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Effectiveness of Moxibustion Therapy in Osteoarthritis Pain Management: A Systematic Review and Meta-Analysis

by

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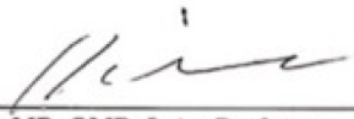

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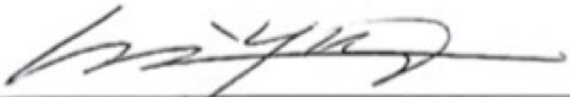

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Moxibustion for Osteoarthritis Pain Management:

A Systematic Review and Meta-Analysis

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Abstract

Pain is one of the major symptoms of most chronic diseases. Ineffective management of pain could result in poor quality of life and functional disabilities. Although there are various clinical trials that examine the importance of moxibustion in the management of pain, evidence regarding the effectiveness of the treatment is still inconclusive.

The systematic review with meta-analysis is to evaluate the effectiveness of moxibustion treatment compared with placebo control, standard treatment, or no treatment in the management of pain among patients with osteoarthritis assessed by pain intensity and functional status or disability.

The study is designed to conduct a systematic review and meta-analysis approach. Randomized controlled trials were collected from databases that included Cochrane Central Register of Controlled Trials (CENTRAL), Medline (PubMed), the Allied and Complementary Medicine Database (AMED), EMBASE, Chinese Biomedical Literature Database (CBM), and

China National Knowledge Infrastructure (CNKI). The primary data items were pain intensity and functional status or disability. The data were collected from the clinical studies and synthesized using mean difference (MD) and 95 % confidence intervals (CI).

Having reviewed the eight randomized control trials with a total of 914 participants, the findings of the study demonstrated that moxibustion treatment is statistically significantly more effective in the management of pain among patients with osteoarthritis compared to control (MD: -7.31[95% CI: -10.32 - -4.43], $p < 0.00001$). The outcome of this review and meta-analysis also showed that moxibustion treatment is statistically significantly more effective in the management of joint dysfunction among patients with osteoarthritis compared to control (MD: -4.74 [95% CI: -7.63 – -1.85], $p = 0.001$).

Therefore, findings reported in this systematic review and meta-analysis suggest that moxibustion therapy is a promising alternative treatment for the management of symptoms associated with knee osteoarthritis.

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INTRODUCTION

Pain constitutes one of the major symptoms of most chronic diseases (Clauw et al., 2019; Leem et al., 2017; Wettstein et al., 2019). Pain negatively affects the quality of life and it is associated with functional disabilities (Clauw et al., 2019; Wettstein et al., 2019; Zahra et al., 2020). The US National Institute of Medicine reported than about 100 million individuals in the country experience chronic pain (Burns & Mullen, 2015). According to Burns and Mullen (2015), the cost of chronic pain management in the US is estimated at $635 billion annually (Simon, 2012). The cost of chronic pain is higher than the combined cost of treating cancer, cardiac diseases and diabetes in the US (Simon, 2012).

Commonly used pain management options involve the use of opioid analgesics (Garland, 2014). However, there are concerns with the use of opioid analgesics, which include toxicity and likelihood of abuse (Garland, 2014). Evidence also suggests that some of the analgesics do not offer clinically significant reduction in chronic pain (Garland, 2014). For patients with chronic pain such as osteoarthritis the failure to get proper care experience excruciating pain (Cheng et al., 2020; Foster et al., 2018; Hu et al., 2016). Traditional Chinese Medicine (TCM) such as moxibustion is being considered as an alternative option in the management of chronic pain such as osteoarthritis (Deng & Shen, 2013; Zheng et al., 2014).

The understanding of pain in the western medicine influences Western therapeutic approaches (Trachsel & Cascella, 2020). The widely accepted theory of pain in Western medicine is the biopsychological model which states that pain occurs due to complex interplay between biological, psychological and sociological factors (Trachsel & Cascella, 2020). Pain is suggested to be a subjective experience that occurs after the processing of nociceptive signals by

the brain (Trachsel & Cascella, 2020). An individual's emotional reaction to nociceptive signals constitute suffering, while actions that result from experiences of pain are referred to as pain behaviors. (Trachsel & Cascella, 2020). According to the Western pain theory, the treatment of the pain needs to align with individual experiences and should be multidimensional (Trachsel & Cascella, 2020).

OBJECTIVES

The objective of the study was to determine the effectiveness of moxibustion treatment compared with placebo control, standard treatment, or no treatment in the management of pain among patients with osteoarthritis assessed by pain intensity and functional status or disability.

LITERATURE REVIEW

Osteoarthritis

Viewpoints of Western medicine:

Definition

In the Western medicine, osteoarthritis is considered a degenerative disorder of the synovial joints that occurs as a result of ageing or due to the effects of trauma (Grässel & Muschter, 2020). Osteoarthritis is defined as the clinical and pathological outcome resulting from the effect of various disorders that causes adverse structural and functional deformation of synovial joints (Sakalauskienė & Jauniškienė, 2010). Osteoarthritis is considered a disease of the cartilage that eventually affects the local tissues and is associated with inflammation and mechanical alterations resulting in the malfunctioning of the cartilage and the entire joint organ (Hunter & Felson, 2006; Felson, 2009). From radiographical analysis, the characteristics indicating osteoarthritis include the narrowing of the joint space, presence of osteophytes, hardening of the bone that is located below the cartilage surface and abnormal bone contours (Zhang et al., 2010). Osteoarthritis is grouped into primary or secondary classes. Common types of osteoarthritis include foot, hand, hip and knee osteoarthritis (Michael et al., 2010).

Etiology

Etiology of osteoarthritis is multifactorial (Sakalauskienė & Jauniškienė, 2010). Osteoarthritis etiology is associated with the damage of hyaline joint cartilage (Michael et al., 2010; Chojnacki et al., 2014). Hyaline joint cartilage is found in the knee joint and it is largely made up of extracellular matrix (Chojnacki et al., 2014). The etiologies associated with secondary osteoarthritis include post-traumatic events, metabolic cases such as hemochromatosis, endocrine disorders such as acromegaly and malposition (Michael et al., 2010).

There are various factors that modulate the etiology of osteoarthritis (Sakalauskienė & Jauniškienė, 2010). Environmental factors such as obesity, occupation, and trauma are involved in the initiation of processes that leads to the damage of the hyaline joint cartilage (Chojnacki et al., 2014). Some form of osteoarthritis such as knee osteoarthritis has been associated with the individual's occupation with the prevalence being higher among athletes and construction workers (Michael et al., 2010). Although some evidence suggests that osteoarthritis is associated with genetic factors, there is limited evidence showing that the condition is associated with a single gene (Michael et al., 2010).

Incidence

Osteoarthritis is considered one of the most prevalent conditions that affect the joints among adults globally (Michael et al., 2010). About 250 million people are affected by osteoarthritis globally (Kotti et al., 2014). Evidence indicates that 33.3 % of adults around the world have radiological signs of osteoarthritis (Chojnacki et al., 2014). However, osteoarthritis is more frequent in developed countries (Sakalauskienė & Jauniškienė, 2010). Morgan et al. (2019)

assessed the patterns of osteoarthritis in England that affect the hand, hip, and knee based on the data obtained from the National Health Service (NHS) Hospital Episode Statistics (HES) database. Morgan et al. (2019) noted an increase in the incidence of osteoarthritis for foot (3.8 %), hand (10.9 %), hip (3.8 %), and knee (2.9 %) per year from 2000/2001 to 2017/2018. According to the Centers for Disease Control and Prevention (CDC), there are over 32.5 million adults in the US affected by osteoarthritis (CDC, 2020).

The occurrence of osteoarthritis varies based on the age and sex (Andrianakos et al., 2006; Michael et al., 2010). The incidence of osteoarthritis increases up to 10 times from the ages of 30 to 65 years (Sakalauskienė & Jauniškienė, 2010). Among individuals aged below 50 years the frequency of osteoarthritis is higher among males (Michael et al., 2010). However, above the age of 50 years, the frequency of osteoarthritis is higher among women with the most frequent being hand, foot, and knee osteoarthritis (Michael et al., 2010, Moghimi et al., 2015). About 40 % of adults aged above 70 have reported cases of knee osteoarthritis (Andrianakos et al., 2006; Michael et al., 2010).

Pathogenesis

During the development of osteoarthritis, the cartilage matrix is altered with one of the significant alterations being the increase in the water content within the superficial zone of articular cartilage, which is associated with proteoglycan degradation (Ruhlen & Marberry, 2014). The matrix then swells towards the deep zone (Goldring & Goldring 2010). Degrading enzymes causes cleavages that result in the loss of the osmotic properties of the cartilage matrix (Primorac et al., 2020). The damage to the cartilage extracellular matrix results in proteinase activation, which further degrades the pericellular matrix (Primorac et al., 2020). The action of inflammatory molecules and the changes in the articular cartilage results in an increase in

mechanical stress and the production of catabolic factors (Primorac et al., 2020). The vascular channels and the sympathetic and sensory nerves from the bone marrow penetrate through subchondral bone to the articular cartilage (Primorac et al., 2020).

Pathogenesis of osteoarthritis is associated with the production of inflammatory molecules that include cytokines, chemokines, and matrix metalloproteinases (Chow & Chin, 2020). The cells that produce inflammatory molecules include the cartilage-forming cells (chondrocytes), cells responsible for the production of synovial fluid components (synoviocytes), and infiltrating immune cells (Chow & Chin, 2020). The inflammatory molecules play a significant role in regulating the anabolic and catabolic processes in the joint (Chow & Chin, 2020). The matrix metalloproteinases cause the degradation of the articular cartilage's extracellular matrix (Haslauer et al., 2013). Chemokines are involved in the transit of the immune cells to the site of injury or infection and are responsible for intensified inflammation of patients with osteoarthritis (Chow & Chin, 2020; Favero et al., 2019). Cytokines such as IL-18, TGFβ1 [14], IL-1 receptor (IL-1R) are involved in the pathogenesis of osteoarthritis (Sun et al., 2015). The cytokines contribute to the degradation of proteoglycans and the collagen cross-links in the articular cartilage (Elford & Cooper, 1991). Cytokines such as tumor necrosis factor-alpha (TNFα) and Interleukin-1 (IL-1) are thought to activate mitogen-activated protein, kinase signaling pathway, and the Toll-like receptor for signaling pathway (Wang et al., 2020). The cytokines also trigger the release of nitric oxide and prostaglandin-E2 that promotes the production of matrix metalloproteinases responsible for the destruction of collagen II (Wang et al., 2020). The cyclooxygenase (COX) that is released by the gastric epithelial cells is also associated with pain and cartilage destruction (Nørregaard et al., 2015).

Clinical manifestations

Osteoarthritis manifest as joint pain that is experienced during activity and which subsides during rest (Sakalauskienė & Jauniškienė, 2010). However advanced osteoarthritis can also be characterized by joint pain even at rest (Sakalauskienė & Jauniškienė, 2010). Although osteoarthritis is associated with the loss of cartilage, the pain may not be contributed directly by cartilage loss since it is poorly innervated (Sakalauskienė & Jauniškienė, 2010). The pain could be associated with the nociceptive stimuli emerging from the richly innervated components of the joint that include the periosteum, synovium, joint capsule, and subchondral bone (Hunter & Felson, 2006). The other manifestation of osteoarthritis is stiffness during mornings, which lasts for close to half an hour (Sakalauskienė & Jauniškienė, 2010). Stiffness is also experienced during moments of immobility and the stiffness fades upon movement (Sakalauskienė & Jauniškienė, 2010). At advanced stage, osteoarthritis may lead to the limitation of joint movement as a result of osteophytes in the joint (Sakalauskienė & Jauniškienė, 2010).

Complications

Osteoarthritis is associated with various adverse outcomes that include pain, loss of function, and disability (Zhu et al., 2018). According to Cheng et al. (2020), pain is the commonest symptom among individuals with knee osteoarthritis. This condition affects more than 9 million Americans (Jafarzadeh & Felson, 2018). Ineffective management chronic pain is associated with disability among knee osteoarthritis patients, which result in poor quality of life (Zhang et al., 2017). The condition is also associated with uses huge financial burden to the globe public health (Puig-Junoy & Zamora, 2015).

Treatments

There are various treatment options available that are used in the management of the osteoarthritis. However, it should be noted that the goal available therapies only alleviate the signs and symptoms of osteoarthritis because the condition is not a curable disease (Michael et al., 2010). The available therapies for osteoarthritis pain management include medication and surgical options (Garland, 2014; Turk et al., 2011). The other treatment approaches used in the management of osteoarthritis include physiotherapy, orthopedic aids and orthoses (Michael et al., 2010). However, evidence indicates that such conventional approaches are associated with low patient satisfaction (Foster et al., 2018; Leem et al., 2017). Although nonsteroidal anti-inflammatory drugs are commonly used in managing pain among patients with knee osteoarthritis, the drugs are associated with significant side effects (Cheng et al., 2020; Zhang et al., 2017).

Viewpoints of Traditional Chinese Medicine (TCM)

Definition

According to the traditional Chinese medicine (TCM), pain consists of two opposing concepts of yin and yang (Khan et al., 2015). The Yin concept is a negative passive force while the Ying concept is a positive active force. For normal state of health to exist, there should be balance between Yin and Yang. Imbalances between the two concepts leads to pain (Khan et al., 2015). The TCM's view of pain can be understood based on the definition of health where emphasis is placed on body, mind, emotions and environment rather than anatomical structures (Burns & Mullen, 2015). Based on TCM's treatment approaches need to ensure that physical and the psychological aspects are addressed (Burns & Mullen, 2015). In TCM, osteoarthritis is considered a form of painful obstruction syndrome and in particular the bi syndrome of bone

(Hua & O'Brien, 2010; Nie et al., 2017; Sudhakaran et al., 2017). The painful obstruction syndrome refers to the pain, numbness, and soreness of the joints and muscles caused by the infiltration of the body by external pathogenic wind, cold, and/ or dampness (Hua & O'Brien, 2010).

Etiology

The causes of osteoarthritis according to TCM are external pathogens that include wind, cold, and dampness (Hua & O'Brien, 2010). Individual genetic factors, traumas, and overuse are also thought to contribute to osteoarthritis pathogenesis (Sudhakaran et al., 2017). The development of osteoarthritis is also linked to the condition of internal organs (Sudhakaran et al., 2017). The pain that moves from one joint to the other is associated with blood deficiency while Yin deficiency is thought to contribute to warm painful joints that are characterized by redness and swelling (Hua & O'Brien, 2010). The blood deficiency is also referred to as wind painful obstruction syndrome, while Yin deficiency is also referred to as heat painful obstruction syndrome. The swelling of joints caused by dampness and pain in a localized area is associated with spleen deficiency (Hua & O'Brien, 2010). The spleen deficiency is also referred to as damp painful obstruction syndrome. Yang deficiency is thought to contribute to severe pain in the joint and it is aggravated by coldness (Nie et al., 2017). The Yang deficiency is also referred to as cold painful obstruction syndrome (Nie et al., 2017).

Pathogenesis

The pathogenesis of osteoarthritis in TCM is linked to the infiltration of external wind, cold, or dampness (Sudhakaran et al., 2017). The development of osteoarthritis as a result of impaired qi and blood circulation is also associated with the depletion of the kidney and liver

zang (Hua & O'Brien, 2010). The depletion of the kidney and liver zang allows wind, cold, and dampness to invade the body. The highlighted factors are responsible for the obstructed flow of Qi and Blood. Body fluids become stagnant and accumulate in the joints exacerbating the problem (Xiao, 2004). The phlegm condenses leading to the formation of bone growths (Robertshawe, 2009). The depletion of the kidney plays a primary role in the development of osteoarthritis (Hua & O'Brien, 2010). With age, the kidney essence, which is important in bone formation and development, declines resulting in the depletion of the qi of the organs causing frailties and stiffness of tendons and impaired movements. The deficiency of the spleen also contributes to the development of osteoarthritis because the organ is involved in the transportation of fluids and qi (Hua & O'Brien, 2010).

Patterns of differentiation

According to TCM, osteoarthritis is differentiated into three patterns (Hochberg, 1995; Wang et al., 2013). The first pattern is *yang deficiency cold coagulation*, which is characterized by pain, stiffness, and the impairment of the function of the affected joints. *Yang deficiency cold coagulation* is exacerbated by coldness, while warmth helps to alleviate it (Wang et al., 2013). During the first pattern of *young deficiency cold coagulation,* patients experience fatigued limbs, and coldness in the tongue, and color of the tongue changes to pale. The pulse is also affected with the patient having slow, thready, and deep arterial palpitations (Wang et al., 2013). *Yang deficiency cold coagulation* can be alleviated using warm therapy (Hochberg, 1995). The second pattern is *kidney essence deficiency*. Patients, during this pattern, have a limited range of motion. The patients also experience dizziness and ringing noises in the ears (Wang et al., 2013). The other symptoms include pink tongue and thready pulse (Wang et al., 2013). The third pattern is

blood stasis (Hochberg, 1995). Symptoms associated with *blood stasis* include fixed pain and a dark face. The patients also experience a limited range of motion and they develop purplish lips and tongue (Wang et al., 2013)

Treatments

Treatment of the osteoarthritis in TCM is focused on tonifying the kidney and liver (Hua & O'Brien, 2010). The therapies also emphasize on the need to promote circulation of blood, expel the wind and address dampness (Hua & O'Brien, 2010). Evidence indicates an increasing number of patients who prefer complementary and alternative therapies to manage pain (Leem et al., 2017; Tzeng et al., 2015). Complementary and alternative medicine is preferred because of its non-invasive nature (Cheng et al., 2020; Hu et al., 2016; Leem et al., 2017). Moxibustion is one of the traditional Chinese medicine that is used in pain management (Deng & Shen, 2013). The treatment has been indicated to help manage chronic knee pain (Tzeng et al., 2015). In Asian countries, moxibustion is widely used in the treatment of knee osteoarthritis (Deng & Shen, 2013). Evidence indicates that moxibustion treatments have been used for over 2,500 years (Deng & Shen, 2013). Moxibustion therapy is an external treatment where the heat generated from the burning of moxa leaves obtained from Asian species of mugwort is used to stimulate acupoints (Deng & Shen, 2013). Moxibustion therapy is non-invasive and painless, and it is associated with limited adverse effects. It should also be noted that the patients can perform moxibustion at their homes since it is considered safe and effective treatment (Xu et al., 2014). The management of pain using the TCM approaches is thought to be based on the gate-control model. The model is based on the assumption that the specific nerve fibers are responsible for transmitting pain. In TCM approaches such as moxibustion it is believed that the stimulation of

the inhibitory nerve fibers for limited period result in limited transmission of the pain signals to the brain, therefore the experiences of pain are halted (Burns & Mullen, 2015; Theodorou & Fleckenstein, 2019). The other model that is used to explain the pain management by TCM is endorphin model where insertions such as needles used in moxibustion trigger the production of endorphins (Zheng et al., 2014). The production of endorphins results in analgesic effect (Zheng et al., 2014).

Moxibustion theory and the practical application

The mechanism of action for moxibustion treatment is associated with its thermal effects (Deng & Shen, 2013; Wang et al., 2000). The burning of the moxa stick has been established to produce temperatures as high as 890 degrees centigrade, which warms the body (Deng & Shen, 2013). The thermal effect resulting from moxa burning has been reported to cause antipyretic and thermolytic effects (Deng & Shen, 2013). The treatment also results in enhanced flow of blood in the peripheral arteries and increased microvascular permeability (Takayama et al., 2011). Evidence also indicates that the moxibustion thermal effects are associated with the induction of heat shock proteins, which are important in responding to environmental stressors (Deng & Shen, 2013).

The two major types of moxibustion are the direct and indirect moxibustion treatments (Yi, 2009). The direct moxibustion treatment involves the burning of a moxa stick directly on acupoints (Daga et al., 2017). The direct moxibustion can either be scarring or non-scarring (Manual, 2015). The scarring moxibustion treatment is characterized by the placement and the ignition of a moxa stick on the acupoints, which is then left to burn out completely (Daga et al., 2017; Yi, 2009). The scarring moxibustion treatment is therefore associated with localized

blisters and scars (Manual, 2015). However, the non-scarring moxibustion is not associated with any scarring or blistering. The moxa stick is placed and ignited on the acupoint but then immediately removed before burning the skin (Manual, 2015). For the indirect moxibustion, the moxa stick is not ignited on the skin. Instead, the practitioner ignites the moxa stick and holds it close to the target area (Manual, 2015). The burning moxa stick is then removed when the target area turns red (Daga et al., 2017; Yi, 2009). The other form of indirect moxibustion involves the insertion of needles in the acupoints. The exposed end of the needle is then wrapped with moxa which is then ignited. The heat generated heats the target area through the needle (Chiu, 2013). Systematic reviews and meta-analyses are important in understanding relevant clinical trials and provide the basis upon which future trials are designed (Leem et al., 2017). There are various systematic reviews and meta-analyses of randomized control trials that focus on the effectiveness of complementary and alternative medicine such as moxibustion in managing pain associated with different conditions (Cheng et al., 2020). Hu et al. (2016) carried out a systematic review of 20 randomized controlled studies to evaluate the effectiveness of acupuncture in managing cancer-related pain. Hu et al. (2016) noted that the effectiveness of acupuncture was realized when it was used alongside conventional and drug therapy. Cheng et al. (2020) evaluated and randomized control studies to determine the efficacy of moxibustion in pain relief among individuals with knee osteoarthritis.

The limitation of systematic reviews and meta-analyses that focus on pain management related to specific conditions is the inadequate number of high-quality multi-center randomized control trials (Hu et al., 2016; Zhang et al., 2017). Without adequate trials with high methodological quality, it is challenging to draw strong conclusions regarding the effectiveness of moxibustion

in managing pain. To address the challenge of inadequate high-quality trials, the proposed study focuses on the expanded scope of pain management using moxibustion by focusing on multiple diseases. In this study, the researcher will focus on the effectiveness of moxibustion in addressing pain intensity and pain-related disability among patients with various chronic conditions such as hand, hip and knee osteoarthritis. A preliminary search carried out by the researchers indicated that various randomized clinical trials assess the effectiveness of moxibustion in the management of pain among patients with various conditions such as osteoarthritis (Kang et al., 2020; Zhu et al., 2017). Thus, the proposed study will be able to overcome the limitations of the inadequacy of quality trials.

MATERIALS AND METHODS

Protocol and registration

The systematic review was carried out per the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P) documented by Moher et al. (2015). The PRISMA-P comprises a checklist that contains 17 items used to ensure the development of a complete, transparent, and robust systematic review protocol (Moher et al., 2015). The study also adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines documented by Liberati et al. (2009). The PRISMA guidelines include a checklist that ensures transparency in reporting of systematic reviews (Liberati et al., 2009).

Eligibility criteria

The eligibility criteria guided the selection of the articles that were included in the review. The criteria focused on the types of studies, participants, and the type of interventions. Concerning the type of studies, only randomized control trials were included in the study. The researcher prioritized the studies in which the randomization method was clearly explained. The studies that adopted incorrect randomization approaches, such as the tossing of the coin, were not considered.

Concerning the type of participants, the researcher included patients with chronic pain associated with various chronic conditions. In addition, the study considered patients diagnosed with forms of pain associated with knee osteoarthritis. The participants were not restricted to age, sex, ethnic background, and disease severity.

Concerning the type of interventions, the researcher included studies that focused on moxibustion therapy, with the control being placebo or any other standard, unproven, or no treatment. However, the researcher excluded any studies investigating moxibustion doses, duration of treatment, or material. In the study, any moxibustion therapy was considered. Therefore, direct and indirect moxibustion, natural moxibustion, heat-sensitive moxibustion, herbal patching, warm needling, and moxa-burning moxibustion were included. Aspects of moxibustion therapy such as treatment frequency, treatment duration, and methods used in the therapy were not considered.

Information sources and search

The researcher conducted searches in various English-based databases from the date the databases were established to June 2021. The databases that were considered include Cochrane Central Register of Controlled Trials (CENTRAL), Medline (PubMed), the Allied and Complementary Medicine Database (AMED), EMBASE, Biomedical Literature Database (CBM), and China National Knowledge Infrastructure (CNKI). Based on the guidelines provided by Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 (Higgins & Green, 2011), searches were carried out in PubMed using the following keywords: (randomized controlled trial OR controlled clinical trial OR randomized OR randomly OR trial OR groups) AND (moxibustion OR moxabustion OR moxa) AND (pain management OR knee osteoarthritis OR hand osteoarthritis OR hip osteoarthritis OR osteoarthritis). The search strategy was adjusted for the other databases based on their specific requirements.

Data collection process

The systematic review was carried out between 1st July 2021 and 15th August 2021. The researcher worked independently in the selection of studies and extraction of data. To ensure a good understanding of the purpose of the review and how to carry out transparent and robust systematic reviews, the researcher carried out self-study by assessing previous related literature and systematic reviews. The titles and abstracts of the records obtained from electronic searches were screened to exclude irrelevant articles. The remaining articles were screened through full text analysis to determine eligibility for inclusion. Full text analysis focused on the participants, outcomes, statistical analysis approaches, reported results and discussion.

Selected Clinical studies

A predefined datasheet designed by the researcher was used in the extraction of data. The data collected include the year of publication, author(s), article title, journal, country, setting, methods, participants, interventions, outcomes, results, conflict of interest, and adverse events. The researcher read the selected studies and retrieved the data to fill the datasheet. To address ambiguous results, the researcher requested further clarifications through emailing the corresponding author.

Data items

The primary data items were pain intensity and functional status or disability. The selection of pain intensity as the primary data item was because the objective of the study was to examine the effectiveness of moxibustion in the management of pain. Pain is also associated with impaired function of status. Systematic reviewers have previously used pain intensity and functional status or disability to assess aspects related to pain. Therefore, the researcher

considered pain intensity, which was measured using data collection tools such as the Numeric Rating Scale (NRS) and the Visual Analog Scale (VAS). The researcher also considered functional status or disability outcomes measured using other validated tools such as Western Ontario and McMaster Universities osteoarthritis index (WOMAC), Patient global assessment (PGA), European quality of life five-dimension five level scale (EQ-5D-5 L). The other data items that were considered included subjective improvement in symptoms, overall improvement in pain, perceived improvement in pain and recovery, and the quality-of-life measurements.

Risk of bias in individual studies

The risk of bias in individual studies was carried out by the researcher working independently and guided by the Cochrane Risk of Bias-2 tool (Higgins et al., 2011; Sterne et al., 2016). The Risk of Bias-2 focused on various domains that included randomization, measurement of the outcomes, selection of the reported results, the deviation from the intended interventions, missing outcome data, and overall bias. The articles were categorized into three categories of risk of bias: low, high, or unclear risk of bias (Sterne et al., 2016).

Summary measures

The data retrieved and used in meta-analysis were continuous. The estimation of the treatment effect from the continuous data retrieved from the included studies was carried out using mean difference and 95 % confidence intervals. The selected data were arranged in tables format for convenient analysis and discussion.

Synthesis of results

The heterogeneity of the included studies was determined quantitatively using I^2 statistics obtained from RevMan's chi-square test. The interpretation of the I^2 values was based on Guidelines provided by Higgins and Thompson (2002), where the values above 50 % are considered to have substantial heterogeneity. Values of 75 % and above were considered to have considerable heterogeneity. The values of 50 % and below are considered to have no heterogeneity. Statistically significant heterogeneity was based on $P < 0.05$ (Lee et al., 2014). Meta-analysis was carried out using Review Manager (RevMan) software. The software facilitated the calculation of mean difference. Meta-analysis was carried out using a fixed-effect model if no significant heterogeneity was detected. However random-effects model was adopted in case significant heterogeneity was detected. A systematic narrative synthesis was also used where the use of quantitative synthesis was not appropriate, such as when the included trials were insufficient or in case of unidentified significant heterogeneity.

RESULTS

Study selection

Article searches conducted in CENTRAL, PubMed, AMED, EMBASE, CBM, and CNKI resulted in the retrieval of 1572 articles. The search in CENTRAL led to retrieval of 338 articles. The search in PubMed led to retrieval of 205 articles. The search in AMED led to retrieval of 122 articles. The search in EMBASE led to retrieval of 387 articles. The search in CBM led to retrieval of 291 articles. The search in CNKI led to retrieval of 229 articles. The bibliographies of the selected studies were also searched, which led to the retrieval of additional 13 articles. Therefore, a total of 1585 articles were retrieved and subjected to selection process. Following the removal of 545 duplicate articles, a total of 1040 articles remained and were subjected to eligibility assessment. The assessment of abstracts and titles resulted in the exclusion of 611 ineligible studies resulting in 429 articles that were subjected full-text analysis. A total of 422 articles were excluded following full-text analysis. The reasons for the exclusion were as following 252 articles were not based on randomized clinical trials, 109 articles did not include participants with pain associated with knee osteoarthritis, 37 articles compared different forms of moxibustion, and 24 articles did not include a control. Therefore, eight articles were included in the systematic review. Three (Dai et al., 2019; Kang et al., 2020; Min et al., 2013) of the included studies were included in the meta-analysis. The flow diagram below provides a summary of the approach that was followed in selecting the studies (Figure 1).

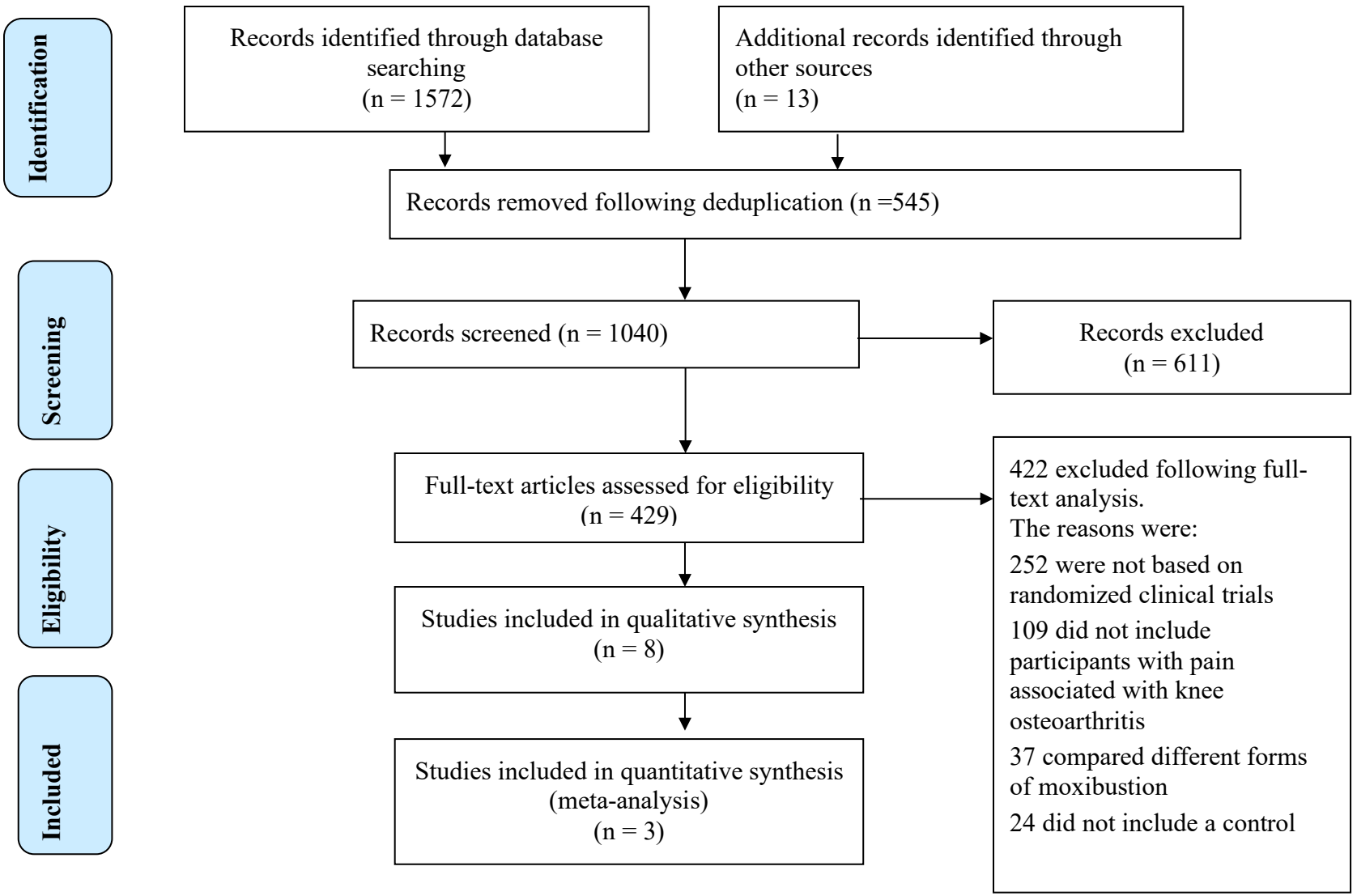

Figure 1: Article selection process

Study characteristics

Participants

A total of 914 participants were included in this review among which 500 participants received Moxibustion therapy while 414 participants were used as controls. Kang et al. (2020) included 138 participants from South Korea, Dai et al. (2019) included 74 participants from China, Min et al. (2013) included 56 participants from South Korea, Zhao et al. (2021) included 392 participants from China, Luo et al. (2019) included 63 participants from China, Xue et al. (2020) included 72 participants from China, and Zhou et al. (2014) included 60 participants from China. Ren et al. (2011) included 59 participants from China. Thus, participants were drawn from two countries (South Korea and China) with 21.2 % (n = 194) from the South Korea and the remaining 78.8 % (n = 720) were from China.

The participants were above the age of 18 years. Kang et al. (2020) and Dai et al. (2019) included participants aged 40 and 70 years. Luo et al. (2019) included participants aged 40 and 75 years. Ren et al. (2011) included 59 participants aged between 45 to 78 years. Min et al. (2013) included participants aged between 50 and 70 years. Zhao et al. (2021) included participants aged 50 years old or older. Xue et al. (2020) and Zhou et al. (2014) included participants aged above 40 years. All participants were diagnosed with KOA

Methodological approach and study design

All included articles (Table 2) were based on randomized clinical trial methodological approach. Kang et al. (2020) and Luo et al. (2019) were based on multicenter, randomized, assessor-blinded, parallel-group clinical trial. The other six (Dai et al., 2019; Min et al., 2013; Ren et al., 2011; Xue et al., 2020; Zhou et al., 2014; Zhao et al., 2021) were based on

randomized controlled trial. The interventions varied across the different studies. Three studies (Dai et al., 2019; Kang et al., 2020; Zhao et al., 2021) compared moxibustion with drug based usual care. Dai et al. (2019) compared oral celecoxib capsule (control group) and moxibustion treatment involving heat and smoke (Moxibustion group). Kang et al. (2020) compared electrical moxibustion, traditional indirect moxibustion and the usual care. Zhao et al. (2021) compared laser moxibustion and drug based sham laser moxibustion. Two articles (Min et al., 2013; Zhou et al., 2014) compared moxibustion therapy and acupuncture therapy. Ren et al. (2011) compared moxibustion treatment involving actual moxa sticks to a placebo involving fake moxa sticks. Min et al. (2013) and Zhou et al. (2014) compared warm needling and acupuncture therapies. The randomization and blinding approaches varied across the different studies. In seven of the eight articles (Luo et al., 2019; Kang et al., 2020; Min et al., 2013; Ren et al., 2011; Xue et al., 2020; Zhao et al., 2021), randomization involved the generation of random number using computerized random number generator. For Dai et al. (2019), the randomization approach involved the use of randomized distribution card created using a random number table. Zhou et al. (2014) randomization approach involved the random division of the participants into an observation group and a control group by their visit order. For case of Kang et al. (2020) participants and practitioner were aware of the allocation arm. In Luo et al.'s (2019) study, participants, assessors, data collectors, statisticians were blinded but the care givers were not blinded. For the case of Min et al. (2013), the practitioners unblinded but participants and investigators were blinded. For case of Zhao et al.'s (2021) study, participants, device operators, outcome assessors, research coordinators, and statistician were blinded. For Ren et al. (2011) the participants and assessors were blinded to the treatment. In three studies (Dai et al. 2019; Xue et al., 2020; Zhou et al., 2014) the blinding details were unclear.

The reviewed studies considered on different acupoints. Kang et al. (2020) considered seven selected points in the affect knee (s). The points included Zusanli (ST36), Dubi (ST35), Liangqiu (ST34), Yinlingquan (SP9), Neixiyan (EX-LE4), Xuehai (SP10) and Ashi points. Luo et al. (2019) focused on three points that included ExLE4, ST35, and ST36. Dai et al. (2019) focused on four acupoints that included Neixiyan (EX-LE 5), Dubi (ST 35), Xuehai (SP 10) and Liangqiu (ST 34). As shown in Table 1, Min et al. (2013) included four local common points (Ex-LE4, ST35, ST36, and Ex-LE2) and eight additional points (SP9, SP10, LR8, GB34, GB33, BL40, ST34, and KI10) while Zhao et al. (2021) included two (ST35 and Ashi point). Xue et al. (2020) considered four acupoints that included Neixiyan (EX-LE 4), Dubi (ST 35), Xuehai (SP 10) and Liangqiu (ST 34). Zhou et al. (2014) considered six points that included Yinlingquan (SP 9), Yanglingquan (GB 34), Neixiyan (EX-LE 4), Dubi (ST 35), Xuehai (SP 10) and Liangqiu (ST 34). Finally, Ren et al. (2011) considered three points that included Neixiyan (EX-LE 4), Dubi (ST 35), and Ashi points.

Table 1: Summary of the acupoints considered by the different studies

Reference	Acupoints
Kang et al. (2020)	ST36, ST35, ST34, SP9, EX-LE4, SP10 and Ashi points
Luo et al. (2019)	ExLE4, ST35, and ST36
Dai et al. (2019)	EX-LE 5, ST 35, SP 10 and ST 34
Min et al. (2013)	Ex-LE4, ST35, ST36, Ex-LE2, SP9, SP10, LR8, GB34, GB33, BL40, ST34, and KI10
Zhao et al. (2021)	ST35 and Ashi point.
Xue et al. (2020)	EX-LE 4, ST 35, SP 10 and ST 34
Zhou et al. (2014)	SP 9, GB 34, EX-LE 4, ST 35, SP 10 and ST 34
Ren et al. (2011)	EX-LE 4, ST 35, and Ashi points

The articles focused on various outcomes. Kang et al. (2020) focused on mean change of pain on the numerical rating scale (NRS) and European quality of life five-dimension five level scale

(EQ-5D-5 L) between before and after treatment. Eight articles (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Min et al., 2013; Ren et al., 2011; Xue et al., 2020; Zhou et al., 2014; Zhao et al., 2021) considered mean changes of scores of Western Ontario and McMaster Universities osteoarthritis index (WOMAC). Five articles (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Xue et al., 2020; Zhao et al., 2021) considered mean changes of scores of Visual analog scale (VAS). Four articles (Luo et al., 2019; Kang et al., 2020; Min et al., 2013; Zhao et al., 2021) considered mean changes of scores of Patients global assessment (PGA). Two articles (Min et al., 2013; Zhao et al., 2021) considered mean changes of scores of Short-Form Health Survey (SF-36). The summary of included studies is provided in Table 2.

Table 2: Summary of the included studies (N = 8)

Reference	Study design	Country	Sample	Intervention	Outcomes	Findings
Kang et al. (2020)	Multicenter, randomized, assessor-blinded, parallel-group clinical trial	South Korea	138 participants (electrical moxibustion (EM): 46, Traditional indirect moxibustion (TIM): 46, usual care: 46) 40 and 70 years; Diagnosed with KOA	EM, TIM, and usual care. Moxibustion treatments were applied in 12 sessions, twice per week for 6 weeks	Primary: Pain measured on numerical rating scale (NRS). Secondary: Pain measured based on Mean changes of scores of Western Ontario and McMaster Universities osteoarthritis index (WOMAC), Visual analog scale (VAS), Patient global assessment (PGA), European quality of life five-dimension five level scale (EQ-5D-5 L)	Electrical moxibustion treatment resulted in significant reduction in pain intensity (7.17 ± 12.89, $p < 0.001$) while traditional indirect moxibustion resulted in 2.17 ± 13.44 mean reduction in pain intensity compared to the mean change in pain in the control (3.09 ± 13.88, $p < 0.001$).
Luo et al. (2019)	Multicentre, randomized, single blinded,	China	138 participants (Conventional moxibustion (CM): 69 and smoke-free	CM and SM for 4 weeks	Primary: Pain and dysfunction measured using WOMAC	For smoke-free moxibustion group, the VAS score was higher before (4.0 ± 1.4)

	parallel-group clinical trial		moxibustion (SM): 69) 40 and 75 years; Diagnosed with KOA		Secondary: Pain measured based on VAS, PGA.	compared to after treatment (2.1 ± 1.3).
Dai et al. (2019)	Randomized controlled clinical trial	China	74 participants (Moxibustion: 38 and control: 36) 40 and 70 years; Diagnosed with KOA	Oral celecoxib capsule (control group) and moxibustion treatment involving heat and smoke for Moxibustion group	Pain and dysfunction measured using WOMAC	The reduction in the VAS scores in the moxibustion group was higher (3.03 ± 0.97) than that in the medication group (2.17 ± 0.89), and the outcome in patients in the control and moxibustion significantly varied). Reduction in joint dysfunction in the moxibustion group was higher (21.61 ± 8.34) than that in the medication group (17.15 ± 5.61), and the outcome in patients in the control and moxibustion significantly varied)
Min et al. (2013)	Randomised clinical trial	South Korea	56 participants (Moxibustion: 28 and acupuncture: 28) Between 50 and 70 years; Diagnosed with KOA	Warm needling and acupuncture therapies	Primary: Pain and dysfunction measured using WOMAC Secondary: Quality of life using Korean version of the 36-Items Short-Form Health Survey (SF-36); PGA.	Moxibustion treatment resulted in significant reduction in joint dysfunction score as indicated by change in WOMAC function scores (17.86 ± 10.87) compared to the acupuncture therapies (11.96 ± 13.91, $p < 0.01$)

Zhao et al. (2021)	Double-blind randomized clinical trial	China	392 participants (Laser moxibustion LM =201; sham LM group =191) Age: 50 years and above and with KOA	LM and sham laser control	Primary: Pain and dysfunction measured using WOMAC Secondary: Quality of life using SF-36, PGA, VAS and WOMAC	At week 4, there was a significant difference in pain reduction between the two groups (2.1; 95% confidence interval [CI], 1.6 to 2.6; $P <$ 0.01) with LM having more reduction in pain. WOMAC total scores including pain, physical function, and stiffness at weeks 2, 4, 8, 12, and 24 improved significantly more in patients who received active LM than those who received sham LM.
Xue et al. (2020)	Randomized controlled trial	China	72 participants (Electronic moxibustion =38; traditional moxibustion group = 34) age >40 years old Diagnosed with KOA	Electronic moxibustion apparatus and traditional moxibustion	Pain and dysfunction measured using WOMAC and VAS	VAS scores in the electronic moxibustion group was higher before (5.95 ± 1.08) compared to after treatment (3.07 ± 1.27, $p < 0.05$). Joint dysfunction scores in the electronic moxibustion group was higher before (33.92±8.44) compared to after treatment (14.37±7.57, $p < 0.05$). For traditional moxibustion group, the joint dysfunction score was higher before (30.97 ± 8.65) compared to

						after treatment (14.15 ± 8.09).
Zhou et al. (2014)	Randomized controlled trial	China	60 patients with KOA (Moxibustion: n = 30; Control: n = 30). not less than 40 years old (Moxibustion 58.9±10.6 years; Control: 58.3±9.3 years) Diagnosed with KOA	Warm needling Moxibustion therapy and acupuncture treatment	Pain measured using WOMAC	WOMAC scores in the warm needling moxibustion treatment was higher before (20.6 ± 2.6) compared to after treatment (9.7 ± 3.8, $p < 0.01$). For acupuncture treatment group, the WOMAC score was higher before (20.3 ± 2.6) compared to after treatment (12.4 ± 5.3, $p < 0.01$)
Ren et al. (2011)	Randomized controlled study	China	59 patients (moxibustion group=31; placebo moxibustion group=28 cases) Diagnosed with KOA 45-78 years old and diagnosed with KOA	Moxa sticks for moxibustion and Placebo (fake moxa sticks).	Pain measured using WOMAC	Patients who received moxibustion treatment registered a reduction in the WOMAC scores in three and six weeks of treatment and during follow-up visit

Risk of bias within the study

The risk of bias was assessed using the Cochrane ROB tool (Higgins et al., 2011). The assessment included the eight randomized control studies that were included in this study. As shown in Figure 2, the assessment of the quality of the study focused on the individual studies. All the studies had low risk of bias across the five domains (randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome and selection of the reported results). The findings shown in Figure 2 also indicate that all the included randomized control studies had overall low level of risk of bias.

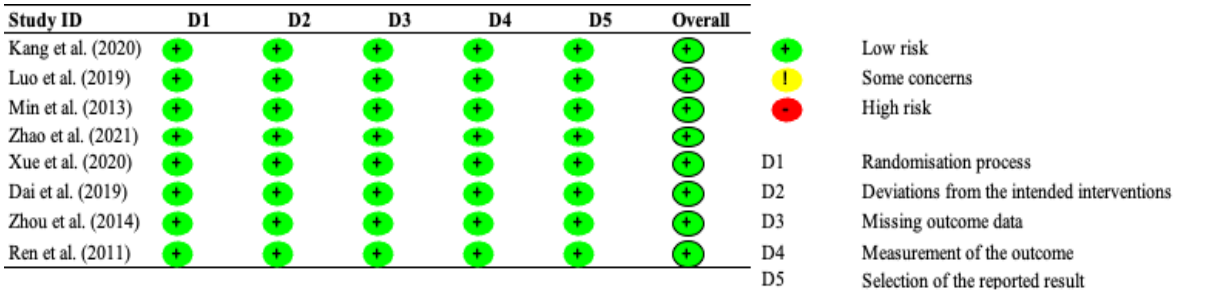

Figure 2: Quality appraisal for individual studies indicating overall low risk of bias across all the studies.

Synthesis of results

Effect of moxibustion therapies on pain management among patients with KOA

All included articles assessed the effectiveness of moxibustion therapies in the management of pain among patients with KOA. Kang et al. (2020) noted that electrical moxibustion treatment resulted in significant reduction in pain (20.50 ± 17.20, $p < 0.001$) while traditional indirect moxibustion resulted in 18.96 ± 15.31 mean reduction in pain compared to the mean change in pain in the control (-1.46 ± 12.59, $p < 0.001$) as measured using NRS.

Change in the WOMAC scores

Eight articles (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Min et al., 2013; Ren et al., 2011; Xue et al., 2020; Zhou et al., 2014; Zhao et al., 2021) evaluated pain based on the mean changes of WOMAC scores. Luo et al. (2019) noted that the WOMAC scores in the conventional moxibustion group was higher before (7.4 ± 3.4) compared to after treatment (4.1 ± 3.0). Luo et al. (2019) also reported that for smoke-free moxibustion group, the WOMAC score was higher before (7.6 ± 2.9) compared to after treatment (4.2 ± 2.9). Ren et al. (2011) also noted that the scores in WOMAC were reduced following the six weeks of moxibustion treatment ($p < 0.01$). Xue et al. (2020) also noted that the WOMAC scores in the electronic moxibustion group was higher before (46.58 ± 11.38) compared to after treatment (19.71 ± 10.36, $p < 0.05$). Xue et al. (2020) also reported that for traditional moxibustion group, the WOMAC score was higher before (42.53 ± 11.84) compared to after treatment (19.53±11.04). Zhou et al. (2014) also noted that the WOMAC scores in the warm needling moxibustion treatment was higher before (20.6 ± 2.6) compared to after treatment (9.7 ± 3.8, $p < 0.01$). Zhou et al. (2014) also reported that for acupuncture treatment group, the WOMAC score was higher before (20.3 ± 2.6) compared to after treatment (12.4 ± 5.3, $p < 0.01$). According to Zhou et al. (2014) the WOMAC scores were significantly low in the warm needling moxibustion treatment compared to acupuncture treatment group ($p < 0.05$).

Kang et al. (2020) noted that electrical moxibustion treatment resulted in significant reduction in pain intensity (10.37 ± 9.57, $p < 0.001$) while traditional indirect moxibustion resulted in 10.96 ± 12.76 mean reduction in pain intensity compared to the mean change in pain in the control (0.72 ± 8.76) ($p < 0.001$). Dai et al. (2019) also noted that the reduction in WOMAC scores in the moxibustion group was higher (28.94 ± 6.48) than that in the medication

group (23.49 ± 6.31), and the outcome in patients in the control and moxibustion significantly varied). Zhao et al. (2021) noted that laser moxibustion treatment resulted in significantly higher reduction in pain intensity of 2.4 (36.4%) compared to the sham treatment with a reduction of 0.1 (1.5%) (2.1; 95% CI,1.6 to 2.6; $P < 0.01$). Min et al. (2013) noted that warm needling moxibustion treatment resulted in significant reduction in pain intensity as indicated by change in WOMAC scores (24.82 ± 13.96) compared to the acupuncture therapies (17.21± 18.86, $p < 0.01$).

Meta-analysis

Meta-analysis of the effect of moxibustion therapies on pain management among patients with KOA based on the change in WOMAC scores

Meta-analysis was carried out to assess the effectiveness of moxibustion therapies in the management of pain among patients with KOA for the studies that compared effects of moxibustion to that of the control group. In this meta-analysis three studies (Ren et al., 2011; Zhou et al., 2014; Zhao et al. 2021) were not included because the studies did not present the outcome as the mean change in WOMAC scores. Zhao et al. (2021) presented the outcome as percentage change while Ren et al. (2011) and Zhou et al. (2014) presented before and after findings in each group (control and moxibustion).

The analysis approach involved the use of continuous data retrieved from three studies (Dai et al., 2019; Kang et al., 2020; Min et al., 2013). The data included in the meta-analysis included the mean (SD) reduction in the WOMAC scores after treatment in the control and the experimental group (Moxibustion treatment). Two of the included studies (Dai et al., 2019; Kang et al., 2020) used drug-based treatment as the control. The assessment of the heterogeneity based

on the I^2 statistic indicate that the included studies did not have significant heterogeneity (I^2 = 34 %, p = 0.22). Therefore, fixed effects model was used. As shown in Figure 3, the meta-analysis included 112 participants in the moxibustion group, and 110 in the control group. The forest plot (Figure 3) indicates that in three studies (Dai et al., 2019; Kang et al., 2020; Min et al., 2013) the reduction in WOMAC scores was significantly different between control and experimental groups because the 95 % confidence intervals (CI) does not cross the line of no effect. The pooled results indicate that the change in the mean WOMAC scores was significantly higher in the moxibustion group compared to the control (mean difference (MD), -7.07 [95% CI: -9.29- -4.85]). The meta-analysis outcome was statistically significant as indicated by the obtained overall effect value (Z = 6.23, p < 0.00001).

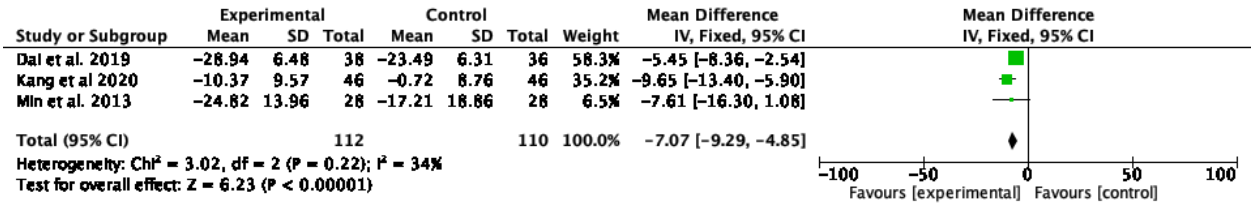

Figure 3: Effect of moxibustion therapies on pain management among patients with KOA based on the change in WOMAC scores

Change in the VAS scores

Four articles (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Xue et al., 2020) reported the pain intensity using considered mean changes of scores of VAS. Luo et al. (2019) noted that the VAS scores in the conventional moxibustion group was higher before (4.1 ± 1.4) compared to after treatment (2.2 ± 1.3). Luo et al. (2019) also reported that for smoke-free moxibustion group, the VAS score was higher before (4.0 ± 1.4) compared to after treatment (2.1 ± 1.3). Xue et al. (2020) also noted that the VAS scores in the electronic moxibustion group was

higher before (5.95 ± 1.08) compared to after treatment (3.07 ± 1.27, $p < 0.05$). Xue et al. (2020) also reported that for traditional moxibustion group, the VAS score was higher before (5.68 ± 1.17) compared to after treatment (3.22 ± 1.30). Kang et al. (2020) noted that electrical moxibustion treatment resulted in significant reduction in pain intensity (7.17 ± 12.89, $p < 0.001$) while traditional indirect moxibustion resulted in 2.17 ± 13.44 mean reduction in pain intensity compared to the mean change in pain in the control (3.09 ± 13.88, $p < 0.001$). Dai et al. (2019) also noted that the reduction in the VAS scores in the moxibustion group was higher (3.03 ± 0.97) than that in the medication group (2.17 ± 0.89), and the outcome in patients in the control and moxibustion significantly varied).

Meta-analysis of the effect of moxibustion therapies on pain management among patients with KOA based on the change in VAS scores

Meta-analysis was carried out to assess the effectiveness of moxibustion therapies in the management of pain among patients with KOA for the studies that compared effects of moxibustion to that of the control group. In this meta-analysis three studies (Luo et al., 2019; Xue et al., 2020; Zhao et al. 2021) were not included despite reporting change in pain based on VAS scores. Zhao et al. (2021) was included because the article presented the outcome as percentage change while Luo et al. (2019) and Xue et al. (2020) presented before and after findings in each group (control and moxibustion). The analysis approach involved the use of continuous data retrieved from two studies (Dai et al., 2019; Kang et al., 2020). The data included in the meta-analysis included the mean (SD) change in the VAS scores after treatment in the control and the experimental group (Moxibustion treatment). Two of the included studies (Dai et al., 2019; Kang et al., 2020) used drug-based treatment as the control. The assessment of

the heterogeneity based on the I^2 statistic indicate that the included studies did not have significant heterogeneity (I^2 = 24 %, p = 0.25). Therefore, fixed effects model was used. As shown in Figure 4, the meta-analysis included 84 participants in the moxibustion group, and 82 in the control group. The forest plot (Figure 4) indicates that in the two studies (Dai et al., 2019; Kang et al., 2020) the change in VAS scores was not significantly different between control and experimental groups because the 95 % CI values crossed the line of no effect. The pooled results indicate that the change in the mean VAS scores was not significantly higher in the moxibustion group compared to the control (MD 0.88 [95% CI: -0.46 – 1.30]). The meta-analysis outcome was not statistically significant as indicated by the obtained overall effect value (Z = 4.08, p < 0.0001).

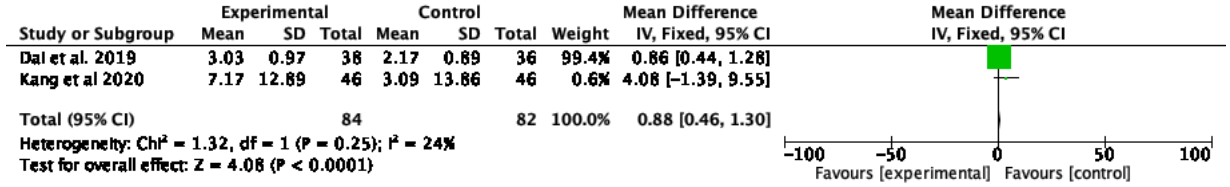

Figure 4: Effect of moxibustion therapies on pain management among patients with KOA based on the change in VAS scores

Effect of moxibustion therapies on joint dysfunction among patients with KOA

The effect of moxibustion treatment on the joint dysfunction was reported based on the recorded WOMAC function scores. Dai et al. (2019) also noted that the reduction in joint dysfunction in the moxibustion group was higher (21.61 ± 8.34) than that in the medication group (17.15 ± 5.61), and the outcome in patients in the control and moxibustion significantly varied). Xue et al. (2020) also noted that the joint dysfunction scores in the electronic moxibustion group was higher before (33.92 ± 8.44) compared to after treatment (14.37 ± 7.57, p < 0.05). Xue et al. (2020) also reported that for traditional moxibustion group, the joint

dysfunction score was higher before (30.97 ± 8.65) compared to after treatment (14.15 ± 8.09). Min et al. (2013) noted that warm needling moxibustion treatment resulted in significant reduction in joint dysfunction score as indicated by change in WOMAC function scores (17.86 ± 10.87) compared to the acupuncture therapies (11.96 ± 13.91, $p < 0.01$).

Meta-analysis of the effect of moxibustion therapies on joint dysfunction among patients with KOA based on the change in WOMAC scores

Meta-analysis was carried out to assess the effectiveness of moxibustion therapies in the management of joint dysfunction among patients with KOA for the studies that compared effects of moxibustion to that of the control group. In this meta-analysis Xue et al. (2020) was not included despite reporting change in pain based on WOMAC scores on joint dysfunction because the article presented before and after findings in each group (control and moxibustion). The analysis approach involved the use of continuous data retrieved from two studies (Dai et al., 2019; Min et al., 2013). The data included in the meta-analysis included the mean (SD) reduction in the WOMAC scores on joint dysfunction after treatment in the control and the experimental group (Moxibustion treatment). Dai et al. (2019) used drug-based treatment as the control while Min et al. (2013) used acupuncture therapy as the control. The assessment of the heterogeneity based on the I^2 statistic indicate that the included studies did not have significant heterogeneity ($I^2 = 0$ %, $p = 0.70$). Therefore, fixed effects model was used. As shown in Figure 5, the meta-analysis included 66 participants in the moxibustion group, and 64 in the control group. The pooled results indicate that the change in the mean WOMAC scores on joint dysfunction was significantly higher in the moxibustion group compared to the control (MD -4.74 [95% CI: -7.63 – -1.85]) since the 95 % CI values did not cross the line of no effect. Overall effect value (Z =

3.21, p = 0.001) further indicates that the meta-analysis outcome was statistically significant (Figure 5).

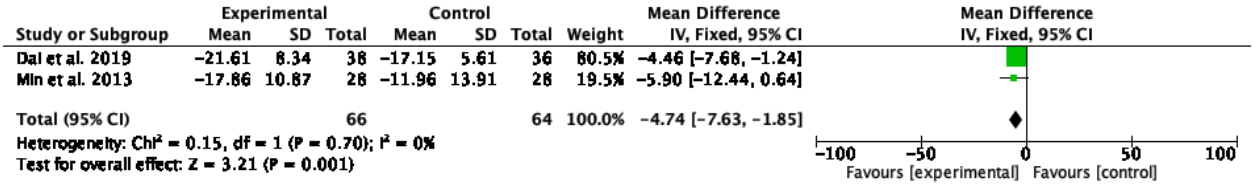

Figure 5: Effect of moxibustion therapies on joint dysfunction among patients with KOA based on the change in WOMAC scores

Effect of moxibustion therapies on overall improvement among patients with KOA

Three articles (Luo et al., 2019; Kang et al., 2020; Min et al., 2013) assessed the overall improvement among patients following treatment using PGA. Kang et al. (2020) noted that electrical moxibustion treatment resulted in significant reduction in pain (0.98 ± 0.71, $p < 0.001$) while traditional indirect moxibustion resulted in 1.17 ± 0.71 mean reduction in pain compared to the mean change in pain in the control 0.07 ± 0.68, $p < 0.001$). Luo et al. (2019) also noted from PGA scores that among the participants who took part in the conventional moxibustion 91 % of them registered improvement while in the smoke-free moxibustion group 97 % of the participants registered improvement. However, there was no difference in the reported overall improvement after the treatment ($p = 0.33$). According to Min et al. (2013) 42 % of the participants who received warm needling treatment ($n = 28$) had excellent KOA conditions while 32.1 % had good, 39.3 % had fair and 3.6 % had poor KOA conditions.

DISCUSSION

Summary of the Evidence

The findings of the systematic reviews and meta-analysis provide important insights into the objective of the study, which focused on the effectiveness of moxibustion treatment compared with placebo control, standard treatment, or no treatment in the management of pain among patients with osteoarthritis assessed by pain intensity and functional status or disability. The outcome of this systematic review and meta-analysis is associated with high reliability since it was based on the data collected from randomized controlled trials. It should be noted that the studies included in meta-analysis did not show significant heterogeneity, which suggests that the studies included in the meta-analysis did not significantly vary in the adopted research approach and could be compared (Koletsi et al., 2018).

Based on the systematic review of eight studies (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Min et al., 2013; Ren et al., 2011; Xue et al., 2020; Zhou et al., 2014; Zhao et al., 2021) it is evident that moxibustion treatment is associated with reduced pain intensity among patients with KOA. The meta-analysis that was performed involving three randomized control trials also indicated that moxibustion treatment results in a significant reduction in pain intensity as indicated by the change in mean WOMAC scores (MD -7.07, [95% CI: -9.29- -4.85], $Z = 6.23$, $p < 0.00001$). The review of the change in mean VAS scores obtained from four articles (Dai et al., 2019; Luo et al., 2019; Kang et al., 2020; Xue et al., 2020) also provided the change in the pain intensity among KOA patients resulting from moxibustion treatment. The reviewed studies indicated that following moxibustion treatment, the recorded VAS scores were lower compared to the score before the treatment suggest reduced pain intensity.

The findings of this study agree with various systematic reviews regarding the effectiveness of moxibustion treatment in addressing pain among patients with knee osteoarthritis (Choi et al., 2011; Li et al., 2016; Park et al., 2020; Yuan et al., 2019). In a review involving 14 randomized control trials and meta-analysis of eight studies, Choi et al. (2011) observed that moxibustion therapy has positive effects in relieving pain among patients with rheumatic conditions such as knee arthritis. The findings of this systematic review and meta-analysis support the observations made by Li et al. (2016) in their study that involved the analysis of data obtained from four studies with 746 participants. Li et al. (2016) reported that the administration of moxibustion treatment in patients with knee osteoarthritis leads to alleviation of symptoms associated with the condition such as pain and joint dysfunction. The outcome of this study also supports the conclusion made from a review that involved the analysis of data obtained from 39 randomized control trials with 3293 patients (Yuan et al., 2019). Based on the analysis of the obtained data, Yuan et al. (2019) reported that moxibustion treatment was more effective compared to western medicine or the placebos. Park et al.'s (2020) observation that indicated that moxibustion therapy was effective in the treatment of knee osteoarthritis supports the findings of this study. Park et al. (2020) based their observation on data that was collected from 27 randomly controlled trials conducted in China.

The meta-analysis that was performed involving two randomized control trials (Dai et al., 2019; Kang et al., 2020) indicated that moxibustion treatment result in a significant reduction in pain intensity as measured based on the change in mean VAS scores (MD 0.88 [95% CI: -0.46 – 1.30], $Z = 4.08$, $p < 0.0001$). It should be noted that the VAS is focused on subjective assessment of acute and chronic pain, therefore the response provided by the participants included in the two studies could have been influenced by other confounders such as prevailing contextual

considerations. There is therefore a need for future researchers to control for the effect of various confounders when using subjective measure such as VAS. The findings of this study also provide insights into the effect of moxibustion treatment on joint dysfunction based on the WOMAC function scores. Based on the systematic review of three randomized controlled studies (Dai et al., 2019; Min et al., 2013; Xue et al., 2020) it is evident that moxibustion treatment is associated with reduced joint dysfunction among patients with KOA. The meta-analysis that was performed involving two randomized control trials (Dai et al., 2019; Min et al., 2013) also indicated that moxibustion treatment results in a significant reduction in joint dysfunction as indicated by the change in mean WOMAC scores on joint dysfunction (MD: -4.74 [95% CI: -7.63 – -1.85], Z = 3.21, p = 0.001).

Based on the outcome of this review, various forms of moxibustion treatment show effectiveness in the management of symptoms associated with knee osteoarthritis. Kang et al. (2020) noted that thermal stimulation facilitates pain management by enhancing the circulation of blood and lymphatic fluid. Kang et al. (2020) comparison of the effectiveness of electrical moxibustion and traditional indirectness to moxibustion show the difference, which suggests that the novel electrical moxibustion therapy is effective. Dai et al. (2019) demonstrated moxibustion treatment involving the ignition of moxa sticks above the acupoint was equally effective in pain management as compared to the use of medical alternatives such as oral celecoxib capsule. As noted in this review. Luo et al. (2019) also demonstrated that conventional moxibustion that involved the ignition of moxa sticks above selected acupoints and smoke-free moxibustion that used a device that directed the moxa smoke to the acupoints were effective in the management of pain among patients with knee osteoarthritis. Based on the outcome of this review, moxibustion therapy that show greater effectiveness in the management of pain compared to acupuncture

treatment (Min et al., 2013; Zhou et al., 2014). According to Min et al. (2013), warm-needling have great effect than acupuncture in relieving pain among patients with knee osteoarthritis. Based on the outcome of this study, moxibustion therapy is effective in the treatment of patients with knee osteoarthritis as evident from the pain-relieving effects and ability to improve joint dysfunction. The reported effectiveness of moxibustion in the management of knee osteoarthritis could be associated with its effects on blood flow and dissolution of stasis (Dai et al., 2019). Based on the Chinese medicine understanding, moxibustion treatment leads to relief of pain among knee osteoarthritis patients by dispersing cold and relieving rigidity of muscles and through the activation of collaterals (Foster et al., 2007). The reported effectiveness of moxibustion therapy could also be linked to the effects on serum interleukin-1 and tumor necrosis factor-alpha (Dai et al., 2019).

Implications

The findings of this review which show moxibustion treatment as effective in addressing pain intensity experienced by patients with knee osteoarthritis is important since a large number of people suffer from the condition globally (Kang et al., 2020). It should be noted that most of the reviewed studies focused on participants aged above 40 years, which increases the relevance of the findings to the elderly population that is most affected by knee osteoarthritis (Choi et al., 2017; Lu & Shi, 2012; Moskowitz, 2007). The findings of this review have important practice implications in the choice of effective treatment of symptoms associated with knee osteoarthritis. Based on the findings of this review the use of moxibustion show greater effectiveness in the management of pain and joint dysfunction compared to western medicine (Dai et al., 2019; Kang et al., 2020; Zhao et al., 2021) and acupuncture (Min et al., 2013; Zhou et al., 2014). Therefore,

based on the outcome of this study, it is recommended that caregivers should consider using moxibustion treatment as opposed to Western medicine for acupuncture therapies. However, caution needs to be practiced in the application of this practice implications because not all western medicine or acupuncture therapies were taken into consideration. Medical practitioners, therefore, may choose moxibustion treatment over the assessed Western medicine such as oral celecoxib capsules. It is also evident from the outcome of this review that the various forms of moxibustion treatments are effectively addressing pain and joint dysfunction associated with knee osteoarthritis. Therefore, according to the findings of this review, the care providers therefore should base their choice of moxibustion on availability, cost, and safety profile. However, this review did not provide information regarding the availability, cost, and safety profile of the various moxibustion treatments. Therefore, future studies need to provide more insights into the highlighted characteristics of moxibustion treatment.

Limitations

There are various limitations that need to be taken into consideration when applying the findings of this study. One of the limitations relates to the fact that the studies were drawn from only two countries (China and South Korea). It should be noted that the use of findings obtained from participants from only the two highlighted countries raise questions relating to whether the unique beliefs, health practices, and cultures in the two countries influenced the reported health impact of moxibustion among knee osteoarthritis patients and whether such influences could be replicated in other countries with different sets of cultures and health beliefs. This limitation restricts the generalizability of the reported findings and conclusions to other countries globally. The other limitation relates to the limited number of studies that were included in the meta-

analysis. In this study, only three randomized control studies were included in meta-analysis. The limited number of studies eligible for meta-analysis was a result of the fact that other studies that could have been included in the meta-analysis were published in Chinese and challenges were faced in translating the text to English. The limited number of studies included in meta-analysis raises concerns regarding the comprehensiveness of the study conclusions. The other limitation in the study is the variation in the manner in which the included studies used pain assessment measures such as WOMAC. As noted from the retrieved data, some studies used WOMAC to determine to mean (SD) change in pain intensity (Dai et al., 2019; Kang et al., 2020; Min et al., 2013) while other studies (Zhao et al., 2021) used the tool to present the change in pain intensity as a percentage. They described variation in the manner in which the measurement tools were used limited the comparability of the findings. Although the included studies used a similar approach where the effect of the treatment was compared between participants in the moxibustion and control group, some of the studies were reading the manner in which the effect was reported. In some of the studies, the change in pain intensity and joint dysfunction was compared between the control and the moxibustion group after the treatment (Dai et al., 2019; Kang et al., 2020; Min et al., 2013). However, in some of the studies, the moxibustion group was not compared to the control but instead pain intensity and joint dysfunction were reported before and after the treatment in the moxibustion and in the control group separately (Ren et al., 2011; Zhou et al., 2014). The variation in the reporting of the primary outcome also meant that the studies were less comparable. The other limitation that needs to be taken into consideration when leads to the variation in the treatment periods. Some researchers considered a treatment period of more than four weeks (Min et al., 2013; Zhao et al., 2021) while others consider the treatment period of four weeks (Dai et al., 2019; Luo et al. (2019).

CONCLUSIONS

This systematic review with meta-analysis evaluated the effectiveness of moxibustion treatment in the management of pain among patients with osteoarthritis assessed by pain intensity and functional status or disability. Following the searches in Scholarly databases such as CENTRAL, PubMed, AMED, EMBASE, CBM, and CNKI eight articles were selected among which three were included in the meta-analysis. In this systematic review and meta-analysis, the effectiveness of moxibustion treatment in the management of pain among patients with knee osteoarthritis was assessed by comparing the treatment with controls that included western medicine and acupuncture therapies. Based on the findings of the study, it is concluded that moxibustion treatment is statistically significantly more effective in the management of pain among patients with osteoarthritis compared to acupuncture therapy or Western medicine (MD: -7.07 [95% CI: -9.29- -4.85], $p < 0.00001$). The outcome of this review and meta-analysis also showed the effectiveness of moxibustion therapies in the management of joint dysfunction among patients with knee osteoarthritis for the studies that compared to controls that included western medicine and acupuncture therapies. Based on the findings of the study, it is concluded that moxibustion treatment is statistically significantly more effective in the management of joint dysfunction among patients with osteoarthritis compared to acupuncture therapy or Western medicine (MD: -4.74 [95% CI: -7.63 – -1.85], $p = 0.001$).

Therefore, findings reported in this systematic review and meta-analysis suggest that moxibustion therapy is a promising alternative treatment for the management of symptoms associated with knee osteoarthritis. However, there are various gaps that future researchers need to address. To facilitate enhanced generalizability, future researchers need to be as they are randomized control trials on participants from various countries globally. There is also a need for

an increased number of English-based randomized control trials examining the effectiveness of moxibustion treatment in order to gather for the need for English speaking population. Given the limited number of studies that were included in the meta-analysis, there is a need for future researchers to adopt a standardized approach in the use of outcome measurement instruments such as WOMAC in the assessment of the effectiveness of moxibustion.

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APPENDIX

Appendix 1. European quality of life five-dimension five level scale (EQ-5D-5L)

EQ-5D-5L Questionnaire (English)

Participant details	
Participant Initials:	
Participant ID:	
Date completed:	DD/MM/YY

Under each heading, please tick the ONE box that best describes your health TODAY.	
1. MOBILITY	
I have no problems in walking about	
I have slight problems in walking about	
I have moderate problems in walking about	
I have severe problems in walking about	
I am unable to walk about	
2. SELF-CARE	
I have no problems washing or dressing myself	
I have slight problems washing or dressing myself	
I have moderate problems washing or dressing myself	
I have severe problems washing or dressing myself	
I am unable to wash or dress myself	
3. USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)	
I have no problems doing my usual activities	
I have slight problems doing my usual activities	
I have moderate problems doing my usual activities	
I have severe problems doing my usual activities	
I am unable to do my usual activities	

iHealth: EQ5D5L – v2 - English

Participant ID	
Participant initials	

4. PAIN / DISCOMFORT	
I have no pain or discomfort	
I have slight pain or discomfort	
I have moderate pain or discomfort	
I have severe pain or discomfort	
I have extreme pain or discomfort	
5. ANXIETY / DEPRESSION	
I am not anxious or depressed	
I am slightly anxious or depressed	
I am moderately anxious or depressed	
I am severely anxious or depressed	
I am extremely anxious or depressed	

6. We would like to know how good or bad your health is TODAY

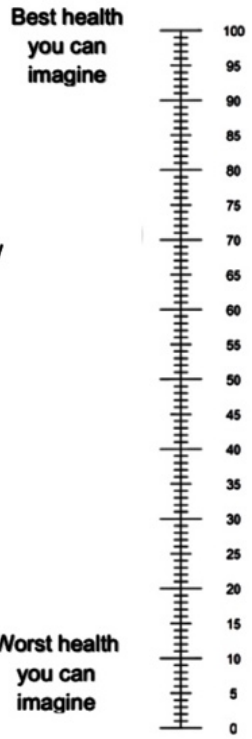
This scale is numbered from 0 to 100.

- ➔ 100 means the best health you can imagine.
- ➔ 0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below

SCORE ➔ ☐



Appendix 2: Western Ontario and McMaster University Osteoarthritis Index (WOMAC)

Name: _____ Date: _____

Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely

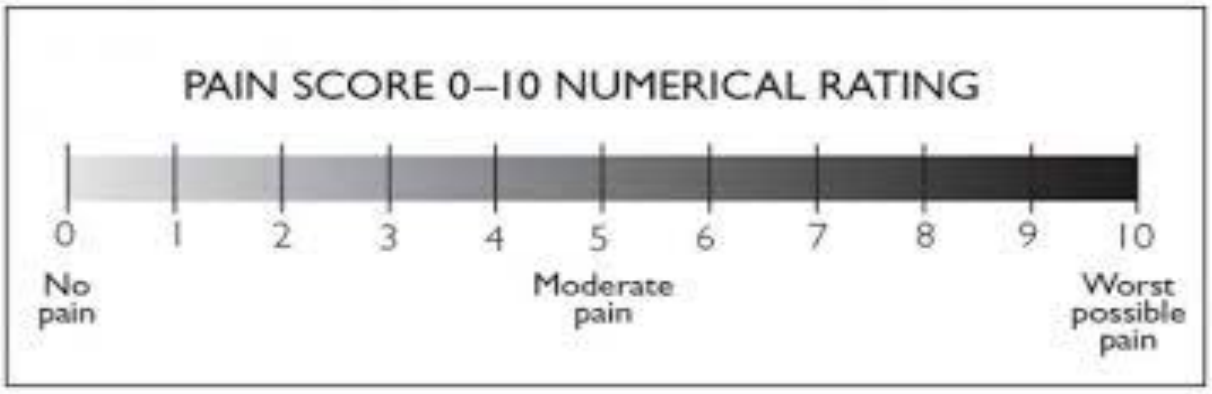
Circle **one number** for each activity

Pain	1. Walking	0 1 2 3 4
	2. Stair Climbing	0 1 2 3 4
	3. Nocturnal	0 1 2 3 4
	4. Rest	0 1 2 3 4
	5. Weight bearing	0 1 2 3 4
Stiffness	1. Morning stiffness	0 1 2 3 4
	2. Stiffness occurring later in the day	0 1 2 3 4
Physical Function	1. Descending stairs	0 1 2 3 4
	2. Ascending stairs	0 1 2 3 4
	3. Rising from sitting	0 1 2 3 4
	4. Standing	0 1 2 3 4
	5. Bending to floor	0 1 2 3 4
	6. Walking on flat surface	0 1 2 3 4
	7. Getting in / out of car	0 1 2 3 4
	8. Going shopping	0 1 2 3 4
	9. Putting on socks	0 1 2 3 4
	10. Lying in bed	0 1 2 3 4
	11. Taking off socks	0 1 2 3 4
	12. Rising from bed	0 1 2 3 4
	13. Getting in/out of bath	0 1 2 3 4
	14. Sitting	0 1 2 3 4
	15. Getting on/off toilet	0 1 2 3 4
	16. Heavy domestic duties	0 1 2 3 4
	17. Light domestic duties	0 1 2 3 4

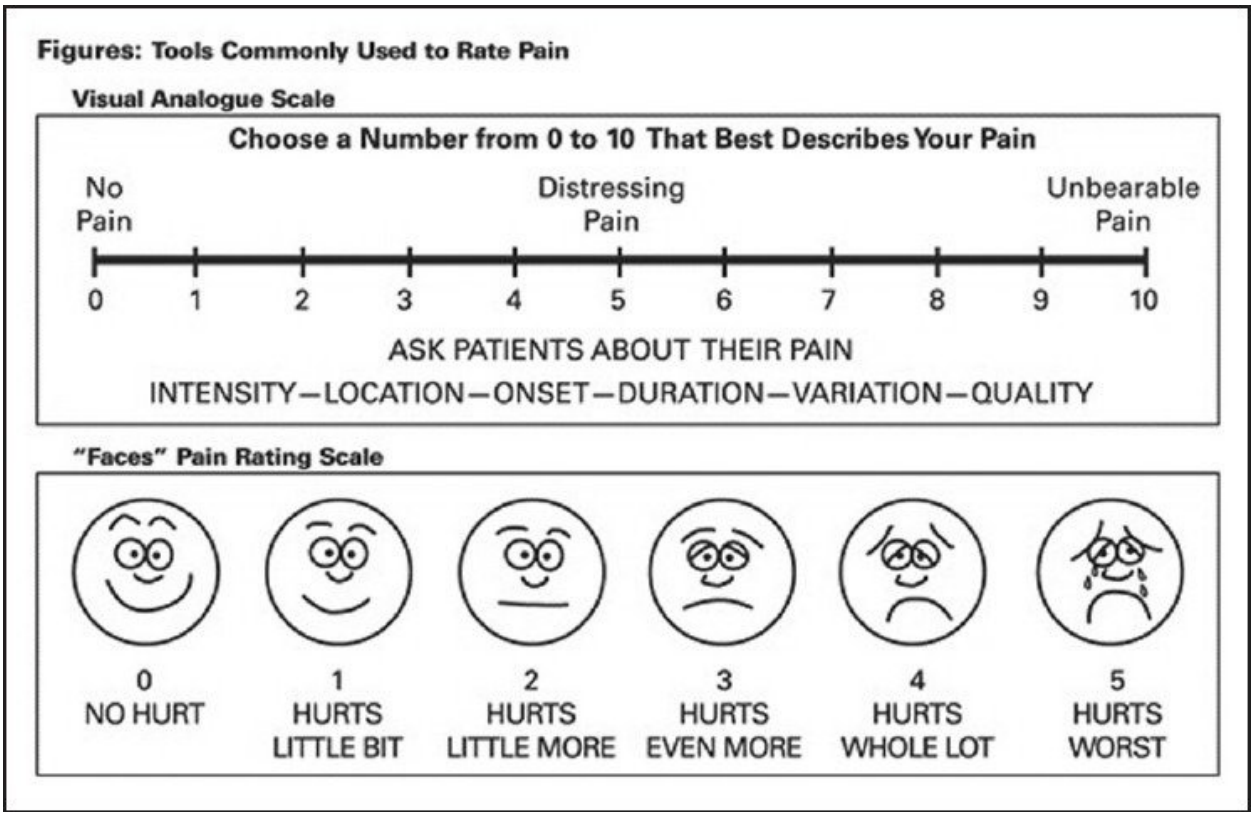
Total Score: _____ / 96 = _____%

Comments / Interpretation (to be completed by therapist only):

Appendix 3. Numeric Rating Scale (NRS)



Appendix 4. Visual Analogue Scale (VAS)



Appendix 5. SF-36 Questionnaire

SF-36 QUESTIONNAIRE

Name:_____ **Ref. Dr:**_____ **Date:** _____

ID#: _____ **Age:** _____ **Gender: M / F**

Please answer the 36 questions of the **Health Survey** completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
○ Excellent ○ Very Good ○ Good ○ Fair ○ Poor

Compared to one year ago, how would you rate your health in general now?
○ Much better now than one year ago
○ Somewhat better now than one year ago
○ About the same
○ Somewhat worse now than one year ago
○ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
○ Yes, Limited a lot ○ Yes, Limited a Little ○ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Lifting or carrying groceries
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing several flights of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Climbing one flight of stairs
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bending, kneeling, or stooping
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking more than a mile
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking several blocks
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Walking one block
○ Yes, Limited a Lot ○ Yes, Limited a Little ○ No, Not Limited at all

Bathing or dressing yourself

Yes, Limited a Lot Yes, Limited a Little No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Were limited in the kind of work or other activities

Yes No

Had difficulty performing the work or other activities (for example, it took extra effort)

Yes No

EMOTIONAL HEALTH PROBLEMS:

During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

Cut down the amount of time you spent on work or other activities

Yes No

Accomplished less than you would like

Yes No

Didn't do work or other activities as carefully as usual

Yes No

SOCIAL ACTIVITIES:

Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all Slightly Moderately Severe Very Severe

PAIN:

How much bodily pain have you had during the past 4 weeks?

None Very Mild Mild Moderate Severe Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely

ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a very nervous person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt calm and peaceful?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you have a lot of energy?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you felt downhearted and blue?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?

- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:

During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time

GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people

○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I am as healthy as anybody I know

○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

I expect my health to get worse

○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

My health is excellent

○ Definitely true ○ Mostly true ○ Don't know ○ Mostly false ○ Definitely false

Appendix 6. Patient Global Assessment (PGA) Form

The remainder of this form will be completed by your doctor, nurse, dietitian, or therapist. Thank you.

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Worksheet 1 - Scoring Weight (Wt) Loss

To determine score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use points below to score weight change and add one extra point if patient has lost weight during the past 2

Wt loss in 1 month	Points	Wt loss in 6 months
10% or greater	4	20% or greater
5-9.9%	3	10 -19.9%
3-4.9%	2	6 - 9.9%
2-2.9%	1	2 - 5.9%
0-1.9%	0	0 - 1.9%

Numerical score from Worksheet 1 ☐

Additive Score of the Boxes 1-4 (See Side 1) ☐ **A**

5. Worksheet 2 - Disease and its relation to nutritional requirements

All relevant diagnoses (specify) _____

One point each:

☐Cancer ☐AIDS ☐ Pulmonary or cardiac cachexia ☐ Presence of decubitus, open wound, or fistula
☐Presence of trauma ☐ Age greater than 65 years ☐ Chronic renal insufficiency

Numerical score from Worksheet 2 ☐ **B**

6. Work Sheet 3 - Metabolic Demand

Score for metabolic stress is determined by a number of variables known to increase protein & calorie needs. The score is additive so that a patient who has a fever of > 102 degrees (3 points) and is on 10 mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	none (0)	low (1)	moderate (2)	high (3)
Fever	no fever	>99 and <101	≥101 and <102	≥102
Fever duration	no fever	<72 hrs	72 hrs	> 72 hrs
Corticosteroids	no corticosteroids	low dose (<10mg prednisone equivalents/day)	moderate dose (≥10 and <30mg prednisone equivalents/day)	high dose steroid (≥30mg prednisone equivalents/day)

Numerical score from Worksheet 3 ☐ **C**

7. Worksheet 4 - Physical Exam

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle, & fluid status. Since this is subjective, each aspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition of categories: 0 = no deficit, 1+ = mild deficit, 2+ = moderate 3+ = severe

Muscle Status:				
temples (temporalis muscle)	0	1+	2+	3+
clavicles (pectoralis & deltoids)	0	1+	2+	3+
shoulders (deltoids)	0	1+	2+	3+
interosseous muscles	0	1+	2+	3+
Scapula (latissimus dorsi, trapezius, deltoids)	0	1+	2+	3+
thigh (quadriceps)	0	1+	2+	3+
calf (gastrocnemius)	0	1+	2+	3+
Global muscle status rating	**0**	**1+**	**2+**	**3+**
Fat Stores:				
orbital fat pads	0	1+	2+	3+
triceps skin fold	0	1+	2+	3+
fat overlying lower ribs	0	1+	2+	3+
Global fat deficit rating	**0**	**1+**	**2+**	**3+**

Fluid Status:				
ankle edema	0	1+	2+	3+
sacral edema	0	1+	2+	3+
ascites	0	1+	2+	3+
Global fluid status rating	**0**	**1+**	**2+**	**3+**

Numerical score from Worksheet 4 ☐ **D**

Total PG-SGA score ☐
(Total numerical score of A+B+C+D above)
(See triage recommendations below)

Global PG-SGA rating (A, B, or C) = ☐

Clinician Signature _____ RD RN PA MD DO Other ___ Date _____

Worksheet 5 - PG-SGA Global Assessment Categories

	Stage A	Stage B	Stage C
Category	Well nourished	Moderately malnourished	Severely malnourished
Weight	No wt loss **OR** Recent wt gain	≤ 5% wt loss in 1 month (or 10% in 6 mos) **OR** Progressive wt loss	> 5% wt loss in 1 month (or >10% in 6 mos) **OR** Progressive wt loss
Nutrient intake	No deficit **OR** Significant recent improvement	Definite decrease in intake	Severe deficit in intake
Nutrition Impact Symptoms	None **OR** Singificant recent improvement allowing adequate intake	Present of nutrition impact symptoms (PG-SGA Box 3)	Present of nutrition impact symptoms (PG-SGA Box 3)
Functioning	No deficit **OR** Recent improvement	Moderate functional deficit **OR** Recent deterioration	Severe functional deficit **OR** recent significant deterioration
Physical Exam	No deficit **OR** Chronic deficint but recent improvement	Evidence of mild to moderate loss of muscle mass / SQ fat / muscle tone on palpation	Obvious signs of malnutrition (eg, severe loss muscle, SQ tissue, possible edema)

Nutritional Triage Recommendations: Additive score is used to define specific nutritional interventions including patient & family education, symptom management including pharmacologic intervention, and appropriate nutrient intervention (food, nutritional supplements, enteral, or parenteral triage).
First line nutrition intervention includes optimal symptom management.

Triage based on PG-SGA point score

0-1	No intervention required at this time. Re-assessment on routine and regular basis during treatment.
2-3	Patient & family education by dietitian, nurse, or other clinician with pharmacologic intervention as indicated by symptom survey (Box 3) and lab values as appropriate.
4-8	Requires intervention by dietitian, in conjunction with nurse or physician as indicated by symptoms (Box 3).
≥ 9	Indicates a critical need for improved symptom management and/or nutrient intervention options.

Scored Patient-Generated Subjective Global Assessment (PG-SGA)

Patient ID Information

History (Boxes 1-4 are designed to be completed by the patient.)

1. Weight *(See Worksheet 1)*

In summary of my current and recent weight:

I currently weigh about _____ pounds
I am about _____ feet _____ tall

One month ago I weighed about _____ pounds
Six months ago I weighed about _____ pounds

During the past two weeks my weight has:
☐ decreased (1) ☐ not changed (0) ☐ increased (0)

Box 1 ☐

2. Food Intake: As compared to my normal intake, I would rate my food intake during the past month as:

☐ unchanged (0)
☐ more than usual (0)
☐ less than usual (1)

I am now taking:

☐ *normal food* but less than normal amount (1)
☐ little solid food (2)
☐ only liquids (3)
☐ only nutritonal supplements (3)
☐ very little of anything (4)
☐ only tube feedings or only nutrition by vein (0)

Box 2 ☐

3. Symptoms: I have had the following problems that have kept me from eating enough during the past two weeks (check all that apply):

☐ no problems eating (0)
☐ no appetite, just did not feel like eating (3)
☐ nausea (1)
☐ constipation (1)
☐ mouth sores (2)
☐ things taste funny or have no taste (1)
☐ problems swallowing (2)
☐ pain; where? (3)_____
☐ other** (1) _____
☐ vomiting (3)
☐ diarrhea (3)
☐ dry mouth (1)
☐ smells bother me (1)
☐ feel full quickly (1)
☐ fatigue (1)

** Examples: depression, money, or dental problems

Box 3 ☐

4. Activities and Function: Over the past month, I would generally rate my activity as:

☐ normal with no limitations (0)
☐ not my normal self, but able to be up and about with fairly normal activities (1)
☐ not feeling up to most things, but in bed or chair less than half the day (2)
☐ able to do little activity and spend most of the day in bed or chair (3)
☐ pretty much bedridden, rarely out of bed (3)

Box 4 ☐

Additive Score of the Boxes 1-4 ☐ **A**