THE RELATIONSHIP BETWEEN CUPPING THERAPY AND INTERLEUKIN-6 LEVELS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS IN REMISSION EXPERIENCING PAIN: A SCOPING REVIEW

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ABSTRACT

Introduction: Pain management in Systemic Lupus Erythematosus (SLE) patients is complex due to the diverse nature of pain and the potential side effects of medicine. Alternative approaches such as physical therapy, mind-body techniques, and complementary therapies show potential in reducing pain and improving overall well-being. A collaborative and personalized pain management plan, involving healthcare providers from multiple disciplines, is critical to addressing the complex challenges associated with pain in SLE patients. Cupping, has been shown to reduce pain complaints. Interleukin-6 (IL-6) as one of the biomarkers in pain and SLE. Limited knowledge about the impact of cupping therapy on IL-6 levels in remission SLE patients who experience pain requires in-depth research. Objective: to understand the effect of cupping on pain and inflammation management based on changes in IL-6 levels. Method: literature study using Publish or Perish application, indexed by Scopus, title "SLE Remission"; "Pain in SLE" Inclusion criteria: free and complete access, limited to review literature in English, period 2018-2023. Articles titled "IL-6 SLE", "Interleukin 6 SLE", "Cupping Interleukin 6", "Cupping IL-6", and "Cupping" with the keywords "IL-6" or "Interleukin-6" with similar inclusion criteria, but covering all types of articles. Results: title "SLE Remission", two articles; "Pain in SLE" two articles; "Cupping Pain", nine articles; "IL-6 SLE" three articles; "Cupping" with the keyword "IL-6", four articles. Conclusion: wet cupping has potential anti-inflammatory effects on musculoskeletal conditions and may affect IL-6 levels in SLE remission patients, while the association between IL-6, dry cupping, and pain in remitted SLE patients still requires further research.

Keywords*: humans; interleukin-6; cupping therapy; pain management; biomarkers*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a disease whose immune system attacks its own body (InfoDatin, 2017), a chronic autoimmune inflammatory disease with diverse signs and symptoms (Tanzilia, Tambunan and Dewi, 2021) with the course of the disease characterized by episodes of remission and repeated exacerbations (Aryaningrum *et al.*, 2021). The high mortality rate due to lupus needs special attention because 25% or around 550 people died

from lupus in 2016 (P2PTM and P2P, 2018).

Globally, the incidence of lupus in the world is around 1-15/100,000 people/ year (Nurudhin, 2020). The distribution of cases in Indonesia based on BPJS Health data trends of SLE cases increasing from year to year; 117,666 (2018), 144,491 (2019), 131,461 (2020), 158,855 (2021) with the most cases in West Java, East Java and DKI Jakarta (Kresnowati, 2022).

Research in Sweden shows that patients perceive LES-related pain as not adequately addressed by a healthcare provider (Waldheim, 2022). British research uses complementary therapies for significant unmet needs in controlling symptoms that are important to patients such as pain and fatigue (Morgan *et al.*, 2018). Research in Taiwan on the relationship between clinical manifestations of SLE(Lu *et al.*, 2022) The clinical manifestation of SLE with the highest prevalence is Raynaud's phenomenon (61.2%), while in Indonesia the most arthritis (32.9-75.5%). The data above shows that complaints of pain and fatigue are still experienced by people with lupus even though they have received treatment.

The Taiwan study surveyed the use of complementary therapies using gua sha/cupping as much as 3.7%, ranking 22nd out of 35 kinds of complementary therapies (Lu *et al.*, 2021). Complementary therapy is one of the modalities in nursing intervention ((PPNI, 2018) in Indonesia while cupping therapy is used in official hospital medicine in China (Wang *et al.*, 2021). In previous research (Wahyuni, Salim, *et al.*, 2023), the use of complementary therapies in the Lupus Association of South Sumatra (PLSS) results as follows for the characteristics of respondents 96% women, 88% adults; and 68% using complementary therapies. In the Social Service activity commemorating World Lupus Day at Kambang Iwak Palembang on May 20, 2023, it was found that 22 out of 32 respondents felt pain, including aches, pain, pain, cramps throughout the body or certain parts only. Markers or biomarkers of pain include the emergence of cytokines ((Zhang and An, 2007)) including Interleukin 6 (IL-6) ((Zhou *et al.*, 2016). Several key player factors, such as cytokines and complement, play an important role in the pathogenesis of systemic lupus erythematosus (Yuliasih *et al.*, 2022), cytokines are also part of the immune system. What's interesting about IL-6 is that it can be both pro-inflammatory and anti-inflammatory (Luo and Zheng, 2016). When associated with cupping therapy there are studies that show that after cupping there are changes in IL-6 levels (Zhang *et al.*, 2018). There are currently not many studies that explain the relationship between cupping and il6 levels in patients in remission patients who experience pain

Management of pain in patients with Systemic Lupus Erythematosus (SLE) remission becomes difficult due to multifactorial and different responses to standard therapy. This indicates the need to look for effective alternative approaches. Cupping, has been shown to reduce pain complaints. Interleukin-6 (IL-6) as one of the biomarkers in pain and SLE. Limited knowledge about the impact of cupping therapy on IL-6 levels in remission SLE patients experiencing pain requires in-depth research.

Objective: collect data to discuss the relationship between cupping and Interleukin-6 levels in SLE Remission patients who experience pain

METHOD

The literature study will be conducted in May-June 2023, using Publish or Perish application, indexed by Scopus, title "SLE Remission"; "Pain in SLE" Inclusion criteria: free and complete access, limited to review literature in English, period 2018-2023. Articles titled "IL-6 SLE", "Interleukin 6 SLE", "Cupping Interleukin 6", "Cupping IL-6", and "Cupping" with the keywords "IL-6" or "Interleukin-6" with similar inclusion criteria, but covering all types of articles. Data Management uses the computer program Excel (for spreadsheets). The selection process also involved two reviewers, namely L, EMS, while DW, IS extracted data from reports relevant to the study.

RESULTS AND DISCUSSION

a. SLE remission and pain

The definition of remission in Systemic Lupus Erythematosus (SLE) measured by several parameters: SLEDAI=0: This refers to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), with a score of zero. SLEDAI is an assessment tool for lupus disease activity, and a score of zero indicates the absence of detectable disease activity. Physician Global Assessment <0.5 (0-3): This is the physician's overall assessment of the patient's condition, with a range of values from 0 to 3. If this value is less than 0.5, it signifies that the physician evaluates the patient as being in clinical remission or in good condition. Irrespective of Serology: This means that this definition of remission applies regardless of the results of serological tests. It emphasizes that clinical remission is not solely based on changes in antibody levels or other serological markers. Medication Use: Antimalarials: Patients in remission may still be using antimalarials as part of their treatment plan. Low-Dose Glucocorticoids (prednisolone <=5mg/day): Patients may continue to use low-dose glucocorticoids, not exceeding 5 mg per day. Stable Immunosuppressants Including Biologics: Patients in remission may use stable doses of immunosuppressants, including biologic drugs (van Vollenhoven *et al.*, 2021). Thus, the definition of SLE remission in this context indicates a state in which the patient shows minimal or no clinical symptoms of lupus, as assessed by clinical parameters and physician evaluation, without considering specific serology. The use of certain medications is allowed as long as they remain within specified dosage ranges (Ruiz-Irastorza *et al.*, 2019). Pain complaints are experienced by all SLE patients (Pisetsky et al., 2021), and chest pain (Manchanda et al., 2022).

b. SLE and interleukin 6

The Macrophage Migration Inhibitory Factor (MIF) within the mononuclear white blood cells (PBMCs) of active SLE patients exhibits an increase in the expression of TNF-α and IL-6 (De la Cruz-Mosso et al., 2018). Another study investigating interleukin-6 levels in mild SLE, using urine analysis, found that elevated levels of Interleukin-6 in urine were associated with increased protein in the urine, heightened oral ulcers, increased facial rashes, and decreased fatigue (Schubert et al., 2021). Similarly, in newly diagnosed SLE patients undergoing initial SLE treatment, there is a demonstration of increased levels of IL-6 (Yuliasih et al., 2022).

c. Cupping and interleukin 6.

The combination of classical cupping technique with non-thermal plasma, termed 'plasma cupping' (PC), demonstrates anti-inflammatory activity by reducing the expression of TNF-α-mediated IL-1β and IL-6 (Lee et al., 2019). Cupping therapy has the ability to reverse the expression of IL-6 and TNF-α induced by Lipopolysaccharide (LPS) in the peritoneal fluid of mice. LPS is often used in research as an inflammatory trigger or observable immune response

(Zhang et al., 2018). Cupping therapy can alleviate the inflammatory response caused by strenuous physical exercise in martial artists. The study indicates that the increase in IL-6 and TNF-α scores after intense physical exercise is lower in the group receiving cupping therapy compared to the group undergoing only intense physical exercise. In other words, cupping therapy appears to have a soothing effect on the inflammatory response typically occurring after intense physical exercise using the wet cupping method (Ekrami et al., 2021). In healthy humans, wet cupping therapy has a long-term effect in reducing several inflammatory markers, showing a significant decrease in markers such as IL-6, IL-10, C3, C4, IgA, IgM, and IgG after undergoing wet cupping therapy. This suggests that wet cupping therapy has the potential as an effective method in reducing inflammation (Al-Tawarah, 2022).

d. Cupping and Pain

Based on 16 articles, a research team from Brazil revealed that the use of cupping to address lower back pain yields positive results in reducing the intensity of chronic back pain in adults, employing various methods and techniques within cupping therapy (Moura et al., 2018). The use of both wet and dry cupping can also be employed as independent therapies to manage LBP, as practiced in China (Shen et al., 2022). In Korea, cupping therapy proves effective in reducing neck pain in patients compared to the group without intervention or active control, positively impacting patients' functional abilities and quality of life (Kim et al., 2018), a finding supported by a research team from Iran (Azizkhani et al., 2018). In cases of chronic pain, the results from a meta-analysis by a German team across 18 trial studies indicate that cupping therapy has a moderate effect in reducing disability in the short term compared to no treatment or other active treatments. However, there is no significant difference in therapeutic effects between cupping therapy and sham cupping. This suggests that cupping therapy may assist in reducing disabilities associated with chronic pain (Cramer et al., 2020). In musculoskeletal pain, seven anatomical points for cupping placement were identified (Setyawan et al., 2022).

e. Inflammation Management Based On Changes In Interleukin 6 Levels

Interleukin-6 (IL-6) plays a crucial role in the inflammatory response and can serve as an indicator of inflammation activity in Systemic Lupus Erythematosus (SLE) patients. The relationship between IL-6 and components of inflammation management in SLE: (1) Immunosuppressive Medications: IL-6 can be produced by immune cells and contribute to inflammation. Immunosuppressive medications such as corticosteroids and immunosuppressants can reduce IL-6 production, thereby decreasing immune system activity and inflammation in SLE. (2) Antimalarials: Hydroxychloroquine, an antimalarial drug used in SLE, can influence IL-6 production and has anti-inflammatory effects. (3) Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs can reduce inflammation and pain, partially through the inhibition of IL-6. (4) Biologic Therapy: Biologic therapies like belimumab can target IL-6 and inhibit its activity, thus reducing inflammation in SLE. (5) Topical Corticosteroids: Topical corticosteroids can reduce local inflammation and its impact on IL-6. (6) Symptom and Complication Management: Monitoring IL-6 levels can aid in assessing disease activity and responding with treatment adjustments to control inflammation. Overall, the management of inflammation in SLE involves interventions that can influence IL-6 levels, either through inhibiting production or directly affecting its activity. Monitoring and adjusting therapies based on IL-6 levels can be a crucial strategy in the holistic management of this disease.

f. The results can be seen in table 1 and figure 1.

Table 1. Articles related to SLE remission phase, interleukin 6 in cupping therapy, interleukin 6 in SLE remission phase, and Cupping Therapy for Pain

No	Heading	Findings
1	2021 DORIS definition of remission in SLE: final recommendations from an international task force(van Vollenhoven *et al.*, 2021)	Consensus on the definition of remission in systemic lupus erythematosus (SLE): Previously, there was no clear consensus on the definition of remission in SLE. The study adds to recommendations from the Definitions Of Remission In SLE (DORIS) Task Force that suggest a definition of remission based on a widely used index (SLEDAI), a Global Assessment by Assessors, and allowing the use of multiple types of treatment. This provides clearer guidelines for clinical practitioners in determining remission in patients with SLE. Influence on clinical practice and future development: The definition of SLE remission proposed by DORIS is expected to be used as an aspirational goal in clinical care, as well as beneficial in education and research. This definition can help improve consistency in remission assessments, improve treatment and patient care, and provide a basis for further research into remission in SLE.
2	Prolonged remission in SLE is possible by using reduced doses of prednisone: An observational study from the Lupus-Cruces and Lupus-Bordeaux inception cohorts (Ruiz-Irastorza *et al.*, 2019)	The use of a therapy plan involving low doses of prednisone and maximal use of hydroxychloroquine, pulse methyl-prednisolone, and methotrexate may achieve long-lasting clinical remission in patients with systemic lupus erythematosus (SLE). The study compared the frequency of clinical remission in SLE patients from two initiation cohorts, the Cruces Lupus Cohort (CC) and the Bordeaux Lupus Cohort (BC). Study results showed that patients from CC treated with low doses of prednisone and adjunct therapies such as hydroxychloroquine, pulse methyl-prednisolone, and methotrexate, more often achieved clinical remission in the first year and had a long-lasting clinical remission rate during 5 years of follow-up compared to patients from BC. Therapeutic strategies that include low doses of prednisone and optimal use of additional medications such as hydroxychloroquine, pulse methyl-prednisolone, and methotrexate may increase the chances of achieving sustained clinical remission in SLE patients. The use of low doses of prednisone may help reduce the side effects associated with high doses of prednisone, while the use of additional medications may provide additional benefits in controlling disease activity.
3	The Categorization of Pain in Systemic Lupus Erythematosus (Pisetsky *et al.*, 2021)	There are **four types** of SLE that are described based on the active or inactive state of SLE and meet or do not meet the criteria for fibromyalgia or polysymptomatic distress (PSD)): -**Type 1 SLE**: Is an active SLE without meeting fibromyalgia criteria or PSD criteria. This means individuals with type 1 SLE have moderately active SLE and do not meet the criteria for a diagnosis of fibromyalgia or PSD. -**Type 2 SLE**: Is an inactive SLE that meets the criteria for fibromyalgia or PSD criteria. This means individuals with type 2 SLE have SLE that is currently inactive, but also meets the criteria for a diagnosis of fibromyalgia or PSD. Type 2 (non-inflammatory) manifestations such as widespread pain,

		fatigue, depression, and sleep disturbances may require a different treatment approach, in addition to immunomodulatory agents. This emphasizes the need for holistic and multidisciplinary treatment in dealing with this complex symptom. -**Mixed SLE**: Is an active SLE that meets fibromyalgia criteria or PSD criteria. Individuals with mixed SLE have moderately active SLE and also meet the criteria for a diagnosis of fibromyalgia or PSD. In this case, the symptoms of SLE and fibromyalgia or PSD interact with each other. -**Minimal SLE**: Is an inactive SLE that does not meet fibromyalgia criteria or PSD criteria. This means individuals with minimal SLE have SLE that is currently inactive and also does not meet the criteria for a diagnosis of fibromyalgia or PSD.
4	Coronary Microvascular Dysfunction in Patients With Systemic Lupus Erythematosus and Chest Pain (Manchanda *et al.*, 2022)	Discusses chest pain in SLE patients, which can be caused by various factors, including those related to the heart and lungs. SLE is an autoimmune disease that can affect many organs, including the cardiovascular and pulmonary systems. Therefore, chest pain in an SLE patient does not necessarily mean there is a problem with his heart, but it could also be with his lungs. The pathophysiology of chest pain in SLE patients varies depending on the cause, but generally involves inflammation of the tissues associated with the heart or lungs. Based on the article, there are several possible causes of chest pain in SLE patients, including: pleurisy, acute lupus pneumonia, pericarditis, myocarditis, angina.
5	MIF promotes a differential Th1/Th2/Th17 inflammatory response in human primary cell cultures: Predominance of Th17 cytokine profile in PBMC from healthy subjects and increase of IL-6 and TNF-α in PBMC from active SLE	Macrophage Migration Inhibitory Factor (MIF) is a cytokine associated with the pathogenesis of autoimmune inflammatory diseases, functions in a positive feedback cycle with proinflammatory cytokines and can prolong the inflammatory process in Systemic Lupus Erythematosus (SLE). This research suggests that MIF can trigger different inflammatory responses in physiological and pathological conditions. MIF tends to induce Th17 cytokine profiles in PBMCs of healthy subjects, while in PBMCs of active SLE patients, there is increased expression of TNF-α and IL-6.

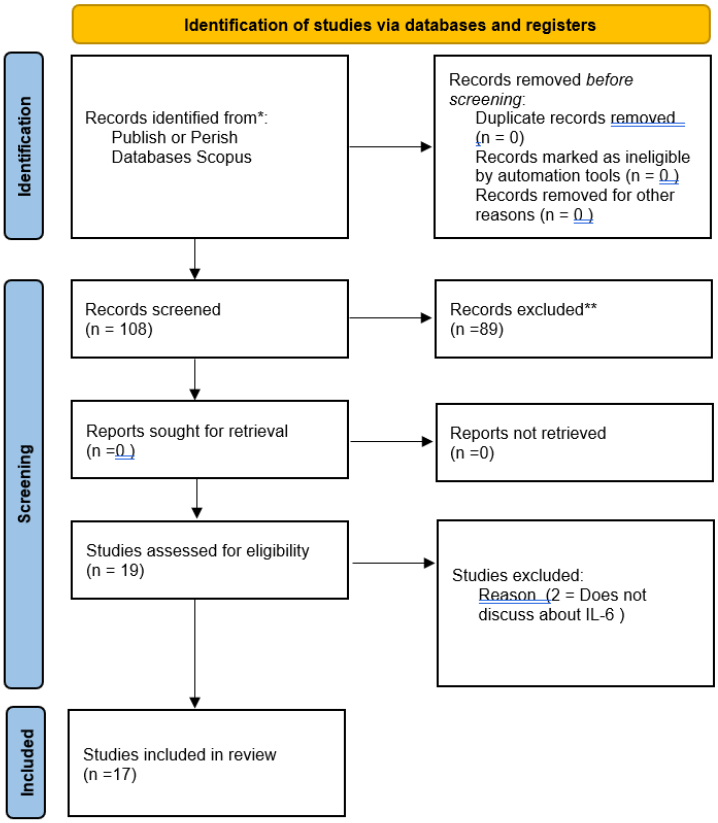
	patients (De la Cruz-Mosso *et al.*, 2018)	
6	Real-Life Cause-Effect Relations Between Urinary IL-6 Levels and Specific and Nonspecific Symptoms in a Patient With Mild SLE Disease Activity (Schubert *et al.*, 2021)	Both TNF-a and IL-6 can regulate the Th1/Th2/Th17/Treg balance which plays an important role in autoimmune pathogenesis through the feedback cycle, and thus contribute to the maintenance of immunological homeostasis. This study provides evidence on the real-time cause-and-effect relationship between IL-6 levels and SLE symptoms. It was found that increased levels of IL-6 in urine were linked to increased protein in the urine, increased oral ulcers, increased facial rashes, and decreased fatigue. These findings suggest that changes in immune activity are linked to changes in SLE symptoms. Reciprocal time between IL-6 and SLE symptoms: Series-time analysis showed a reciprocal relationship between IL-6 levels and SLE symptoms. For example, elevated levels of IL-6 in urine may precede a decrease in oral ulcer symptoms after 48-60 hours, whereas an increase in oral ulcers may precede a decrease in IL-6 levels after 84-96 hours. These findings suggest that changes in IL-6 may play a role as cause or effect of changes in SLE symptoms.
7	The Association of Complements, TGF-β, and IL-6 with Disease Activity, Renal Damage, and Hematological Activity in Patients with Naïve SLE (Yuliasih *et al.*, 2022)	"Naïve SLE" refers to patients who have recently been diagnosed with SLE or those who have not received specific treatment for SLE before. This study showed that there was an association between decreased C3 and C4 levels, as well as increased levels of IL-6 and TGF-β with the severity of SLE disease measured using SLAM scores. These findings indicate that these factors may play a role in the pathogenesis and activity of SLE disease. Association between C3, leukocytes, and hematological activity: It was found that patients with higher SLAM scores had a significant decrease in C3 complement levels, as well as an increase in leukocyte count. This suggests a correlation between SLE disease activity, changes in complement, and hematologic activity. Association between IL-6, TGF-β, and kidney damage: Findings showed that patients with high serum creatinine levels had significant increases in TGF-β levels. This suggests an association between TGF-β levels and kidney damage in SLE patients.
8	Plasma Cupping Induces Vegf Expression In Skin Cells Through Nitric	In this study, the medical property of the latest medical technology i.e. non-thermal plasma was added to classical cupping and referred to as 'plasma cupping' (PC). In the results of this study, the effectiveness of plasma formation increased under semi-vacuum conditions such as cupping (410 Torr) than at normal atmospheric pressure (760 Torr).

	Oxide-Mediated Activation Of Hypoxia Inducible Factor 1 (Lee *et al.*, 2019)	PC treatment of human keratinocytes HaCaT significantly induced VEGF-A expression. The increase in VEGF-A gene expression after PC treatment is expected to be the result of PC-mediated activation of the ERK protein. PC-mediated ERK activation is important for hypoxic parent factor (HIF) 1 alpha activity, which is responsible for PC-mediated VEGF-A expression. The increase in HIF-1 protein activity by PC is thought to be due to increased levels of NO in the media. In addition to the angiogenesis promotion action, PC also exhibits anti-inflammatory activity by reducing TNF-α mediated IL-1β and IL-6 expression.
9	Anti-Versus Pro-Inflammatory Metabololipidome Upon Cupping Treatment (Zhang *et al.*, 2018)	This study aimed to explore metabololipidomes in mice after cupping treatment. A naked mouse model that simulated cupping treatment in humans was formed by administering four sets of cupping on the skin of the back for 15 minutes. UPLC-MS/MS is used to determine PUFA metabolomes (Monounsaturated Fatty Acids) in the skin and blood of mice before and after cupping treatment. Lipids that underwent significant changes were tested on macrophages to evaluate the production of proinflammatory cytokines IL-6 and TNF-α using the ELISA method. The results showed that anti-inflammatory lipids such as PGE1, 5,6-EET, 14,15-EET, 10S,17S-DiHDoHE, 17R-RvD1, RvD5, and 14S-HDoHE increased significantly, while pro-inflammatory lipids such as 12-HETE and TXB2 decreased after cupping treatment in the skin or plasma. Cupping treatment can reverse LPS-induced IL-6 and TNF-α expression in mouse peritoneal fluid. In addition, some lipids such as 5,6-EET, PGE1, and 14,15-EET have the effect of decreasing IL-6 and TNF-α production in macrophages. Another important finding was that lipids such as 17-RvD1, RvD5, and PGE1 significantly reduced LPS-induced TNF-α expression, whereas TXB2 and 12-HETE increased LPS-6 and TNF-α expression enhanced by LPS (lipopolysaccharide) in macrophages.
10	Wet-cupping induces anti-inflammatory action in response to vigorous exercise among martial arts athletes: A pilot	Cupping therapy before strenuous training in martial artists can have anti-inflammatory effects. The results showed that IL-6 (interleukin-6) and TNF-α (tumor necrosis factor-α) values, which are inflammatory markers, were lower in the group that received cupping therapy before exercise compared to the group that only did strenuous exercise. Cupping therapy can reduce the inflammatory response caused by strenuous exercise in martial artists. The study showed that the increase in IL-6 and TNF-α scores after strenuous exercise was lower in the group receiving cupping therapy, compared to the group that only did strenuous exercise.

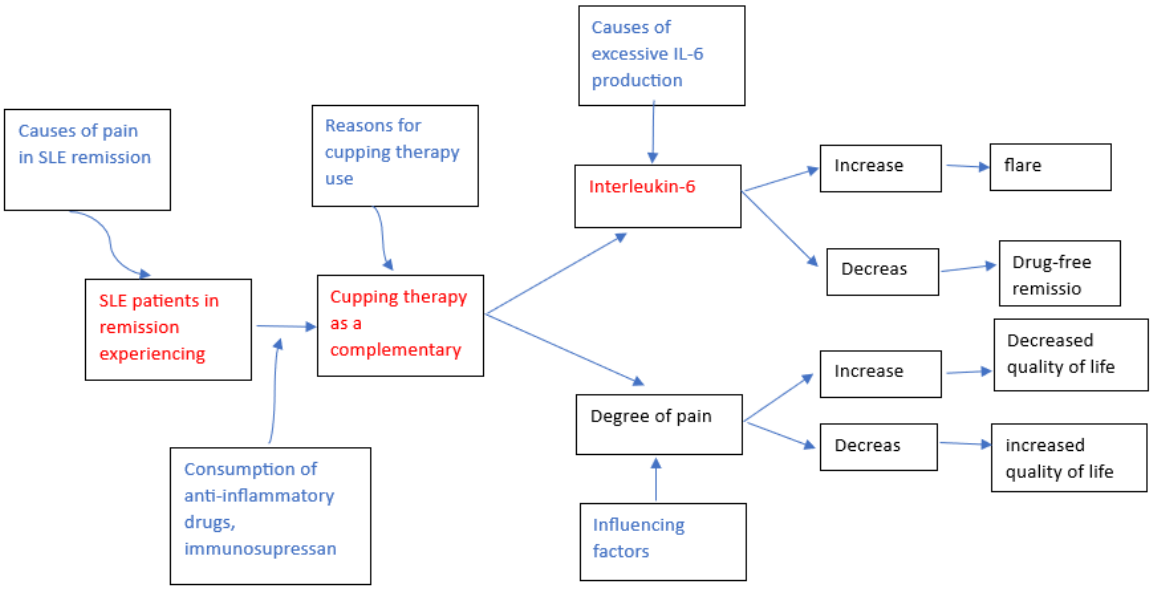
	study (Ekrami *et al.*, 2021)	
11	Long-Term after-Effects of Wet Cupping Therapy on Some Inflammatory Mediators and Antioxidant parameters in Jordanian Healthy Adult Men (Al-Tawarah, 2022)	Therapy (WCT) had a long-term effect on decreasing several inflammatory markers in healthy volunteers. The results showed a significant reduction in inflammatory markers such as IL-6, IL-10, C3, C4, IgA, IgM, and IgG after undergoing wet cupping therapy. This suggests that WCT could have potential as an effective method in reducing inflammation. Wet cupping therapy also increases antioxidant levels in the body of healthy individuals after the intervention. The study showed improvements in antioxidant parameters such as GPX, GR, SOD, and GST after receiving wet cupping therapy. This indicates that WCT can boost the body's defense system against potentially damaging reactive oxygen species (ROS).
12	Cupping therapy and chronic back pain: systematic review and meta-analysis (Moura *et al.*, 2018)	The results showed that cupping therapy had positive results in reducing the intensity of chronic back pain in adults. Lack of standardization in treatment protocols: This means that the methods and techniques used in cupping therapy can vary from one practitioner to another. The study found that the primary evaluated outcomes were pain intensity, physical disability, quality of life, and pain threshold prior to mechanical stimulation. The study concluded that it was necessary to develop a standardized application protocol for cupping therapy.
13	Is cupping therapy effective in patients with neck pain? A systematic review and meta-analysis (Moura *et al.*, 2018)	The results showed that cupping therapy was effective in reducing neck pain in patients compared to the group without intervention or active control group. Cupping therapy is also associated with significant improvements in terms of function and quality of life. The study reported that the incidence of side effects in cupping therapy is rare and mostly mild and temporary. This suggests that cupping therapy has a good safety profile. This study found that the quality of evidence from studies contained in the literature is still low. Therefore, definitive conclusions about the effectiveness of cupping therapy on neck pain cannot be drawn from this review. The need for further research: to corroborate the existing evidence and provide a deeper understanding of the effectiveness of cupping therapy in neck pain.

14	Cupping for Patients With Chronic Pain: A Systematic Review and Meta-Analysis (Cramer *et al.*, 2020)	The results of this meta-analysis showed cupping therapy had a major effect in reducing pain intensity in the short term compared to no treatment. However, there was no significant difference in the therapeutic effect of cupping compared to sham cupping or other active treatment. This suggests that cupping therapy may be an option in the treatment of chronic pain, but the results still need further review. The results of this meta-analysis also showed that cupping therapy had a moderate effect in reducing disability in the short term compared to no other active medication and treatment. However, there was no significant difference in the therapeutic effect of cupping compared to sham cupping. This suggests that cupping therapy may help reduce chronic pain-related disabilities, but more research is needed to confirm these findings. Safety of cupping therapy: Although side effects were more common in patients undergoing cupping therapy compared to none of the treatment, the difference was not statistically significant compared to sham cupping or other active treatments. This suggests that cupping therapy has a similar safety profile to the comparison method. Limitations in studies that have been conducted by clinical heterogeneity and risk of bias. This can affect the validity and generalizability of research results.
15	The Effect of Cupping Therapy on Non-specific Neck Pain: A Systematic Review and Meta-Analysis (Azizkhani *et al.*, 2018)	The results of the meta-analysis showed that cupping therapy was effective in reducing pain intensity in patients with non-specific neck pain. Cupping therapy was significantly better than the control group in reducing neck pain, as well as improving patients' quality of life. In addition to reducing pain, cupping therapy has also been shown to improve the quality of life of patients with neck pain. Heterogeneity between studies and risk of bias may affect the validity of results. More research is needed to confirm these findings, evaluate the long-term effects of cupping therapy, study possible side effects, and compare cupping therapy with other treatment methods.
16	Anatomical Points of Cupping Therapy for Musculoskeletal Pain: A Systematic Review (Setyawan *et al.*, 2022)	1. This study successfully identified seven anatomical points used in cupping therapy to reduce musculoskeletal pain. 2. More research is needed to thoroughly understand the benefits of each of these points.
17	Effectiveness of self-management of dry and wet cupping therapy for low back pain: A systematic review and meta-	This study showed that wet cupping therapy significantly reduced pain intensity in patients with low back pain (LBP). The study found that wet cupping therapy resulted in a more significant reduction in pain compared to dry cupping therapy in patients with LBP. In addition to reducing pain intensity, wet cupping therapy also improves the quality of life of patients with LBP.

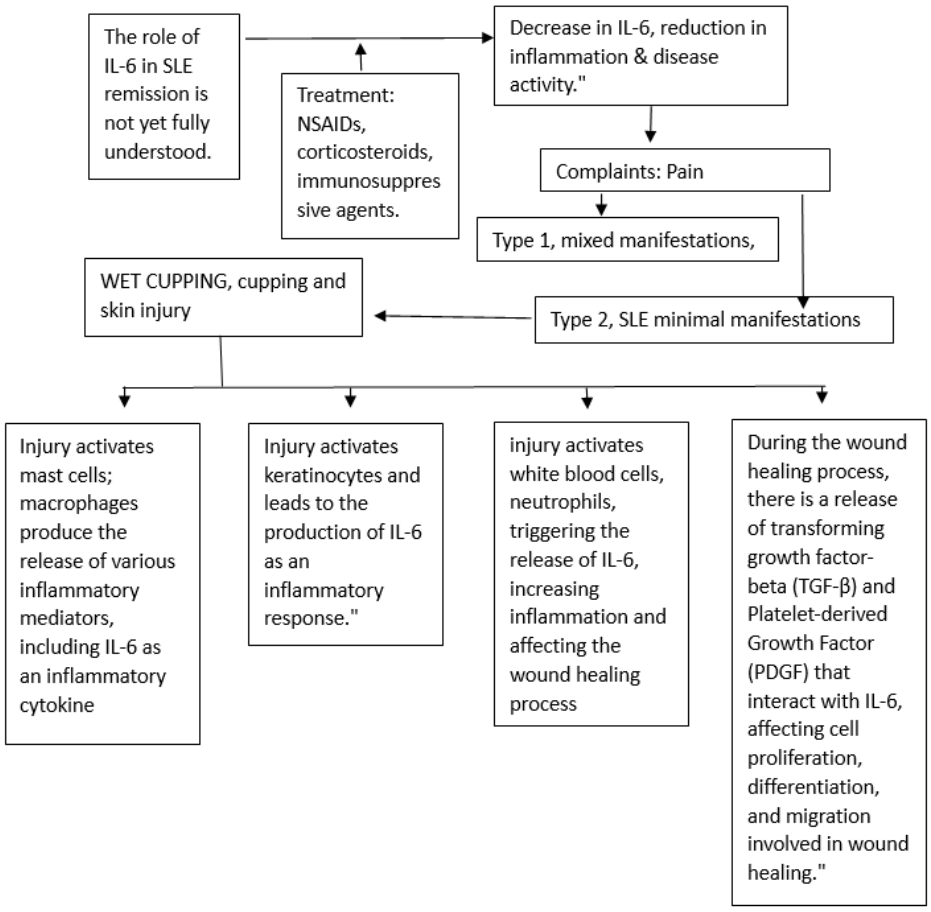
analysis (Shen *et al.*, 2022)	Variability in treatment protocols suggests that there is no clear standardization in wet cupping therapy treatment protocols in randomized clinical trials.



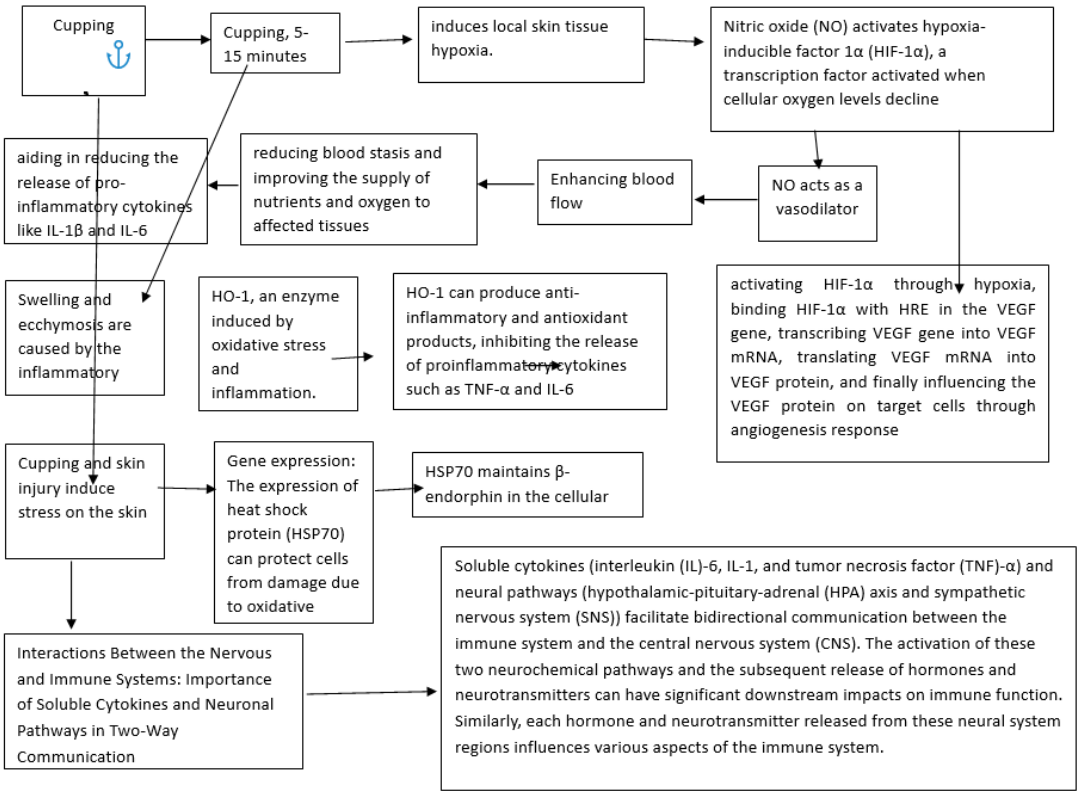
Picture 1. PRISMA 2020 Flow Diagram



Picture 2. Overview of cupping therapy usage in remissive SLE (Wahyuni, Salim, *et al.*, 2023), (Wahyuni and Salim, 2022), (Wahyuni, Legiran, *et al.*, 2023)



Picture 3. The relationship between il-6, sle remission, and cupping therapy (Ruiz-Irastorza *et al.*, 2019), (Pisetsky *et al.*, 2021), (Lee *et al.*, 2019), (Rodrigues *et al.*, 2019), (Raziyeva *et al.*, 2021)



Picture 4. The Relationship between Cupping Therapy and Pain Reduction (Hou *et al.*, 2021), (Lee *et al.*, 2019), (Subadi *et al.*, 2017), (Guo *et al.*, 2017), (Reza *et al.*, 2023), (Lowe, 2017)

CONCLUSION

Wet cupping, which involves the use of a device that produces straws on the skin, can stimulate blood circulation, increase lymphatic flow, and affect local immune responses. In some cases, wet cupping has been reported to have anti-inflammatory effects by reducing pain and inflammation in musculoskeletal conditions. Hypothetically, wet cupping may affect IL-6 levels in SLE remission patients. If wet cupping can reduce local inflammation or inhibit IL-6 release, it may help reduce pain in SLE remission patients. There may be a link between IL-6, dry cupping, and pain in SLE remission patients. IL-6 is a pro-inflammatory cytokine that can be involved in the inflammatory process. Elevated levels of IL-6 have been linked to SLE disease activity and more severe symptoms. Dry cupping, which involves the use of a device that produces pressure on the skin, can stimulate local reactions involving the release of cytokines and other inflammatory mediators. Although dry cupping is commonly used for other purposes such as improving blood circulation and reducing muscle stiffness, there have not been many studies that have specifically examined the relationship between dry cupping, IL-6, and pain in SLE remission patients.

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