COMBINED EFFECTS OF TURMERIC SUPPLEMENTATION AND STRENGTHENING EXERCISES ON KNEE PAIN, PHYSICAL FUNCTION AND QUALITY OF LIFE AMONG KNEE OSTEOARTHRITIS PATIENTS

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by

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TABLE OF CONTENT

ACKNOWLEDGEMENT…… ii

TABLE OF CONTENT…… iii

LIST OF TABLES…… vii

LIST OF FIGURES…….. viii

LIST OF ABBREVATIONS…… ix

LIST OF APPENDICES…….. x

ABSTRAK……. xi

ABSTRACT……... xiii

CHAPTER 1 INTRODUCTION……. 1

1.1 Background of the Study……...….... 1

1.2 Statement of Research Problem……. 4

1.3 Objectives of the Study……. 5

1.3.1 General Objective……. 5

1.3.2 Specific Objectives…… 5

1.4 Research Questions…….. 6

1.5 Hypotheses of the Study……... 7

1.6 Significance of the Study……. 8

1.7 Operational Definitions…… 9

1.7.1 Knee Osteoarthritis…… 9

1.7.2 Pain…….. 9

1.7.3 Turmeric…… 9

1.7.4 Quality of Life…….. 9

1.7.5 Physical Function…….. 10

1.7.6 Strengthening Exercise…… 10

CHAPTER 2 LITERATURE REVIEW…… 11

2.1 Knee Osteoarthritis…… 11

2.2 Turmeric Supplementation and Knee Osteoarthritis…… 15

2.3 Exercise and Knee Osteoarthritis…… 19

2.4 Strengthening Exercises and Knee Osteoarthritis…….. 20

2.5 Summary of Chapter 2…… 23

CHAPTER 3 METHODOLOGY…… 24

3.1 Research Design…… 24

3.2 Study Location and Population…… 24

3.3 Study Duration and Study Period…… 24

3.4 Selection Criteria of Participants…… 25

3.4.1 Inclusion Criteria…… 25

3.4.2 Exclusion Criteria……. 25

3.5 Sampling Method Recruitment Process…… 26

3.6 Sample Size Determination…….. 26

3.7 Experimental Procedures…… 27

3.8 Research Tools……. 29

3.8.1 Anthropometric Measurements…… 29

3.8.2 Visual Analogue Scale (VAS)…… 29

3.8.3 Western Ontario and McMaster UniversitiesOsteoarthritis Index (WOMAC)……. 30

3.8.4 Quality of life questionnaires-Malay version (WHOQOL-BREF) …….. 30

3.8.5 6-minute Walking Test (6MWT) ...…… 31

3.8.6 Strengthening Exercise……. 33

3.8.7 Turmeric Supplementation and Placebo…… 36

3.9 Statistical Analysis……..... 37

CHAPTER 4 RESULTS 38

4.1 Physiological Characteristics of the Participants…… 38

4.2 Adherence to the Exercise Training and Supplementation Regimen…….. 40

4.3 Pain Score (VAS)…… 40

4.4 6-minute Walk Test (6MWT)…… 42

4.5 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)……. 44

4.5.1 WOMAC-Pain Score…… 44

4.5.2 WOMAC-Stiffness…… 46

4.5.3 WOMAC-Difficulty in Physical Function Score…… 48

4.6 Quality of Life 50

4.6.1 4.6.1 Physical Health Score……. 50

4.6.2 Psychological Health Score……. 52

4.6.3 Social Relationships Score……... 54

4.6.4 Environmental Health Score……. 56

CHAPTER 5 DISCUSSION 58

5.1 Participants…… 58

5.2 Knee Pain…… 60

5.3 Physical Function…… 62

5.4 Quality of Life…… 64

5.5 Limitations of the Study…… 66

CHAPTER 6 CONCLUSION 67

6.1 Summary and Conclusion…… 67

6.2 Recommendations for Future Studies…… 68

REFERENCES…… 70

APPENDICES

LIST OF TABLES

		Page
Table 3.1	Strengthening exercises	34
Table 3.2	Progressive loading of the exercise programme	35
Table 4.1	Physiological characteristics of the participants	39
Table 4.2	Mean pain score at pre, mid and post-test in all groups	41
Table 4.3	Mean distance of walking in the 6MWT	43
Table 4.4	Mean WOMAC-Pain Score	45
Table 4.5	Mean WOMAC-stiffness score	47
Table 4.6	Mean score for WOMAC-Difficulty in Physical Function	49
Table 4.7	Mean physical health score (WHOQOL-BREF)	51
Table 4.8	Mean psychological health score (WHOQOL-BREF)	53
Table 4.9	Mean social relationship score (WHOQOL-BREF)	55
Table 4.10	Mean environmental health score (WHOQOL-BREF)	57

LIST OF FIGURES

		Page
Figure 3.1	Flow chart of research procedures	28
Figure 3.2	Illustration of 6min walking test (6MWT)	32
Figure 3.3	Turmeric supplementation	36
Figure 4.1	Mean pain score (VAS) for both groups at pre, mid and post-test	41
Figure 4.2	Mean walking distance (m) in the 6MWT for both groups at pre, mid and post-test	43
Figure 4.3	Mean WOMAC-pain score for both groups at pre, mid and post-test	45
Figure 4.4	Mean WOMAC-stiffness score for both groups at pre, mid and post-test	47
Figure 4.5	Mean score for WOMAC-difficulty in physical function for both groups at pre, mid and post-test	49
Figure 4.6	Mean physical health score for both groups at pre, mid and post-test	51
Figure 4.7	Mean psychological health score for both groups at pre, mid and post-test	53
Figure 4.8	Mean social relationship score for both groups at pre, mid and post-test	55
Figure 4.9	Mean environmental health score for both groups at pre, mid and post-test	57

LIST OF ABBREVIATIONS

IQR	Inner range quadriceps
OA	Osteoarthritis
PE	Placebo and exercise group
QoL	Quality of life
SLAS	Static low angle squatting
SLR	Straight leg raise
TE	Turmeric and exercise group
VAS	Visual analog scale
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life Assessment
6MWT	Six-minute walk test

LIST OF APPENDICES

Appendix A	The CONSORT flow diagram
Appendix B	Ethical Approval
Appendix C	Participants' informed consent form
Appendix D	Data Collection Form
Appendix E	Visual Analogue Scale
Appendix F	Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
Appendix G	Quality of life questionnaires-Malay version (WHOQOL-BREF)
Appendix H	6-minute walking test (6MWT)
Appendix I	Log book of Weekly Activity
Appendix J	Halal Certificate
Appendix K	Supplementation Compliance Log
Appendix L	Study pamphlet

KESAN GABUNGAN SUPLEMEN KUNYIT DAN SENAMAN KEKUATAN TERHADAP SAKIT LUTUT, FUNGSI FIZIKAL DAN KUALITI HIDUP DALAM KALANGAN PESAKIT ARTHRITIS SENDI LUTUT

ABSTRAK

Latihan pengukuhan meningkatkan fungsi fizikal dan kualiti hidup (QoL) individu yang mengalami osteoartritis lutut (OA). Selain itu, pengambilan suplemen kunyit telah terbukti mempunyai sifat melegakan kesakitan, yang secara tidak langsung memperbaiki fungsi fizikal dan QoL. Oleh itu, tujuan kajian ini adalah untuk menyiasat kesan gabungan suplemen kunyit dan latihan pengukuhan terhadap kesakitan lutut, fungsi fizikal, dan QoL dalam kalangan pesakit OA lutut. Seramai 35 orang pesakit OA lutut tahap II atau III (59.0 ± 1.0 tahun) telah direkrut dan secara rawak dibahagikan kepada dua kumpulan: kumpulan Plasebo dan senaman (PE) (n = 17) dan kumpulan Suplemen kunyit dan senaman (TE) (n = 18). Peserta dalam kumpulan PE mengambil satu kapsul plasebo (300 mg maltodekstrin), manakala peserta dalam kumpulan TE mengambil satu kapsul kunyit (697 mg) setiap hari selama 12 minggu. Peserta dalam kedua-dua kumpulan mengikuti preskripsi latihan pengukuhan yang sama selama 12 minggu, tiga kali seminggu. Pengukuran telah dijalankan pada ujian awal, ujian pertengahan, dan ujian akhir yang merangkumi pengukuran antropometrik, ujian berjalan selama 6 minit (6MWT), serta menjawab soal selidik kualiti hidup versi Melayu (WHOQOL-BREF), Indeks Osteoartritis Universiti Western Ontario dan McMaster (WOMAC), dan Skala Analog Visual (VAS). Hasilnya, skor kesakitan (VAS) menurun dengan ketara dalam kedua-dua kumpulan pada ujian akhir, dengan skor kesakitan dalam kumpulan TE jauh lebih rendah pada ujian akhir berbanding kumpulan PE ($p < 0.001$). Untuk jarak berjalan semasa 6MWT, jarak berjalan

meningkat dengan ketara ($p > 0.05$) dalam kumpulan TE sahaja pada ujian pertengahan dan ujian akhir. Tambahan pula, jarak berjalan dalam kumpulan TE adalah lebih tinggi secara ketara berbanding kumpulan PE ($p < 0.001$). Skor kesakitan WOMAC dalam kumpulan TE menurun dengan ketara pada ujian pertengahan dan ujian akhir, manakala dalam kumpulan PE, ia hanya berkurang dengan ketara pada ujian akhir ($p < 0.05$). Selain itu, skor kesakitan WOMAC jauh lebih rendah pada ujian pertengahan dan ujian akhir dalam kumpulan TE berbanding kumpulan PE ($p < 0.001$). Skor kekakuan WOMAC menurun dengan ketara pada ujian akhir dalam kedua-dua kumpulan, dengan skor dalam kumpulan TE lebih rendah pada ujian akhir berbanding kumpulan PE ($p < 0.01$). Tahap kesukaran dalam fungsi fizikal WOMAC berkurangan dengan ketara ($p < 0.01$) dalam kumpulan TE pada ujian akhir, tetapi tiada perubahan ketara ($p > 0.05$) diperhatikan dalam kumpulan PE. Selain itu, skor adalah jauh lebih rendah ($p < 0.01$) pada ujian akhir dalam kumpulan TE berbanding kumpulan PE. Bagi skor QoL, kedua-dua skor kesihatan fizikal dan psikologi meningkat dengan ketara dalam kedua-dua kumpulan ($p < 0.05$) pada ujian pertengahan dan ujian akhir, dengan skor dalam kumpulan TE jauh lebih tinggi ($p < 0.05$). Skor kesihatan sosial QoL meningkat dengan ketara ($p < 0.05$) pada ujian akhir dalam kumpulan TE tetapi tidak dalam kumpulan PE. Walau bagaimanapun, skor kesihatan persekitaran QoL tidak menunjukkan perbezaan ketara ($p> 0.05$) antara atau dalam kumpulan pada mana-mana ujian. Kesimpulannya, pengambilan suplemen kunyit yang digabungkan dengan latihan pengukuhan menghasilkan peningkatan yang lebih baik dalam tahap kesakitan, fungsi fizikal, dan kualiti hidup berbanding latihan pengukuhan sahaja. Oleh itu, suplemen kunyit boleh disyorkan untuk meningkatkan fungsi fizikal, mengurangkan kesakitan, dan memperbaiki kualiti hidup dalam kalangan pesakit osteoartritis lutut selain latihan fisioterapi.

COMBINED EFFECTS OF TURMERIC SUPPLEMENTATION AND STRENGTHENING EXERCISES ON KNEE PAIN, PHYSICAL FUNCTION AND QUALITY OF LIFE AMONG KNEE OSTEOARTHRITIS PATIENTS

ABSTRACT

Strengthening exercises improve the physical function and quality of life (QoL) of individuals with knee osteoarthritis (OA). In addition, the ingestion of turmeric supplementation has been shown to have pain-relieving properties, which indirectly improve physical function and QoL. Hence, the purpose of this study is to investigate the combined effects of turmeric supplements and strengthening exercises on knee pain, physical function, and QoL in knee OA patients. A total of 35 grade II or III knee OA patients (59.0 ± 1.0 years old) were recruited and randomly assigned into two groups: the placebo and strengthening exercise (PE) group (n = 17) and turmeric supplementation and exercise (TE) group (n = 18). Participants in the PE group consumed one capsule of placebo (300 mg of maltodextrin), whereas participants in the TE group consumed one capsule of turmeric (697 mg) daily for 12 weeks. Participants in both groups followed the same strengthening exercise prescription for 12 weeks, three times per week. Measurements were carried out at pre-test, mid-test, and post-test, which included anthropometric measurements, the 6-minute walk test (6MWT), and administration of the Quality of Life Questionnaire-Malay version (WHOQOL-BREF), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and the Visual Analogue Scale (VAS). As a result, the VAS-pain score significantly decreased in both groups at post-test, with the pain score in the TE group significantly lower at post- test compared to the PE group ($p < 0.001$). For walking

distance during the 6MWT, it was significantly increased ($p < 0.05$) at mid- and post-test in TE group only. In addition, the walking distance was significantly higher compared to the PE group ($p < 0.001$). WOMAC-pain scores in the TE group significantly decreased at mid- and post-test, while in the PE group, they were significantly reduced only at post-test ($p < 0.05$). Furthermore, WOMAC-pain scores were significantly lower at mid- and post-test in the TE group compared to the PE group ($p < 0.001$). WOMAC-stiffness scores were significantly reduced at post-test in both groups, with scores in the TE group significantly lower at post-test compared to the PE group ($p < 0.01$). WOMAC-difficulty in physical function scores significantly reduced ($p < 0.01$) in the TE group at post-test, but no significant change ($p > 0.05$) was observed in the PE group. Additionally, scores were significantly lower ($p < 0.01$) at post-test in the TE group compared to the PE group. For QoL scores, both physical health and psychological health scores significantly increased in both groups ($p < 0.05$) at mid- and post-test, with scores in the TE group significantly higher ($p < 0.05$). QoL-social health scores significantly increased ($p < 0.05$) at post-test in the TE group but not in the PE group. However, QoL- environmental health scores did not significantly differ ($p > 0.05$) between or within groups at any time point. In conclusion, turmeric supplementation combined with strengthening exercises results in greater improvements in pain level, physical function, and quality of life than strengthening exercises alone. Therefore, turmeric supplementation can berecommended to improve physical function, pain, and quality of life amongknee osteoarthritis patients in addition to physiotherapy exercises.

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Knee osteoarthritis (OA) is one of the most common conditions affecting our community. The most common symptom of knee OA is pain. There is evidence indicating that pain is linked with the quality of life (QoL) of an individual. Recent research proves that engaging in regular knee strengthening exercises reduces pain and improves QoL of an individual with knee OA. Osteoarthritis is a joint disease, which affects more and more individuals nowadays. According to WHO (2010) global disease report, osteoarthritis causes an individual to live years with disabilities, specifically the knee joint OA, which contributed 80% burden compared to the other joints. Research shows that the biggest problem faced by knee OA patients is pain, which further affects QoL (Vitaloni et al., 2019). The pain must be addressed so that it does not further cause joint limitation leading to disabilities in the end. Numerous studies have found that performing regular strengthening exercises has been associated with reducing pain among knee OA patients. Most of the people with knee OA present with weaker muscle compared to people without knee OA. In a research conducted by Cheing & Hui-Chan (2001), it has been identified that the quadriceps muscle's peak torque of a knee OA person dropped about 26% in comparison to a person without knee OA.

Ingestion of certain supplements, such as turmeric, ginger extract etc., has been shown to have pain-relieving properties comparable to modern medicine. Turmeric is a traditional eastern medicine and has been used in recent research to investigate its effects on reducing pain among knee OA patients due to its anti-

inflammatory properties (Paultre et al., 2021). Curcumin is the active component of turmeric that makes up 3% to 10% of turmeric. These components of turmeric present with anti-inflammatory effects similar to non-steroidal drugs.

Regarding the supplements, the general populace is usually unsure about the appropriate supplements for their knee OA condition. This may be due to the sheer number of supplements that are available which are marketed as treatments for osteoarthritis. OA is now characterized as an inflammatory, mechanical and metabolic disease rather than a wear and tear disease (Berenbaum, 2013). The progression and pathogenesis of this condition is governed by the inflammation process. Turmeric consists of curcumin as the active ingredient making up about 3% to 10% of the total composition. This active component has strong anti-inflammatory properties comparable to non- steroidal medications. There are many studies with evidence of the benefits of turmeric for knee OA patients in reducing pain as it retards the inflammatory processes at the joints. There are also studies which compare curcumin supplements and diclofenac, comparing their efficacy and safety. It was shown that both curcumin and diclofenac have similar effectiveness, but curcumin supplements form a better tolerance among patients (Hewlings & Kalman, 2017). Curcumin was chosen for this study as it was safer and had relatively low side effects when compared to diclofenac.

There are several conservative managements targeted towards treating knee OA. A systematic review conducted by Fransen et al. (2015) proved that employing therapeutic exercises lead to pain reduction and increased QoL and body function in knee OA patients. Furthermore, through integrating rehabilitation tools, the therapist's supportand the patient own strength, exercise therapy has the potential to improve any

component of the body's functionality (Sheikh & Vissing, 2019). According Garber et al. (2011), exercise improves the body's stability, cardiac and pneumonic functions, muscle strength and mental health. In conclusion, therapeutic exercise can be an invaluable tool in the knee OA treatment regime.

In addition, it has been determined in a meta-analysis of randomized controlled trials that strengthening exercise is one of the exercises that has the ability to effectively reduce pain (Jansen et al., 2011) among knee OA patients. This is because muscle weakness, specifically in the quadriceps femoris, is the prime reason in increased pain among knee OA patients (Bennell et al., 2012). According to Valderrabano & Steiger (2011), weak muscles create more shear forces and peak joint forces, which causes damage to the joints. These problems can be resolved with strengthening exercises. However, the studies that investigate the usage of strengthening exercises alone to improve QoL among knee OA patients is still limited. Thus, this study will be able to contribute in that respect.

Evidence shows that both strengthening exercises and supplements have the potential to reduce pain among knee OA patients. Therefore, this research aims to investigate the combined effectiveness of turmeric supplements and strengthening exercises on pain and QoL of knee OA patients by measuring the changes in degrees of pain, stiffness and functional abilities.

1.2 Statement of Research Problem

In current practice holistic approach is needed so that we can provide a beneficial treatment to the patients. Not only in our prospect of job but we need to take in count all the other factors that influence a condition. So that all the other factors tackled in order to cure a condition. Since, there are no studies conducted to examine the combined effectiveness of turmeric supplements and strengthening exercises as an intervention for knee osteoarthritis, this study will be able to create new knowledge for future physiotherapists to prescribe a multimodal treatment for patients. Furthermore, this study can potentially fill a gap that was identified in a systematic review by Paultre et al. (2020) which states that researches studying the relationship between turmeric supplements and physical therapy with relation to knee osteoarthritis is currently lacking.

1.3 Objectives of the Study

1.3.1 General Objective

To investigate the effects of turmeric supplementation combined with strengthening exercises on knee pain, physical function and quality of life of patients with knee osteoarthritis following a 12-week intervention period.

1.3.2 Specific Objectives

1. To compare the effects of turmeric supplementation combined with strengthening exercises and strengthening exercise alone on knee pain among knee OA patients following a 12-week intervention period.
2. To compare the effects of turmeric supplementation combined with strengthening exercises and strengthening exercise alone on physical function among knee OA patients following a 12-week intervention period.
3. To compare the effects of turmeric supplementation combined with strengthening exercises and strengthening exercise alone on quality of life among knee OA patients following a 12-week intervention period.

1.3.3 Research Questions

RQ_1: What are the combined effects of strengthening exercises and turmeric supplements on knee pain [Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)] among knee osteoarthritis patients?

RQ_2: What are the combined effects of strengthening exercises and turmeric supplements on physical function (6 min walking test (6MWT) and WOMAC) among knee osteoarthritis patients?

RQ_3: What are the combined effects of strengthening exercises and turmeric supplements on quality of life (WHOQOL-BREF) among knee osteoarthritis patients?

RQ_4: Does combination effects of strengthening exercises and turmeric supplements are significantly better than strengthening exercises alone?

1.3.4 Hypotheses of the Study

H_{O1}: There are no significant differences on knee pain [Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)] between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

H_{A1}: There are significant differences on knee pain [Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)] between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

H_{O2}: There are no significant differences on physical function (6 min walking test (6MWT) and WOMAC) between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

H_{A2}: There are significant differences on physical function (6 min walking test (6MWT) and WOMAC) between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

H_{O3}: There are no significant differences on quality of life (WHOQOL-BREF) between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

H_{A3}: There are significant differences on quality of life (WHOQOL-BREF) between placebo combined with strengthening exercise and turmeric supplementation combined with strengthening exercise among knee OA patients.

1.4 Significance of the Study

This research on combined effects of turmeric supplementation and strengthening exercises on knee pain, physical function and quality of life among knee osteoarthritis patients is important to fill a certain knowledge gap plaguing the community. Numerous studies have identified the beneficial effects of turmeric supplements on reducing pain among knee OA. Whereas, strengthening exercises also has caused a great reduction in pain and improved the functionality of knee OA patients. Hence, it is interesting to investigate the combination of both of these treatments on pain, QoL and functionality of knee OA patients. Furthermore, there are no researches conducted on this topic to date. Therefore, the results that gathered through this study hopefully will act as guidance in planning a holistic treatment for knee.

1.5 Operational Definitions

1.5.1 Knee Osteoarthritis

Knee osteoarthritis is a deterioration disease of knee joint which usually caused by the loss of articular cartilage, also the wears and tear process that happened in the knee joint (Hsu & Siwiec, 2021).

1.5.2 Pain

Pain is defined as an uncomfortable emotional and sensory ordeal related to, or seeming to relate to, real or possible tissue injury (Raja et al., 2020). It can be subjectively measured through several tools such as Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

1.5.3 Turmeric

Curcuma longa (Turmeric) is a perennial plant of the herbaceous variety. It has been reported that curcumin's primary bioactive component, diferuloylmethane, displays an array of biological activities such as anti-inflammation, anti-microbial, anti-carcinogenic, antioxidant, and hepatoprotection (Liju *et al.,* 2011).

1.5.4 Quality of Life

The welfare of an individual or a population, encompassing positive and negative aspects of their entire existence in any given time frame is expressed as their Quality of Life (QoL). QoL is usually made up of personal health markers, including but not limited to mental, physical and spiritual health. It also includes other factors such as relationships, work conditions, social and educational status, financial stability,

freedom and sense of safety and their general physical surroundings (Teoli & Bhardwaj, 2023).

1.5.5 Physical Function

Physical function is defined as the ability to perform fundamental and complicated activities. Physical function is closely related to an elderly person's capability to coexist in a community, a high level of physical function leads to high levels of independence (Garber et al., 2010).

1.5.6 Strengthening Exercise

Strengthening exercises are physical activities designed to improve muscle strength by making the muscles work against resistance. These exercises typically involve the use of resistance in the form of weights, resistance bands, or body weight. The goal is to increase muscle mass, endurance, and power by challenging the muscles to adapt to progressively

higher levels of resistance. Strengthening exercises help improve overall physical function, enhance mobility, support joint stability, and reduce the risk of injury. Examples include weightlifting, squats, push-ups, and resistance band exercises (Bennie et al., 2020).

CHAPTER 2

LITERATURE REVIEW

2.1 Knee Osteoarthritis

Based on the study by Global Burden Disease, patients diagnosed with knee or hip OA are the 11th highest group suffering with a disability on a global scale (Cui et al., 2020) Malaysian Elders Longitudinal Research (MELoR) did a cross sectional study which concluded that knee pain is complained by 33% out of 1212 subjects of the study (Mat et al., 2019). Besides, as stated in Global Burden of Disease (GDB, 2015) knee OA contributes almost 85% to burden and disability. This is also evidenced by a 32.7% increase of knee OA from 2005 to 2015, thus making OA a leading cause of global years lived with disability (YLD). OA is at the root of an annual economic burden of 1% to 2.5% of the gross domestic product of high-income countries, which translates to at least USD USD 89.1 Billion (Cross et al., 2023). Knee and hip joint replacements make up the bulk of that cost (Gandhi et al., 2023).

Knee OA is the most common form of arthritis which gradually causes structural changes to the cartilage and joints. This paves way for pain and functional disability (Theis et al., 2021). Knee OA can be divided into two groups, which are primary and secondary knee OA. Primary OA is caused by gradual and somewhat natural changes and degeneration to the articular cartilage whereas secondary OA is caused by the changes altered on the articular cartilage by trauma or byany condition such as rheumatoid arthritis (RA) (Hsu et al., 2021). Osteoarthritis is considered as a progressive disease which ultimately causes disability. The severity of the symptoms varies from patient to patient. However, the always tend to increase in severity, frequency and debilitating as time goes by, with the degree of progression also varying

between individuals. Most prevalent symptoms include a gradual onset of knee pain which worsens with activity, stiff and swollen knees, knee pain following lengthy periods of sitting or resting and pain that increases in severity over time. As for treatments, conservative methods are first employed. In case they fail to make a significant enough impact, then surgical treatments employed (Elsiwy et al., 2019).

Current evidence proves that knee OA is not solely about the degeneration of joints and cartilages but mechanical, inflammatory and metabolic factors that occurs in the joints has also been found to cause pain and limitations to the individual. The root cause of KOA is made up of multiple factors such as metabolic dysregulation, pro- inflammatory mediators, biomechanical forces and changes in local tissue metabolism (Shen et al., 2016). The loss of cartilage strength at the early stage causes a compositional change in the knee joint. This leads to the knee joint becoming vulnerable to damage due to physical impact (Loeser et al., 2016). Continued joint damage leads to an increase in chondrocyte activity, which in turn leads to secondary degradation and an increase in pro- inflammatory mediators in the synovium (Adam et al., 2024). The NF-kB protein complex plays a major role in joint homeostasis. However, when it becomes unregulated it leads to an increase in cytokine activity. When all these different factors are taken into account it becomes apparent that inflammation has a more significant role in OA pathogenesis than once considered (Loeser et al., 2016).

The inflammatory mediation that occurs in the synovial joint plays a pivotal role in initiating and perpetuating the OA condition. Such mediators come from two categories of sources: local and systemic. Example of a local source would be joint cells whereas systemic mediators may come from other tissues. One such example is

adipose tissue, which can reach the joint through the subchondral bone vasculature when released into the blood (Berenbaum, 2013). These mediators cause a lot of damage to the bone, cartilage and synovium when they reach the joint (Sellam & Berenbaum, 2009). Inflammation and synovitis due to a thickening synovium takes place as a result of the swelling joint. A swollen joint is a clinical feature of OA. Traumatic meniscal injury often leads to synovial inflammation, causing dysfunction and heightened pain levels (Scanzello et al., 2011).

Based on the newly discovered evidence of the importance of inflammation in OA pathogenesis and progression, it is imperative for clinicians and researchers to find new methods to hamper inflammation advancement (Paultre et al., 2021). In a recommendation published by the American College of Rheumatology (ACR) and Osteoarthritis Research Society International (OARSI) on conservative KOA treatment, both bodies advocate for exercise and weight loss, hyaluronic acid and corticosteroid injections and topical non-steroidal anti-inflammatory drugs (NSAIDs) (Bannuru et al., 2019 & Kolasinski et al., 2019). It is worth noting that analysis from 60 well known interventions and MTA analysis used to in the OARSI to make up the statements. The ACR report on nutraceuticals such as fish oil, vitamin D, glucosamine and chondroitin sulfate concluded that in a general sense, there was insufficient evidence of their efficacy in treating KOA. This finding was echoed in a systematic review and meta-analysis by Liu et al. (2018). In randomized placebo-controlled trials researching the safety and effectiveness of supplements aimed at treating knee, hip or hand OA, it was found that the majority of supplements, including chondroitin and glucosamine, fail to present a clinically consequential impact on OA. A few less common supplements such as curcumin, *Boswellia serrata* extract and pycnogenol showed positive results. However, it was in an insufficient quality and quantity, thus

disqualifying them from being recommended.

Currently, the standard of treatment based on the Management of Osteoarthritis (2013) for non-pharmacological intervention is patient education through awareness programs based upon the specific needs, aim and functional abilities of the patients. This is followed by lifestyle modifications, including increased physical activity, weight loss, occupational therapy, and physiotherapy. As for pharmacological treatments, simple analgesics such as paracetamol or Non-Steroidal Anti-Inflammatory Drugs can be administered to manage pain. Intra-articular or topical treatments are also an option. Alternative treatments such as unsaponifiable avocado soybean and ginger, and acupuncture can also be considered to reduce pain. These interventions sum up the recommended conservative clinical practice guidelines to manage osteoarthritis (Kamaruzaman, 2013).

2.2 Turmeric Supplementation and Knee Osteoarthritis

Recent studies found that traditional supplements help reduce inflammation by increasing antioxidant levels. The deterioration of the OA condition is most related to the inflammation that occurs in a joint (Berenbaum, 2013). Therefore, it has been found that one of the most effective ways in reducing the progression and pathogenesis of knee OA is by reducing inflammation. This will indirectly manage the symptoms and progression of the condition. Since the primary goal in knee osteoarthritis management is to reduce pain caused by inflammation (Daily et al., 2016), supplements or traditional medicine that exhibit anti-inflammatory properties will be helpful in reducing pain among knee OA patients.

The current available dugs to treating joint pain and joint inflammation are non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and steroids (Suokas et al., 2014). Commonly classic NSAIDs reducing inflammation by inhibiting prostaglandin and thromboxane synthesis due to theyare medicine which categorized as cyclooxygenase (COX) inhibitors. Whereas, new NSAIDs selectively inhibit COX- 2 which used to particularly reduce the risk of peptic ulcer and aim to the specific inflamed tissues (Drina., 2017). However, NSAIDs are not viable to be used long term as they are not strong enough to provide adequate pain relief. Furthermore, NSAIDs cause immune disturbances and severe cardiovascular and gastrointestinal complications (Schnitzer, 2006). The withdrawal of numerous FDA-approved anti- inflammatory medications has significantly increased the demand for herbal anti- inflammatory drugs with minimal side effects to treat arthritis (including rheumatoid arthritis and osteoarthritis) (Funk et al., 2006).

Turmeric is the powdered form of the dried rhizome from the Curcuma longa plant, containing numerous phytochemicals (Soleimani et al., 2018). Regarding its approximate composition, turmeric consists of water (80–90%), carbohydrates (about 13%), proteins (2%), minerals (2%), and lipids (<1%) (13). Curcuminoids, which are minor constituents of turmeric, play a key role and can account for as much as 10% of dry turmeric powder. This category primarily includes curcumin, dimethoxy-curcumin, and bisdemethoxycurcumin, which can constitute 62–90, 9–23, and 0.3–14 mg/g of commercial turmeric products (extracts and powders), respectively. Moreover, over 50 curcuminoids (including bisabocurcumin, curcumalongin, cyclocurcumin, and terpecurcumin) have been discovered in turmeric (Thangavel & Dhivya, 2019 & Meng et al., 2018), which gives it the yellow hue.

Curcumin is the active agent that makes up 3% to 10 % of turmeric (Hewlings & Kalman, 2017). It is a spice that belongs to the ginger family which is widely used in Ayurvedic and Chinese medicine (Goel et al., 2008), and Indo-Asian cuisine (Hewlings & Kalman, 2017). Curcumin is one of the natural supplements that is emerging in recent studies as having properties such as anti-inflammation (Mobasheri et al., 2012), anti- oxidative (Panahi et al., 2015) and reduces pain (Dantas et al., 2019). The anti- inflammatory properties of curcumin is said to even rival NSAIDs (Kocaadam & Şanlier, 2015).

The curcumin extract found in turmeric restricted on the macrophage inhibitory factor-induced upregulation of matrix metalloproteinase MMP-3 (stromelysin) enzymes and MMP-1 (interstitial collagenase) this is due to the active ingredients in turmeric influenced NF kappa Beta activity (Mobasheri et al., 2012). By affecting the signaling of

pro-inflammatory cytokines such as interleukins, phospholipase A2, 5-lipoxygenase enzyme and COX-2. In the end all these activities and changes will expedite catabolic changes in the articular cartilage and consequently the development of OA.

In an experiment conducted by Shep et al. (2019) on the effectiveness of turmeric against diclofenac in knee OA, it was found that both showed comparable improvements in pain reduction and in quality of life. This proves that the mode of action of turmeric is similar to NSAID's. As for the safety, participants who received curcumin showed a statistically significant reduction ($p < 0.01$) in flatulence compared to the diclofenac group. Curcumin also displayed anti-ulcer properties in this research ($p < 0.01$). In addition, in the diclofenac group, there were 19 patients that required H2 blockers (28%). Compared to curcumin, none of the patients required H2 blockers (0%). The cumulative side effects suffered by patients in the curcumin group was significantly lower (13%) than diclofenac (38%), $p < 0.01$. Therefore, this evidence support that turmeric supplements show comparable efficacy but better tolerance among knee OA patients when compared with diclofenac.

In a randomized double-blind placebo-controlled trial by Panahi et al., (2014), the participants were assigned into two group in which one group received curcuminoid 500mg per day in three divided doses while the other group received placebo. The treatment ran for six weeks. When comparing pre and post treatment values, the WOMAC scores for the group which received curcuminoids significantly improved in terms of pain and physical function ($p<01001$), whereas in the placebo group there was no discernable changes observed ($p>0.05$). For stiffness, both groups had no significant difference with results of $p=0.0043$ for curcuminoid group and $p=0.009$ for the placebo group. These findings show that the supplement succeeded in

reducing pain and improving functionality in knee OA patients but failed to show any improvement in joint stiffness.

Similarly, Panahi et al. (2014) reported that, the turmeric supplement does not aid in reducing stiffness of knee OA patients. Knee joint stiffness is a common clinical symptom faced by knee OA patients (Hall et al., 2014). The stiffness in symptomatic knee OA patient group is significantly higher compared to the control group. The WOMAC mean stiffness co-efficient tallies with the self-reported stiffness co-efficient is ($r = 0.3$, $p<0.01$). In this study it has been shown that the WOMAC stiffness score is directly proportionate to the pain VAS score. It can be concluded that joint stiffness has a correlation with joint pain. Hence, joint stiffness must be addressed in order to holistically treat joint pain in patients diagnosed with knee OA.

In one study, strengthening exercise was proven to reduce stiffness among knee OA patients (Panahi et al., 2014). Land-based therapeutic exercise, mainly strength training, is recommended by the Ottawa Panel to treat pain, joint stiffness, and disability (Brosseau et al., 2016). It is also recommended for increasing range of motion and improving physical function and does so in a relatively short period of time (8 – 24 weeks). Therefore, combining both treatments may return promising results which will be more effective than treating patients with a single treatment alone.

2.3 Exercise and Knee Osteoarthritis

The definition for exercise is "a particular form of recurring physical activity which follows a set pattern targeted towards maintaining or improving physical fitness (Södergren et al., 2008). Exercise can be grouped into many categories, such as agility workouts, aerobics and anaerobics, stretching, strengthening etc. Each type of exercise offers its own set of benefits depending on the person doing the exercise. However, certain benefits can be reaped by anybody who does any exercise properly. One example is improved physical and mental health through weight reduction, reduced risk of contracting chronic diseases, promotes relaxation and better sleep quality and more. The World Health Organization has released a guideline regarding physical activity and sedentary behaviors for people aged between 16 and 65. They suggest that, in a week, adults need to perform 150-300 minutes of moderate-intensity aerobic exercise or 75-150 minutes of vigorous-intensity exercise or a combination of both types to a sufficient level, in order to reap maximum health benefits.

Knee OA patients can benefit from exercise, particularly muscle strengthening, as quadriceps muscle weakness is the most common problem they face. It is also one of the risk factors of knee OA. A weak quadricep leads to knee joint pain because the quadricep is a primary dynamic contributor aiding in stabilizing the knee joint. If the muscle becomes weak, then shock absorption and neuromuscular control decreases, leading to diminished structural strength of the knee joint. This, in turn, may cause bone attrition or bone marrow lesions as a result of abnormal loading on the knee joint (Hernandez-Molina et al., 2008,) This indirectly increases the pain among knee OA patients.

2.4 Strengthening Exercise and Knee Osteoarthritis

Muscle building exercises (also known as resistance, weight, or strength exercise) typically involves weight machines, resistance bands, free weights or subject's body weight (e.g., squats and pull ups). These exercises improve muscle mass, strength and endurance when performed consistently (Garber et al., 2011), be it at home or at any outdoor or public facility (Loustalot et al., 2013). People who exercise may have vastly varying goals and objectives. Some examples would be training for strength-related sports such as weightlifting, aesthetic goals such as bodybuilding, physiotherapy for injury recovery, improve body functions for better sports performance, and for better health and fitness in general (Haff & Triplett, 2015). Since the 1970s, public health recommendations have been centered upon promoting moderate-to-vigorous intensity aerobic physical activity (MVPA) when it comes to physical health. The types of exercises which were endorsed were cycling, jogging and walking (Oja & Titze, 2011). However, in the past ten or so years, the focus has shifted to muscle-building exercises. They were first promoted in the "2008 Physical Activity Guidelines for Americans" in the Physical Activity Guidelines Advisory Committee Report, 2008. This was followed by the World Health Organization which published the "2010 Global Recommendations on Physical Activity for Health" (WHO, 2010). After which, many national public health committees followed suit.

Strengthening exercises proved to be a more effective type of exercise for knee OA compared to aerobic exercise in a recent meta-analysis of RCT's by Tanaka et al., (2014). This study found that the standardized mean difference (SMD) in relieving pain is -1.42 among non-weight exercises and SMD -0.7 for weight bearing strengthening exercises compared to aerobic exercise (SMD -0.45). Furthermore, in the study conducted by Lin et al. (2009), the knee strengthening exercise results in

greater rise in muscle strength of knee extensor (10.3 - 14.9Nm) which is a clinically significant result compared to proprioception training. Also, the WOMAC function score was greater at a 17.3 points difference in improvement for the strengthening group when compared to the control group. Three walking tests were used to measure the outcome of this study. Walking up and down stairs is deemed to be the most physically challenging exercise as it puts a lot of stress on the knee extensors (Riener et al., 2002). The results of the study show that the group which underwent strength training therapy exhibited the greatest improvement in terms of the speed with which they could climb up and down the stairs (effect size, 1.20). As a hypothesis, it was noted that ST mainly aides in elevating knee extension strength, which, in turn increases walking speed and functionality.

Commonly in Asian countries, the practice of squatting as well as kneeling is habitual among Malaysians (Veerapen et al., 2004). Patients who are diagnosed with knee OA usually aggravate the pain and discomfort through said squatting (Ahmad et al., 2018). This causes the activity of daily living to slowly degrade, ultimately resulting in reduced QoL. For example, Muslim patients will have a hard time performing their daily prayers as it involves a lot of movements of the knee joint. The main issue that needs to be addressed is the joint pain that arises due to inflammation and muscle weakness at the knee joint. Strengthening exercises could be employed to make the knee extensor muscles to grow stronger and perform at peak condition. As for the internally caused inflammation, turmeric supplements could be taken to alleviate the issue. In conclusion, it would be interesting to investigate the efficacy of combining these treatments and studying their effects on knee OA patients.

In 2003, the Technical Committee of the Malaysian Ministry of Health's Physiotherapy Profession had released a care protocol for knee osteoarthritis. The

exercise program contained within approves of three types of exercises to be performed at home, which were stretching, strengthening and low-impact aerobics, along with patient education regarding their condition. In terms of pain relief, modalities such as thermotherapy, Transcutaneous Electrical Nerve Stimulation (TENS) or cryotherapy can be applied, depending on whether the patient presents with acute or chronic pain. After an assessment, if the patient's condition proves to have recovered and they acquire a minimal disability score, they will be discharged and placed under the home exercise program. However, if pain does not decrease or becomes chronic and the disability worsens, then the patient will be referred back to the doctor for further treatment. Since there are no researches conducted to study these methods, it is difficult to conclude the effectiveness of the treatment provided by the physiotherapists in Malaysia.

Yeap et al. (2021) states in a consensus on knee OA management that a multimodal intervention regime should be the foundation OA care. Choosing a single or multimodal intervention should not be final as it may change based on the condition's progression. All knee OA patients are entitled to receive a non-pharmacological base therapy regiment, the core components consisting of weight loss, exercise and patient education. At the beginning stages of the disease, if pharmacotherapy is necessary, it is advisable to use symptomatic slow-acting osteoarthritis medication. The medications are most effective when used as a supplementary treatment in the initial stages in conjunction with the physiotherapy management, as opposed to only treating patients with physiotherapy as it may not be a holistic approach to treating knee OA.

2.5 Summary of Chapter 2

Several studies have found that turmeric supplements are effective in alleviating pain related to knee osteoarthritis. In contrast, resistance exercises have significantly diminished pain and enhanced the function of individuals with knee osteoarthritis. Therefore, it is intriguing to examine the interplay of these two treatments on pain, quality of life, and functionality in knee osteoarthritis patients. Additionally, no studies have been carried out on this subject so far. Consequently, the findings obtained from this study should ideally serve as a reference in planning a comprehensive approach to knee treatment.

CHAPTER 3

METHODOLOGY

3.1 Research Design

This is a double blinded, placebo controlled randomized control trial (RCT) with pre-test, mid-test and post-test measurements. The CONSORT flow diagram of the progress through the phases of both groups in this study is as in the attached appendix (Appendix A). In this study, a total of 36 participants were randomly assigned into two groups; Turmeric supplementation + Strengthening Exercise (TE) group or Placebo + Strengthening Exercise (PE) group Ethical approval for this study was obtained from the Human Research Ethics Committee USM (Approval code: USM/JEPeM/22060360; Appendix B). The research protocol was carried out in accordance with the Declaration of Helsinki.

3.2 Study Location and Population

Data collection and analysis was carried out at the Heath Campus Universiti Sains Malaysia (USM). Participants were recruited from the Orthopedics Clinics of Hospital Universiti Sains Malaysia (HUSM).

3.3 Study Duration and Study Period

The intervention period was 12 weeks. Participant's involvement in this study starting from baseline data collection until post-test was approximately 13 weeks. The study was conducted between Jan to May 2023.