheumatoid arthritis: a focus on regulatory *T* cells," *Journal of clinical and translational research*, vol. 2, no. 3, pp. 84–90, 2016.

[115] H.-J. Jeong, H. N. Koo, H. J. Na et al., "Inhibition OF TNF-α and IL-6 production BY aucubin through blockade OF NF-κB activation IN RBL-2H3 mast cells," *Cytokine*, vol. 18, no. 5, pp. 252–259, 2002.

[116] E. Gonzalo-Gil and M. Galindo-Izquierdo, "Role of transforming growth factor-beta (TGF) beta in the physiopathology of rheumatoid arthritis," *Reumatología Clínica*, vol. 10, no. 3, pp. 174–179, 2014.

[117] Q. Niu, B. Cai, Z. C. Huang, Y. Y. Shi, and L. L. Wang, "Disturbed Th17/Treg balance in patients with rheumatoid arthritis," *Rheumatology International*, vol. 32, no. 9, pp. 2731–2736, 2012.

[118] B. Arellano, D. J. Graber, and C. L. Sentman, "Regulatory *T* cell-based therapies for autoimmunity," *Discovery Medicine*, vol. 22, pp. 73–80, 2016.

[119] H. Y. Yap, S. Tee, M. Wong, S. K. Chow, S. C. Peh, and S. Y. Teow, "Pathogenic role of immune cells in rheumatoid arthritis: implications in clinical treatment and biomarker development," *Cells*, vol. 7, 2018.

[120] Y. Li, M. R. Lefever, D. Muthu, J. M. Bidlack, E. J. Bilsky, and R. Polt, "Opioid glycopeptide analgesics derived from endogenous enkephalins and endorphins," *Future Medicinal Chemistry*, vol. 4, no. 2, pp. 205–226, 2012.

[121] T. Dada, D. Mittal, K. Mohanty et al., "Mindfulness meditation reduces intraocular pressure, lowers stress biomarkers and modulates gene expression in glaucoma," *Journal of Glaucoma*, vol. 27, no. 12, pp. 1061–1067, 2018.

[122] M. Gagrani, M. A. Faiq, T. Sidhu et al., "Meditation enhances brain oxygenation, upregulates BDNF and improves quality of life in patients with primary open angle glaucoma: a randomized controlled trial," *Restorative Neurology and Neuroscience*, vol. 36, no. 6, pp. 741–753, 2018.

[123] C. C. Streeter, T. H. Whitfield, L. Owen et al., "Effects of yoga versus walking on mood, anxiety, and brain GABA levels: a

randomized controlled mrs study," *Journal of Alternative and Complementary Medicine*, vol. 16, no. 11, pp. 1145–1152, 2010.

[124] G. H. Naveen, S. Varambally, J. Thirthalli, M. Rao, R. Christopher, and B. N. Gangadhar, "Serum cortisol and BDNF in patients with major depression-effect of yoga," *International Review of Psychiatry*, vol. 28, no. 3, pp. 273–278, 2016.

[125] N. Maninger, O. M. Wolkowitz, V. I. Reus, E. S. Epel, and S. H. Mellon, "Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS)," *Frontiers in Neuroendocrinology*, vol. 30, no. 1, pp. 65–91, 2009.

[126] P. J. Schmidt, R. C. Daly, M. Bloch et al., "Dehydroepiandrosterone monotherapy in midlife-onset major and minor depression," *Archives of General Psychiatry*, vol. 62, no. 2, pp. 154–162, 2005.

[127] R. Pal, S. N. Singh, A. Chatterjee, and M. Saha, "Age-related changes in cardiovascular system, autonomic functions, and levels of BDNF of healthy active males: role of yogic practice," *Age*, vol. 36, no. 4, p. 9683, 2014.

[128] L. Schwarz and W. Kindermann, "Changes in beta-Endorphin levels in response to aerobic and anaerobic exercise," *Sports Medicine*, vol. 13, no. 1, pp. 25–36, 1992.

Hindawi
Evidence-Based Complementary and Alternative Medicine
Volume 2022, Article ID 6149052, 9 pages
https://doi.org/10.1155/2022/6149052

Research Article

Reduced Pain by Mind-Body Intervention Correlates with Improvement of Shoulder Function in People with Shoulder Pain: A Randomized Controlled Trial

Hojung Kang,[1] Seung Chan An,[1] Byeongkwan Kim,[2] Youngjae Song,[1] Jaesung Yoo,[1] Eugene Koh,[3] Seungheun Lee,[1] and Hyun-Jeong Yang[1,4]

[1]*Korea Institute of Brain Science, Seoul 06022, Republic of Korea*
[2]*Bomunsan Hospital, Daejeon 35052, Republic of Korea*
[3]*Temasek Life Sciences Laboratories, Singapore 117604, Singapore*
[4]*Department of Integrative Health Care, University of Brain Education, Cheonan, Republic of Korea*

Correspondence should be addressed to Hyun-Jeong Yang; yang@ube.ac.kr

Received 7 October 2021; Revised 6 January 2022; Accepted 8 March 2022; Published 24 March 2022

Academic Editor: Shirley Telles

Meditation and acupressure-like stimulations have been shown to relieve pain. The aim of this study was to determine whether a short bout of mind-body intervention combined with meditation and acupressure-like stimulation was able to alleviate shoulder pain and improve its function in a short time window. Sixty-five adults with shoulder pain were recruited and randomly classified into two groups. One group participated in an intervention which consisted of acupressure-like stimulation and meditation over a 5 min period. The other group was instructed to rest during this time. A visual analog scale (VAS) pain score and objective constant scores were measured before and after intervention to determine shoulder pain and range of motion (ROM), respectively. A two-way repeated measures analysis of variance with Bonferroni correction and a regression analysis were performed. VAS pain, objective constant score, flexion, abduction, and external rotation score showed significant interactions between time and group. The pain intensity was significantly reduced, while flexion and abduction were significantly improved, in the experimental group compared to the control group, after the intervention. In addition, the change of flexion negatively correlated with the change of pain intensity in the experimental group, but not in the control group. These results show that a short-term application of mind-body intervention significantly alleviates shoulder pain and improves shoulder movement, suggesting its potential use as a therapy for people with shoulder pain.

1. Introduction

Shoulder pain is one of the most common musculoskeletal complaints. A significant percentage of patients seeking medical attention have shoulder pain. The reported lifetime prevalence of shoulder pain ranges from 6.7% to 66.7% of the population [1]. The shoulder is a complex joint whose function is to position the hand for activities of daily living, work, and sports [2]. Failure of this mechanism can have a dramatic effect on one's lifestyle. A large number of patients with shoulder pain are treated nonoperatively by using alternative interventions such as massage, physiotherapy, yoga, and meditation [3–6].

Meditation shows promise for alleviating chronic pain [7, 8]. In a recent meta-analysis of 30 RCTs, meditation was related with a small decrease of pain compared to different types of controls [9]. Reduction of pain by meditation is associated with activation of the following brain areas: subgenual ACC for cognitive and affective pain control, orbitofrontal cortex for supporting contextual evaluation of sensory events, and right anterior insula for afferent nociceptive signal modulation and interoception awareness [10, 11]. Moreover, ascending nociceptive signals in the thalamus were also downregulated by executive attention during meditation [10, 11]. A series of changes in the brain

induced by meditation suggests that meditation reduces pain through recontextualizing the pain as innocuous sensory information. The pain modulatory pathway based on mindfulness is mediated nonopioidergically [12], distinct from the placebo-based pain relief pathway [11, 12]. In a recent study, intravenous administration of an opioid antagonist naloxone does not antagonize meditation-induced pain relief, suggesting that pain relief by meditation is possibly mediated by the nonopioid pathway [13]. Moreover, meditation techniques often include breathing modulation, and in a study which investigated the role of breathing on pain relief, slow-paced breathing was suggested to relieve pain via the nonopioid pathway [14], showing that the breathing component in meditation is an effective means of pain regulation.

Acupressure has been studied extensively as a method for pain management. A meta-analysis of 15 studies showed that acupressure is effective for relieving a variety of pains including dysmenorrhea, labor pain, low back pain, chronic headache, and other traumatic pain [15]. In a recent systemic review about the effects of auricular acupressure on pain management, 12 studies showed a significant improvement in the pain outcomes of auricular acupressure compared with the control groups [16]. In a randomized controlled trial (RCT) of 33 women suffering from chronic neck pain, acupressure provided significant pain relief [17]. In another RCT with 24 individuals with chronic neck pain, a manual therapy technique reduced the visual analog scale (VAS) pain score and increased range of motion (ROM) of the neck [18]. In an RCT with 62 patients who had undergone a total knee replacement operation, a 3-day postoperation auricular acupressure treatment significantly reduced the use of analgesic drug usage, indicating relief of postoperative pain by acupressure and significantly improved passive knee motion on the 3rd day after surgery [19]. When pain is reduced by various methods as above, improvements in ROM of joints are also observed. In professional tennis players, shoulder ROM seems to be associated with shoulder pain history [20], supporting the association between pain and motion.

As described above, mind-body interventions such as meditation and acupressure have the potential to relieve pain intensity and improve joint mobility. In this study, we performed a randomized controlled trial for people with shoulder pain under the hypothesis that a short-term intervention which combined acupressure-like stimulation and meditation may help to relieve shoulder pain and improve shoulder function.

2. Materials and Methods

2.1. Participants. The participants were recruited through flyers and online and offline poster announcements (local clinics and public centers). The inclusion criteria were as follows: people with shoulder pain for at least 2 months, people who consented to participate in the research voluntarily, and people who could hear the explanation of the experiment (are not hearing impaired), read, understand the manual, speak their opinions, and follow the instructions. Exclusion criteria were as follows: people with shoulder pain due to rheumatic arthritis, osteoarthritis, bone defect injury, osteoporosis, and malignant tumor and people with low pain intensity (VAS pain score <4) during shoulder movement of flexion, abduction, internal rotation, and external rotation. Based on a pilot study, a sample size of 27 participants per group was sufficient to give over 90% of power with an alpha level set at 0.05 for a two-tailed unpaired t-test model (g-power software 3.1.9.7). Considering the dropout rate, a total of 65 participants were recruited. Sixty-five people volunteered for the study and were randomly divided into two groups: the experimental ($N = 33$) and control ($N = 32$) groups. Two and one individuals were dropped from each group, respectively, due to low pain intensity (VAS pain score <4) during ROM measurement (Figure 1).

All participants were given an explanation of the experiments and participated in the measurement of four subscales (pain, activities of daily living, ROM (flexion, abduction, internal rotation, and external rotation), and strength) of the constant score and VAS pain intensity. Constant score has been adopted as an official tool for assessing the shoulder by the European Society for Surgery of the Shoulder and the Elbow [21]. The intervention protocol was applied for 5 min for individuals in the experimental group, while the participants of the control group took rest. After the intervention period, VAS pain intensity and two subscales (ROM and strength) of the constant score were measured again. To minimize bias, the participants were asked not to reveal information to the evaluators about the treatment to which they had been assigned. Participants were rewarded with 50,000 KRW for their participation. The research has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. All subjects signed an informed consent form before their inclusion. The Institutional Review Board of the University of Brain Education approved this study. All the experiments were performed in Bomunsan Hospital in Daejeon, Korea. The current protocol is registered as a clinical trial in the Clinical Research Information Service (CRIS registration number: KCT0005602).

2.2. BHP Meditation Intervention. Brain education meditation (BEM) (also referred as brain wave vibration meditation) is a modernized mind-body training method which is rooted in Korean Sundo tradition and consists of several techniques including exercises which improves the connection between the brain and body, such as qigong, breathing postures, body awareness meditation, and brain wave vibration meditation with rhythmic body movement [22–28], and has been investigated for its differences from other mind-body interventions such as mindfulness meditation and yoga [23, 26]. BEM is associated with its effects on various body systems such as changes in brain structure and function [24, 29–31], improvements in emotion and cognition [32–34], and suppression of inflammation [25, 35]. Brain education healing point (BHP) meditation, which is used in the current study, is a meditation program that combines acupressure-like stimulation with the meditation of the abovementioned BEM tradition [36]. During BHP

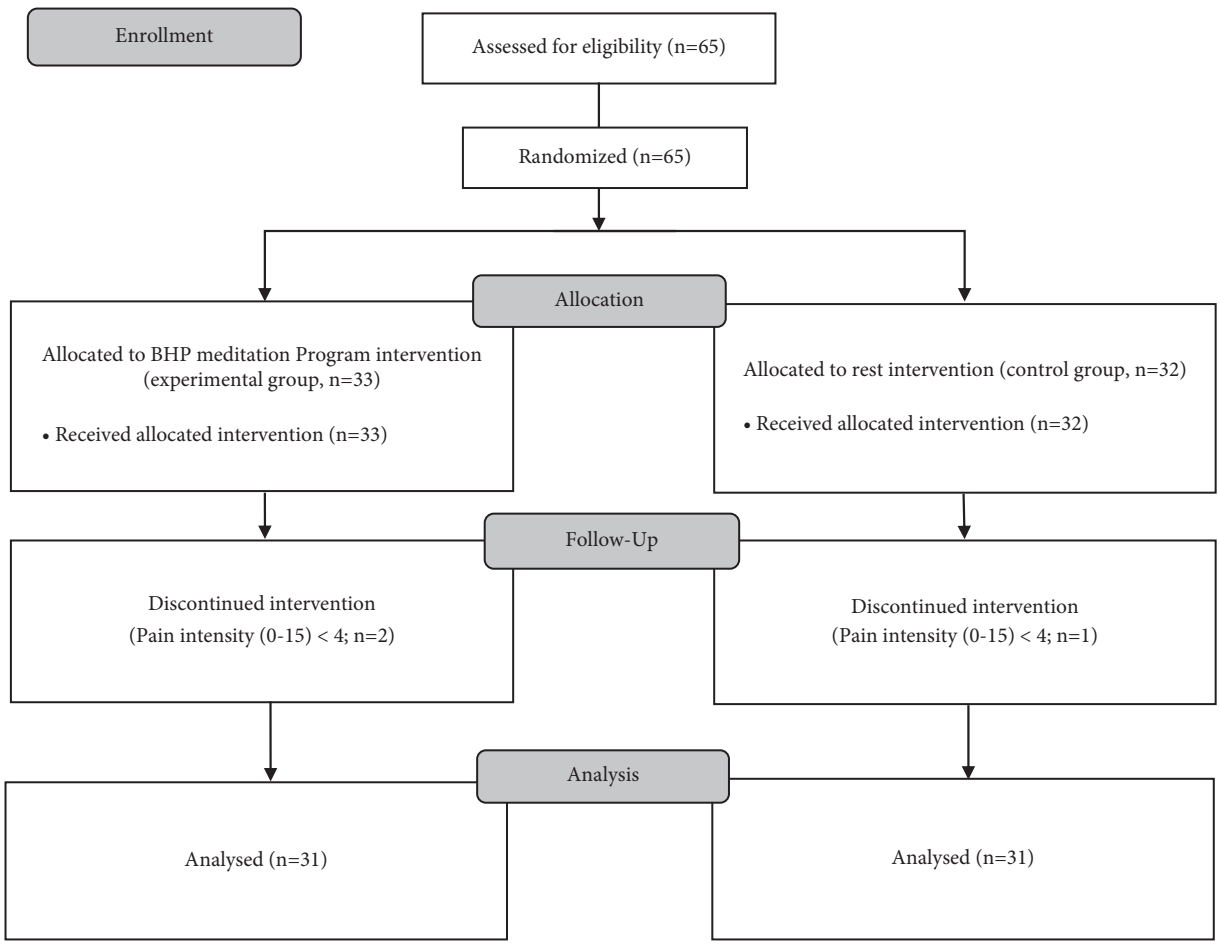

Figure 1: Constant 2010 flow diagram. Sixty-five participants were recruited. The participants were randomly divided into two groups: experimental and control groups. Sixty-two participants (experimental, 31; control, 31) completed the study, with 3 dropouts (experimental, 2; control, 1). The dropouts showed less than 4 points of pain intensity.

meditation, specific body points are stimulated with pressure, and improvements of the body area of attention are visualised via imagery meditation combined with breathing regulation [36]. BHP meditation is a short and intense meditation program that can lead even beginners to deep meditation.

BHP meditation consists of acupressure-like stimulation and breathing/body awareness meditation. The first step in BHP meditation is to find a "healing point," where subjects report more pain than other places when a specific part of the body is pressed. This point is called the BHP point and can be found anywhere on the body. BHP meditation first applies acupressure-like stimulation and then induces relaxed attention by body awareness and imagery meditation combined with breathing [36]. In this study, we restricted the BHP point to within 0.5 cm from the end of the eponychium to exclude confounding factors related to body parts. This specific region is most frequently used for BHP meditation [36]. The second step is to press the BHP point with moderate force using a BHP finder (HSP World, AZ), which resembles a thick pen with a blunt end. The BHP points of all participants were stimulated by one experienced trainer to remove variability. The trainer pressed the BHP point with moderate force for few seconds, released, and repeated this cycle for 1 min. After 1 min of pressing the BHP point, participants were guided to meditate on body awareness with breathing for an additional 4 min under the trainer's guidance. The total participation time for BHP meditation was 5 min.

2.3. Control Condition. A waitlist control group design was employed. Participants in the control group were seated and asked to relax for 5 min. Data were collected from the control group on the same schedule as the experimental group. Control participants were offered the BHP mediation program only after the experiments. No further data were collected from control participants at this time point.

2.4. Constant Score. The Constant score was divided into four subscales, including pain during the last 24 h (15 points maximum), activities of daily living for the last one week (20 points maximum), range of motion (ROM; 40 points maximum), and strength (25 points maximum) [21]. For ROM, abduction, flexion, internal rotation, and external rotation were measured. To exclude any bias during measurement, physical

Table 1: Demographics.

Characteristics	Experimental group ($n = 33$)	Control group ($n = 32$)	Statistics	
			χ^2 or t	P
Gender, n (male/female)	7/26	6/26	0.0616	0.8041
Ages, years	57.48 ± 10.33	59.28 ± 11.82	0.6530	0.5161
Sleep	0.85 ± 0.67	1.06 ± 0.67	1.2912	0.2013
Work	2.09 ± 0.98	2.09 ± 1.15	0.0108	0.9915
Recreation	2.09 ± 1.04	1.71 ± 0.89	1.5475	0.1268
Position	6.06 ± 2.85	6.19 ± 2.40	0.1938	0.8469
Pain	6.24 ± 3.21	6.59 ± 3.22	0.4403	0.6613

Values indicate mean ± SD. Scores of sleep, work, recreation, and position, which are subjective subscales of constant score, were assessed based on the previous week, while pain score was obtained by assessment based on the previous 24 h.

therapists were blinded from the details of the experiments and technically measured ROM and pain score. Strength was tested with scoring based on the number of kilograms of pull the patient can resist in abduction for 3 seconds, up to a maximum of 90°. The higher the score, the better the quality of function (minimum 0, maximum 100). The subjective scores (i.e., pain for last 24 h and activities of daily living for the last 1 week) were used for demographics, and the objective scores (i.e., ROM and strength before and after the intervention) were compared to analyze shoulder function. The combination of subjective and objective tests to estimate shoulder function is given in Supplementary Table 1. Additionally, the pain intensity experienced by the participant during ROM activities was measured on a 16-point numerical pain VAS.

2.5. Statistical Analysis. The association between BHP meditation and shoulder pain was analyzed using two-way repeated analysis of variance (ANOVA), including the between-subjects factor of intervention condition (BHP meditation or control) and the within-subjects factor of assessment time. For the constant scores, the assessments included pretreatment scores (before the BHP meditation session) and posttreatment scores (after the BHP meditation session). Multiple comparisons were corrected using critical values from the t distribution after Bonferroni adjustment. Regression analysis was performed to confirm the relationship between the change of pain intensity and the change of each objective constant score affected by the intervention.

3. Results

3.1. Demographics. A total of 65 subjects participated in the current study. The distribution of gender was similar in both groups ($p = 0.8041$, χ^2 test, Table 1). The age of the experimental group (57.48 ± 10.33 years old) and control group (59.28 ± 11.82 years old) did not differ significantly ($p = 0.5161$, Student's t-test). The subjective subscales of constant score, including sleep, work, recreation, position, and pain scores, were not significantly different between the two groups, as given in Table 1.

3.2. Constant Score and Pain Intensity. The VAS pain score was analyzed via a two-way repeated measures ANOVA with group (experimental/control) and time (pre/post) as factors. Pre/postmeasurement results in experimental and control groups are given in Supplementary Table 2. We found a main effect in the time factor (F (1, 60) = 51.32, $p = 1.31 \times 10^{-9}$, $\eta_p^2 = 0.461$, Figure 2(a)). In the interaction analysis between the group and time factors, a significant interaction was found (F (1, 60) = 16.69, $p = 1.33 \times 10^{-4}$, $\eta_p^2 = 0.218$, Figure 2(a)). Post hoc tests using the Bonferroni correction revealed that there was no significant difference between the experimental group and the control group before intervention in the VAS pain score. However, the VAS pain score of the experimental group was significantly lower compared with that of the control group after the intervention (experimental group = 5.52 ± 1.05, control group = 8.16 ± 0.81, $p = 3.76 \times 10^{-4}$, Figure 2(a)). For the objective constant score, there was a main effect in the time factor (F (1, 60) = 28.36, $p = 1.59 \times 10^{-6}$, $\eta_p^2 = 0.321$, Figure 2(b)) and interaction between the group and time factors (F (1, 60) = 16.44, $p = 1.47 \times 10^{-4}$, $\eta_p^2 = 0.215$, Figure 2(b)). However, no significant difference was found in the group factor. For the flexion, abduction, and external rotation score, significant results were found in the main effect of time (F (1, 60) = 21.13, $p = 2.26 \times 10^{-5}$, $\eta_p^2 = 0.26$, Figure 2(c); F (1, 60) = 36.07, $p = 1.20 \times 10^{-7}$, $\eta_p^2 = 0.38$, Figure 2(d); F (1,60) = 16.04, $p = 1.49 \times 10^{-4}$, $\eta_p^2 = 0.21$, Figure 2(e), respectively) and the interaction between group and time factors (F (1, 60) = 24.73, $p = 5.84 \times 10^{-6}$, $\eta_p^2 = 0.29$, Figure 2(c); F (1, 60) = 21.89, $p = 1.69 \times 10^{-5}$, $\eta_p^2 = 0.27$, Figure 2(d); F (1,60) = 5.54, $p = 2.18 \times 10^{-2}$, $\eta_p^2 = 0.08$, Figure 2(e), respectively). In internal rotation, there was a significant main effect of time; however, no significant interaction between group and time factors was found (Figure 2(f)). In strength, there were no significant main effects of time (Figure 2(g)). Post hoc tests using the Bonferroni correction revealed that there was no significant difference between the experimental group and the control group before the intervention in the flexion and abduction performance. However, after the intervention, it was confirmed that the flexion and abduction performance of the experimental group was significantly improved compared to the control group (experimental group = $136 \pm 2°$, control group = $115 \pm 2°$, $p = 7.27 \times 10^{-5}$; experimental group = $143 \pm 2°$, control group = $120 \pm 3°$, $p = 6.36 \times 10^{-4}$, respectively, with Bonferroni post hoc test).

According to the regression analysis for confirming the relationship between the change of pain intensity and the change of each objective constant score (Figure 3), VAS pain

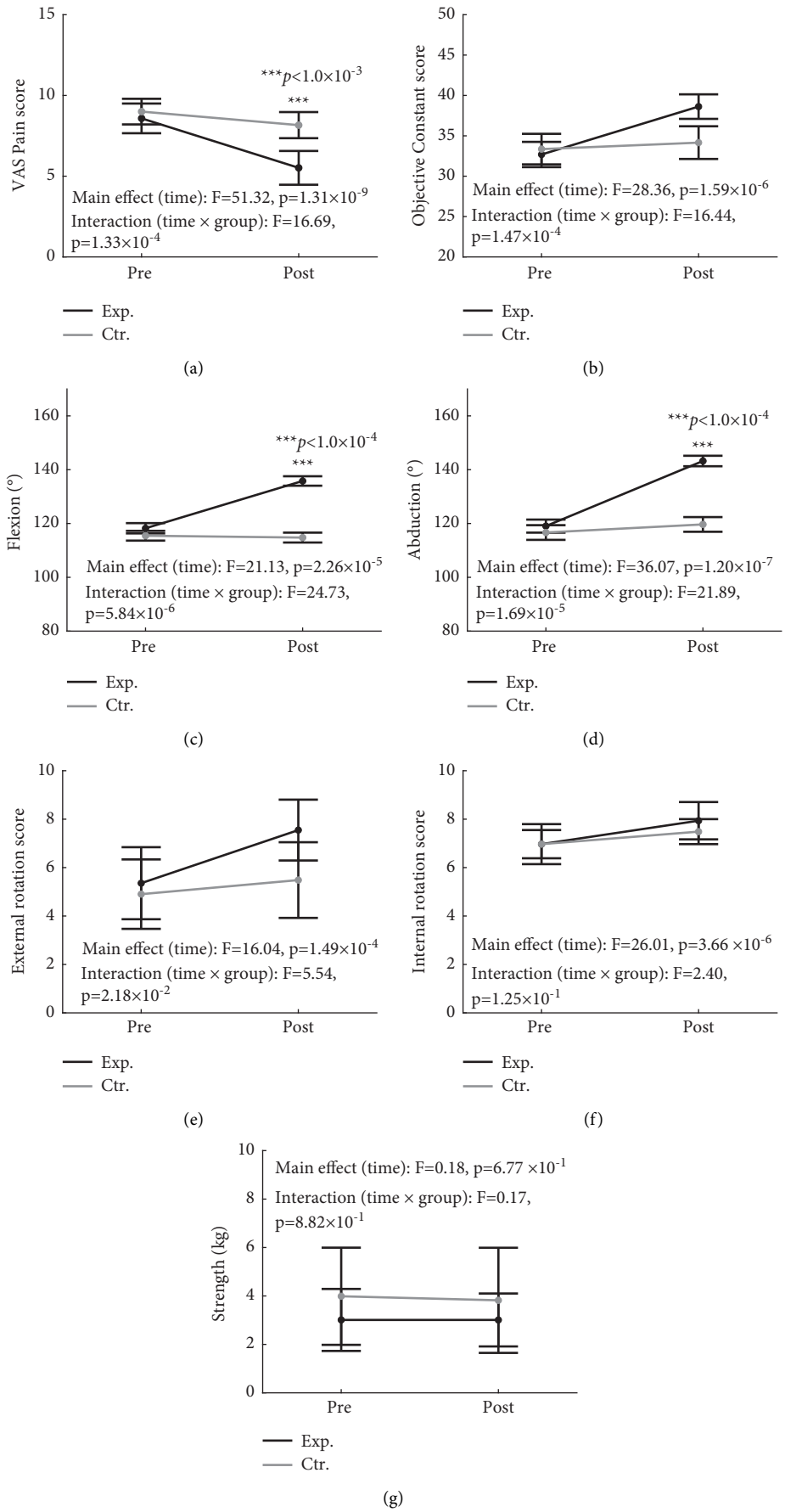

Figure 2: The effects of the intervention on pain, range of shoulder movement, and shoulder strength. Two-way repeated measures ANOVA of following measurements are indicated: (a) VAS pain score; (b) objective constant score; (c) flexion; (d) abduction; (e) external rotation score; (f) internal rotation score; (g) strength. Post hoc Bonferroni correction, $p < 1.0 \times 10^{-3}$, ***. The dots and error bars of pre and postintervention indicate mean ± SD.

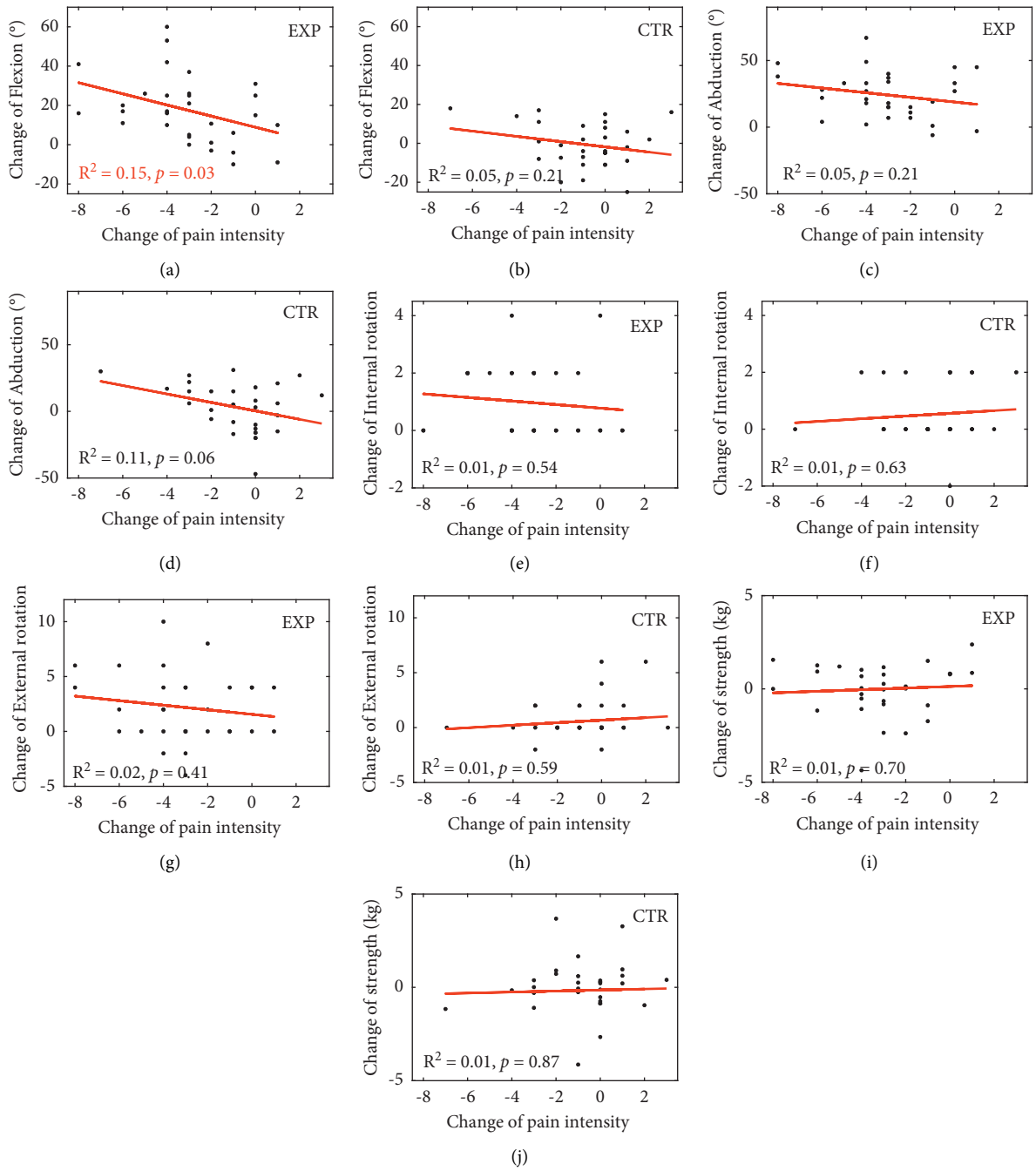

Figure 3: Regression analysis between change of each objective task of constant score and change of VAS pain score. Regression analysis of change of VAS pain score with change of flexion ((a)-(b)), abduction ((c)-(d)), internal rotation ((e)-(f)), external rotation ((g)-(h)), and abduction strength ((i)-(j)). Results of experimental ((a), (c), (e), (g), (i)) and control ((b), (d), (f), (h), (j)) groups are indicated. EXP, experimental group. CTR, control group.

score change was associated with a change in forward flexion ($R^2 = 0.15$, $p = 0.03$) in the experimental group (Figure 3(a)) but not in the control group (Figure 3(b)). The obtained R^2 value for endogenous variables is greater than 0.1, which is deemed adequate [37]. No other objective constant score task changes were significantly associated with pain intensity in either group (Figures 3(c)–3(j)).

Our results indicated that BHP meditation intervention significantly reduced shoulder pain during motion (Figure 2(a)) and improved shoulder ROM (Figures 2(c)–2(d)). Moreover, the pain reduction was associated with the improved forward flexion (Figure 3(a)), one of the tasks for shoulder function evaluation.

4. Discussion

In this study, we aimed to examine the effects of mind-body intervention on the treatment and recovery of shoulder pain.

Previous work has shown the effects of mind-body intervention on pain relief [9, 38] and the relationship between pain and motion of joints [39, 40]. Acupressure techniques have been reported to reduce pain and improve joint maneuverability [15, 18, 19, 41]. BEM has also been studied for its effects on inflammation reduction [25, 35], which exacerbate pain [42, 43]. In this study, we found that BHP intervention, which combines acupressure-like stimulation with BEM, can help relieve pain and improve shoulder motion for people with chronic shoulder pain.

The beneficial effects of meditation on pain reduction have been reported [44–46]. As meditation contributes to pain reduction via the reinterpretation of the nociceptive signal [47], the meditative component of BHP intervention may contribute to pain reduction via such mechanisms. Additionally, different types of breathing training such as virtual reality breathing and traditional mindful breathing also appear to improve pain thresholds. Interestingly, stimulation of different brain regions has been reported which varies depending on the breathing training method [48]. This suggests that breathing may have also independently affected pain regulation.

The acupressure-like component of BHP intervention may affect pain signaling which can be explained by gate control theory. During BHP intervention, pressure is applied to the participant's fingertips [36]. In the gate control theory of pain reduction, Melzack and Wall theorized that the experience of pain can be reduced by competing stimuli, such as pressure or cold, because these stimuli travel along faster nervous system pathways than pain [49]. In this way, stimulating the fingertips with sufficient pressure may interfere with the transmission of preexisting chronic shoulder pain to the brain, effectively "closing the gate" to the reception of pain before it can be processed.

Among the shoulder motions comprising the objective constant scores (i.e., flexion, abduction, internal rotation, and external rotation), BHP affected flexion and abduction, but not internal and external rotation. Each motion uses the following muscles: anterior deltoid, pectoralis major, and coracobrachialis for flexion [50]; supraspinatus, deltoid, trapezius, and serratus anterior for abduction [51]; subscapularis, latissimus dorsi, teres major, and deltoid (anterior fiber) for internal rotation [52]; and infraspinatus and teres minor for external rotation [52]. Therefore, the effect of BHP may be associated with the supraspinatus, trapezius, serratus anterior, pectoralis major, and coracobrachialis muscles which are related with flexion and abduction, although more measurements such as electromyogram data are required to make more concrete conclusions.

Furthermore, we found that pain intensity was negatively correlated with flexion in the BHP intervention group (Figure 3(a)). Previous work has also shown the relationships between pain intensity and shoulder function. During a repetitive shoulder flexion task, upper trapezius muscle pain induced reorganization in the coordinated activity of the subdivisions of the trapezius muscle [39]. In a study which investigated the contributing factors for shoulder function among 142 subjects with nonoperative shoulder disorders, pain intensity was found to contribute significantly to shoulder function score [40]. Based on the previous reports between pain reduction and performance improvement, it is plausible to think that the improved flexion performance may be at least partially contributed by pain reduction via BHP intervention. Compared to this, abduction performance was significantly improved regardless of pain intensity after BHP (Figure 2(d)). Abduction performance may respond to pain reduction with high sensitivity, i.e., exhibiting significant performance improvement under even a small pain reduction, although the mechanism requires further study.

The short nature of the intervention in this study currently only provides insights into the short-term effects of BHP intervention. In this study, the single short-term BHP intervention contributes to shoulder pain reduction and improvement in function. We surmise that the observed effects are likely to be direct responses of BHP intervention as they occurred within a short time window (i.e., 5 minutes). However, it is not known if BHP intervention over a longer-term period would retain its effectiveness as a treatment for shoulder pain; thus, data on the effectiveness of longer-term BHP interventions remains to be examined in a future study.

The method of recruiting participants is an additional limitation in this study. The participants applied for care on their own initiative and, thus, may have a positive attitude toward the treatment. This positive attitude may have created a group with high expectations. In addition, the control group did not receive a placebo. To minimize bias, the patients were asked not to reveal information to the evaluators about the treatment to which they had been assigned. We used an intention-to-treat analysis, provided standardized information to the participants, and used reliable and valid outcome measures. However, as the control group was a rest control rather than an active control or a placebo group, we cannot confirm if the effects of the intervention would be better than the placebo or other preexisting methods.

5. Conclusions

This RCT revealed that a single short-term BHP meditation not only relieves pain but also improved ROM (i.e., flexion and ablation) performance. Interestingly, flexion performance was found to be significantly related to pain reduction. These results indicate that pain reduction through BHP meditation has a direct effect on improving shoulder range of motion. Further studies utilizing active controls or comparisons against other therapies would provide more insight into the efficacy of BHP as a therapy for shoulder pain. Also, studies of long-term BHP intervention could validate that this intervention is effective in prolonging the effects of pain reduction and shoulder mobility observed here. The reduction of shoulder pain and functional improvements by BHP intervention would significantly contribute to improving the quality of life for patients with chronic shoulder pain.

Data Availability

The data generated or analyzed during this study are included within the article and Supplementary Materials.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

The authors thank the staff of Bomunsan Hospital and all the participants for helping to perform this study. This study was supported by the Korea Institute of Brain Science.

Supplementary Materials

Supplementary Table 1. The constant scoring system for individual parameters. Supplementary Table 2. Pre/post-measurement results in experimental and control groups. (*Supplementary Materials*)

References

[1] J. J. Luime, B. W. Koes, I. J. Hendriksen et al., "Prevalence and incidence of shoulder pain in the general population; a systematic review," *Scandinavian Journal of Rheumatology*, vol. 33, no. 2, pp. 73–81, 2004.

[2] S. Tempelhof, S. Rupp, and R. Seil, "Age-related prevalence of rotator cuff tears in asymptomatic shoulders," *Journal of Shoulder and Elbow Surgery*, vol. 8, no. 4, pp. 296–299, 1998.

[3] L. J. Kong, H. S. Zhan, Y. W. Cheng, W. A. Yuan, B. Chen, and M. Fang, "Massage therapy for neck and shoulder pain: a systematic review and meta-analysis," *Evidence-Based Complementary and Alternative Medicine*, vol. 2013, Article ID 613279, 10 pages, 2013.

[4] M. M. Shnayder, D. Brannan, L. A. Murphy et al., "Musculoskeletal pain and interest in meditation and yoga in home health aides: evidence from the home health occupations musculoskeletal examinations (HHOME) study," *Home Healthcare Now*, vol. 36, no. 2, pp. 103–113, 2018.

[5] S. Eyigor, R. Uslu, S. Apaydin, I. Caramat, and H. Yesil, "Can yoga have any effect on shoulder and arm pain and quality of life in patients with breast cancer? A randomized, controlled, single-blind trial," *Complementary Therapies in Clinical Practice*, vol. 32, pp. 40–45, 2018.

[6] R. Chester, C. Jerosch Herold, L. Shepstone, and J. Lewis, "Shoulder pain, prognostic factors for the outcome of physiotherapy treatment. Results from a prospective multicentre cohort study," *Manual Therapy*, vol. 25, pp. e53–e54, 2016.

[7] K. Reiner, L. Tibi, and J. D. J. P. M. Lipsitz, "Do mindfulness-based interventions reduce pain intensity? A critical review of the literature," *Pain Medicine*, vol. 14, no. 2, pp. 230–242, 2013.

[8] A. Chiesa and A. Serretti, "Mindfulness-based interventions for chronic pain: a systematic review of the evidence," *Journal of Alternative & Complementary Medicine*, vol. 17, no. 1, pp. 83–93, 2011.

[9] L. Hilton, S. Hempel, B. A. Ewing et al., "Mindfulness meditation for chronic pain: systematic review and meta-analysis," *Annals of Behavioral Medicine*, vol. 51, no. 2, pp. 199–213, 2017.

[10] F. Zeidan, K. T. Martucci, R. A. Kraft, N. S. Gordon, J. G. McHaffie, and R. C. Coghill, "Brain mechanisms supporting the modulation of pain by mindfulness meditation," *Journal of Neuroscience*, vol. 31, no. 14, pp. 5540–5548, 2011.

[11] F. Zeidan, N. M. Emerson, S. R. Farris et al., "Mindfulness meditation-based pain relief employs different neural mechanisms than placebo and sham mindfulness meditation-induced analgesia," *Journal of Neuroscience*, vol. 35, no. 46, pp. 15307–15325, 2015.

[12] F. Zeidan, A. L. Adler-Neal, R. E. Wells et al., "Mindfulness-meditation-based pain relief is not mediated by endogenous opioids," *Journal of Neuroscience*, vol. 36, no. 11, pp. 3391–3397, 2016.

[13] L. M. May, P. Kosek, F. Zeidan, and E. T. Berkman, "Enhancement of meditation analgesia by opioid antagonist in experienced meditators," *Psychosomatic Medicine*, vol. 80, no. 9, pp. 807–813, 2018.

[14] R. E. Wells, J. Collier, G. Posey et al., "Attention to breath sensations does not engage endogenous opioids to reduce pain," *Pain*, vol. 161, no. 8, pp. 1884–1893, 2020.

[15] Y. W. Chen and H. H. Wang, "The effectiveness of acupressure on relieving pain: a systematic review," *Pain Management Nursing*, vol. 15, no. 2, pp. 539–550, 2014.

[16] E. You, D. Kim, R. Harris, and K. D'Alonzo, "Effects of auricular acupressure on pain management: a systematic review," *Pain Management Nursing*, vol. 20, no. 1, pp. 17–24, 2019.

[17] T. Matsubara, Y. C. Arai, Y. Shiro et al., "Comparative effects of acupressure at local and distal acupuncture points on pain conditions and autonomic function in females with chronic neck pain," *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 543291, 6 pages, 2011.

[18] J. H. Kim, H. S. Lee, and S. W. Park, "Effects of the active release technique on pain and range of motion of patients with chronic neck pain," *Journal of Physical Therapy Science*, vol. 27, no. 8, pp. 2461–2464, 2015.

[19] L. H. Chang, C. H. Hsu, G. P. Jong, S. Ho, S. L. Tsay, and K. C. Lin, "Auricular acupressure for managing postoperative pain and knee motion in patients with total knee replacement: a randomized sham control study," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 528452, 7 pages, 2012.

[20] V. Moreno-Perez, J. Moreside, D. Barbado, and F. J. Vera-Garcia, "Comparison of shoulder rotation range of motion in professional tennis players with and without history of shoulder pain," *Manual Therapy*, vol. 20, no. 2, pp. 313–318, 2015.

[21] C. R. Constant and A. H. Murley, "A clinical method of functional assessment of the shoulder," *Clinical Orthopaedics and Related Research*, vol. 214, pp. 160–164, 1987.

[22] I. Lee, *Brain Wave Vibration: Getting Back into the Rhythm of a Happy, Healthy Life*, BEST LIFE, Gilbert, AZ, USA, 2009.

[23] D. Bowden, C. Gaudry, S. C. An, and J. Gruzelier, "A comparative randomised controlled trial of the effects of brain wave vibration training, iyengar yoga, and mindfulness on mood, well-being, and salivary cortisol," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 234713, 13 pages, 2012.

[24] J. H. Jang, J. H. Kim, J. Y. Yun, S. H. Choi, S. C. An, and D. H. Kang, "Differences in functional connectivity of the insula between brain wave vibration in meditators and non-meditators," *Mindfulness*, vol. 9, 2018.

[25] S. H. Lee, S. M. Hwang, D. H. Kang, and H. J. Yang, "Brain education-based meditation for patients with hypertension

and/or type 2 diabetes: a pilot randomized controlled trial," *Medicine (Baltimore)*, vol. 98, no. 19, Article ID e15574, 2019.

[26] D. E. Bowden, D. McLennan, and J. Gruzelier, "A randomised controlled trial of the effects of Brain Wave Vibration training on mood and well-being," *Journal of Complementary and Integrative Medicine*, vol. 11, no. 3, pp. 223–232, 2014.

[27] D. H. Lee, H. Y. Park, U. S. Lee et al., "The effects of brain wave vibration on oxidative stress response and psychological symptoms," *Comprehensive Psychiatry*, vol. 60, pp. 99–104, 2015.

[28] I. Lee, *Water up Fire Down*, Best Life Media, Gilbert, AZ, USA, 2020.

[29] D. H. Kang, H. J. Jo, W. H. Jung et al., "The effect of meditation on brain structure: cortical thickness mapping and diffusion tensor imaging," *Social Cognitive and Affective Neuroscience*, vol. 8, no. 1, pp. 27–33, 2013.

[30] J. H. Jang, W. H. Jung, D. H. Kang et al., "Increased default mode network connectivity associated with meditation," *Neuroscience Letters*, vol. 487, no. 3, pp. 358–362, 2011.

[31] W. J. Lee, S. H. Choi, J. E. Shin et al., "Effects of an online imagery-based treatment program in patients with workplace-related posttraumatic stress disorder: a pilot study," *Psychiatry Investigation*, vol. 15, no. 11, pp. 1071–1078, 2018.

[32] Y. H. Jung, T. M. Ha, C. Y. Oh et al., "The effects of an online mind-body training program on stress, coping strategies, emotional intelligence, resilience and psychological state," *PLoS One*, vol. 11, no. 8, Article ID e0159841, 2016.

[33] H. Kang, S. C. An, N. O. Kim et al., "Meditative movement affects working memory related to neural activity in adolescents: a randomized controlled trial," *Frontiers in Psychology*, vol. 11, 2020.

[34] M. K. Sung, U. S. Lee, N. H. Ha, E. Koh, and H. J. Yang, "A potential association of meditation with menopausal symptoms and blood chemistry in healthy women: a pilot cross-sectional study," *Medicine (Baltimore)*, vol. 99, no. 36, Article ID e22048, 2020.

[35] J. H. Jang, H. Y. Park, U. S. Lee, K. J. Lee, and D. H. Kang, "Effects of mind-body training on cytokines and their interactions with catecholamines," *Psychiatry Investigation*, vol. 14, no. 4, pp. 483–490, 2017.

[36] I. Lee, *Connect*, Best Life Media, Gilbert, AZ, USA, 2019.

[37] M. N. Falk Rf, *A Primer for Soft Modeling*, University of Akron Press, Akron, OH, USA, 1992.

[38] E. L. Garland, C. E. Brintz, A. W. Hanley et al., "Mind-body therapies for opioid-treated pain: a systematic review and meta-analysis," *JAMA Internal Medicine*, vol. 180, no. 1, pp. 91–105, 2020.

[39] D. Falla, D. Farina, and T. Graven-Nielsen, "Experimental muscle pain results in reorganization of coordination among trapezius muscle subdivisions during repetitive shoulder flexion," *Experimental Brain Research*, vol. 178, no. 3, pp. 385–393, 2007.

[40] T. A. Lentz, J. A. Barabas, T. Day, M. D. Bishop, and S. Z. George, "The relationship of pain intensity, physical impairment, and pain-related fear to function in patients with shoulder pathology," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 39, no. 4, pp. 270–277, 2009.

[41] E. Godley and M. A. Smith, "Efficacy of acupressure for chronic low back pain: a systematic review," *Complementary Therapies in Clinical Practice*, vol. 39, Article ID 101146, 2020.

[42] R. R. Ji, A. Chamessian, and Y. Q. Zhang, "Pain regulation by non-neuronal cells and inflammation," *Science*, vol. 354, no. 6312, pp. 572–577, 2016.

[43] M. Matsuda, Y. Huh, and R. R. Ji, "Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain," *Journal of Anesthesia*, vol. 33, no. 1, pp. 131–139, 2019.

[44] F. Zeidan, N. S. Gordon, J. Merchant, and P. Goolkasian, "The effects of brief mindfulness meditation training on experimentally induced pain," *The Journal of Pain*, vol. 11, no. 3, pp. 199–209, 2010.

[45] S. Rosenzweig, J. M. Greeson, D. K. Reibel, J. S. Green, S. A. Jasser, and D. Beasley, "Mindfulness-based stress reduction for chronic pain conditions: variation in treatment outcomes and role of home meditation practice," *Journal of Psychosomatic Research*, vol. 68, no. 1, pp. 29–36, 2010.

[46] P. la Cour and M. Petersen, "Effects of mindfulness meditation on chronic pain: a randomized controlled trial," *Pain Medicine*, vol. 16, no. 4, pp. 641–652, 2015.

[47] A. Jinich-Diamant, E. Garland, J. Baumgartner et al., "Neurophysiological mechanisms supporting mindfulness meditation-based pain relief: an updated review," *Current Pain and Headache Reports*, vol. 24, no. 10, p. 56, 2020.

[48] X. S. Hu, K. Beard, M. C. Sherbel et al., "Brain mechanisms of virtual reality breathing versus traditional mindful breathing in pain modulation: observational functional near-infrared spectroscopy study," *Journal of Medical Internet Research*, vol. 23, no. 10, Article ID e27298, 2021.

[49] R. Melzack and P. D. J. S. Wall, "Pain mechanisms: a new theory," *Science*, vol. 150, no. 3699, pp. 971–979, 1965.

[50] H. Hislop, D. Avers, and M. Brown, *Daniels and Worthingham's Muscle Testing-E-Book: Techniques of Manual Examination and Performance Testing*, Elsevier Health Sciences, London, UK, 9th edition, 2013.

[51] J. H. Lam and B. Bordoni, *Anatomy, Shoulder and Upper Limb, Arm Abductor Muscles*StatPearls, Treasure Island, FL, USA, 2021.

[52] T. W. Woodward and T. M. Best, "The painful shoulder: part I. Clinical evaluation," *American Family Physician*, vol. 61, no. 10, pp. 3079–3088, 2000.