EFFICACY OF *MOMORDICA CHARANTIA* (BITTER MELON) SUPPLEMENTATION AMONG PRIMARY KNEE OSTEOARTHRITIS PATIENTS: A SINGLE-BLINDED, RANDOMIZED CONTROLLED TRIAL

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Abstrak

Pengenalan: Osteoartritis (OA) atau keradangan sendi merupakan penyakit sendi yang kerap berlaku di kalangan warga tua, rawatannya sering melibatkan pengambilan ubat tahan sakit, namun ini boleh menyebabkan kesan sampingan yang tidak diingini. Secara tradisional, pengambilan Momordica charantia (MC) atau peria dipercayai dapat membantu dalam mengurangkan sakit berkaitan keradangan termasuk keradangan sendi.

Objektif: Mengenal pasti keberkesanan suplemen peria dalam mengurangkan kesakitan untuk penyakit keradangan sendi lutut.

Metodologi: Ini adalah sebuah kajian yang melibatkan tujuh puluh lima pesakit osteoarthritis, yang dibahagi kepada dua kumpulan (tiga puluh lapan dalam kumpulan peria dan tiga puluh tujuh dalam kumpulan placebo). Semua peserta telah mengambil suplemen peria atau placebo harian untuk tempoh tiga bulan. Peserta dibenarkan mengambil ubat tahan sakit sekiranya diperlukan, dan pengambilan ubat ini telah direkodkan. Tahap kesakitan dinilai setiap bulan dengan menggunakan "Knee Injury and Osteoarthritis Outcome Score" (KOOS) dan EQ-5D-3L (EuroQol- 5 Dimensions- 3 Levels) Health Questionnaire. Perbandingan dan analisis antara dua kumpulan dibuat untuk menentukan perubahan dalam markah KOOS, EQ-5D-3L dan pengambilan ubat tahan sakit sebelum dan selepas pengambilan suplemen, menggunakan 'repeated measures ANOVA'.

Keputusan: Selepas pengambilan suplemen selama tiga bulan, markah KOOS dan EQ-5D-3L telah menunjukkan peningkatan, dan pengambilan ubat tahan sakit dikurangkan. Berat badan, BMI dan tahap gula berpuasa telah berkurang dalam peserta kumpulan MC.

Kumpulan placebo turut menunjukkan peningkatan dalam subset tertentu KOOS dan EQ-5D-3L, tetapi pengambilan ubat tahan sakit telah bertambah.

Kesimpulan: Suplemen Momordica charantia merupakan alternatif yang berkesan untuk mengurangkan kesakitan penyakit osteoarthritis, serta mengurangkan pengambilan ubat tahan sakit. Manfaatnya dapat dikesan seawal tiga bulan.

Kata kunci: Ubat tahan sakit, peria, momordica charantia, keradangan lutut

Abstract

Introduction: Osteoarthritis (OA) is a common problem affecting the joints in the elderly, and its conservative treatment includes the usage of analgesia, which frequently leads to undesirable side effects. Traditionally, Momordica charantia (MC) or bitter melon is believed to be effective in relieving pain, including that caused by knee osteoarthritis.

Objective: To determine the effects of MC in reducing pain among primary knee osteoarthritis (OA) patients.

Methodology: This study involves 75 patients with primary knee osteoarthritis, who were divided into two groups **(**thirty-eight patients in the MC group and thirty-seven in the placebo group). The patients underwent 3 months daily supplementation of either MC or placebo. Rescue analgesia was allowed as needed, and rescue analgesia intake was recorded. Pain and symptoms during supplementation period were assessed monthly using Knee Injury and Osteoarthritis Outcome Score (KOOS) and EQ-5D-3L (EuroQol- 5 Dimensions- 3 Levels) Health questionnaire. Comparison and analysis between the two groups were done using "repeated measures ANOVA" to determine the changes in KOOS, EQ-5D-3L and analgesic scores after supplementation.

Results: After 3 months supplementation period, there were significant improvements in KOOS subscale and EQ-5D-3L score with a reduction in analgesic score. Body weight, BMI and FBS reduced significantly in the MC group. The placebo group had also shown significant improvements in certain KOOS subscale and EQ-5D-3L dimension score, but with increased of analgesic score.

Conclusion: Momordica charantia supplementation offers a safe alternative in reducing pain among the primary knee OA patients, while reducing the need for analgesia consumption. These beneficial effects can be seen as early as 3 months of supplementation.

Key words: Analgesic, bitter melon, momordica charantia, osteoarthritis

Chapter 1

INTRODUCTION

1.1 INTRODUCTION

Osteoarthritis (OA) is the major cause of chronic disability at older ages, notably when the knee and hip joints are involved. The prevalence of knee OA increases rapidly with advancing age. It has been estimated that, with regards the incidence of knee OA among persons between 60 to 79 years of age in western European countries, there will be an increase from 18% to 25% and from 24% to 40% in men and women respectively[1]. In Malaysia, the prevalence of knee OA among the population aged more than 65 years old is estimated to be at 30%. In addition, about 9.3% of Malaysian adults have experienced knee pain, and there was a trend that showed a rise in pain rate, whereby it had increased to 23% for population aged more than 55 years old, and to 39% in population more than 65 years old[2]. Indeed, as the world population is expected to live longer, the prevalence of OA is also being predicted to increase and affect more people around the globe.

Knee OA patients seek treatment for joint pain and daily life activity limitations. OA is one of the major health problems in which patients prefer to use alternative methods of treatment[3], particularly after experiencing side effects of painkillers; or failure of conventional medication to improve the symptoms. Alternative treatments that are used for OA include herbs, supplements, acupuncture, and electromagnets. Traditional or herbal medicine has long been a viable treatment option for a large majority of people in this region. Globally, the use of traditional/herbal medicine has been garnering growing attention as it offers better accessability and affordability in the face of rising cost of health care services[4].

Momordica charantia (MC), a type of tropical plant of the Cucurbitaceae family, is widely planted in Asia, East Africa and South America. Famously recognised for its bitter taste, it is

commonly used in cooking and traditional medicine. MC is locally referred to as bitter melon, karela, balsam pear or bitter gourd[5, 6].

Previous studies have reported the healing properties of MC such as antidiabetic, antioxidative, antiviral, anti-inflammatory, cholesterol-lowering effects, as well as treatment of infections[6,7,8,9]. Most studies done on the effects of MC pertain to diabetes mellitus in humans. There were also studies performed among adult subjects where metabolic syndrome incidence rate was decreased with MC supplementation[10].

Several animal studies have demonstrated the analgesic response of MC[11, 12, 13], including one conducted by Patel and Ullah *et al*, which revealed that ethanolic MC extract had significantly reduced acetic acid-induced writhing as well as offered significant protection in tail-immersion test in mice[12, 13]. Acetic acid-induced writhing method is an effective approach to assess analgesics that are peripherally active; agents that successfully decrease the writhing count most possibly demonstrated its analgesic activity via peripheral mechanism by inhibition of prostaglandin synthesis. The pain reduction of MC extract may be led by its activity in inhibiting the production of prostaglandin[12,13], which is involved in causing inflammatory pain in knee OA. None of such studies have been carried out in the human population. Therefore, this study is done to assess the analgesic effect of MC supplement among primary knee OA patients.

Chapter 2

OBJECTIVES

2.1. General Objective

1. To determine the efficacy of MC supplement in pain reduction among primary knee OA patients.

2.2. Specific Objectives

1. To determine the effectiveness of MC supplement in pain reduction, improvement of symptoms and in carrying out activities of daily living, sports/recreational activities, and quality of life by measuring **Knee injury and Osteoarthritis Outcome Score (KOOS)**.

2. To determine the efficacy of MC supplement in improving the quality of life among OA patients using the **EQ-5D questionnaire**.

3. To determine the change of frequency of analgesia intake with MC supplementation.

Chapter 3

MANUSCRIPT

3.1. TITLE: Efficacy of Momordica charantia (bitter melon) Supplementation among Primary Knee Osteoarthritis Patients: A Single-Blinded, Randomized Controlled Trial

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3.2 ABSTRACT

Introduction: Osteoarthritis (OA) is a common problem affecting the joints in the elderly, and its conservative treatment includes the usage of analgesia, which frequently leads to undesirable side effects. Traditionally, Momordica charantia (MC) or bitter melon is believed to be effective in relieving pain, including that caused by knee osteoarthritis.

Objective: To determine the effects of MC in reducing pain among primary knee osteoarthritis (OA) patients.

Methodology: This study involves 75 patients with primary knee osteoarthritis, who were divided into two groups **(**thirty-eight patients in the MC group and thirty-seven in the placebo group). The patients underwent 3 months daily supplementation of either MC or placebo. Rescue analgesia was allowed as needed, and rescue analgesia intake was recorded. Pain and symptoms during supplementation period were assessed monthly using Knee Injury and Osteoarthritis Outcome Score (KOOS) and EQ-5D-3L (EuroQol- 5 Dimensions- 3 Levels) Health questionnaire. Comparison and analysis between the two groups were done using "repeated measures ANOVA" to determine the changes in KOOS, EQ-5D-3L and analgesic scores after supplementation.

Results: After 3 months supplementation period, there were significant improvements in KOOS subscale and EQ-5D-3L score with a reduction in analgesic score. Body weight, BMI and FBS reduced significantly in the MC group. The placebo group had also shown significant improvements in certain KOOS subscale and EQ-5D-3L dimension score, but with increased of analgesic score.

Conclusion: Momordica charantia supplementation offers a safe alternative in reducing pain among the primary knee OA patients, while reducing the need for analgesia consumption. These beneficial effects can be seen as early as 3 months of supplementation.

Key words: Analgesic, bitter melon, momordica charantia, osteoarthritis

3.3 INTRODUCTION

Osteoarthritis (OA) is the major cause of chronic disability at older ages, notably when the knee and hip joints are involved. The prevalence of knee OA increases rapidly with advancing age. In the European Union only, there are approximately 100 million people who are suffering from knee OA. In fact, it has been estimated that, with regards the incidence of knee OA among persons between 60 to 79 years of age in western European countries, there will be an increase from 18% to 25% and from 24% to 40% in men and women respectively[1]. In Malaysia, the prevalence of knee OA among the population aged more than 65 years old is estimated to be at 30%. In addition, about 9.3% of Malaysian adults have experienced knee pain, and there was a trend that showed a rise in pain rate, whereby it had increased to 23% for population aged more than 55 years old, and to 39% in population more than 65 years old[2]. Indeed, as the world population is expected to live longer, the prevalence of OA is also being predicted to increase and affect more people around the globe.

Knee OA patients seek treatment for joint pain and daily life activity limitations, especially walking, kneeling or squatting, and climbing upstairs. The main goal of treatment is improvement of function and quality of life. OA is one of the major health problems in which patients prefer to use alternative methods of treatment[3], particularly after experiencing side effects of painkillers; or failure of conventional medication to improve the symptoms. Alternative treatments that are used for OA include herbs, supplements, acupuncture, and electromagnets. Owing to cultural traditions or lack of choices, traditional or herbal medicine has long been a viable treatment option for a large majority of people in this region. Globally, the use of traditional/herbal medicine has been garnering growing attention as it offers better accessability and affordability in the face of rising cost of health care services[4].

Momordica charantia (MC), a type of tropical plant of the Cucurbitaceae family, is widely planted in Asia, East Africa and South America. Famously recognised for its bitter taste, it is commonly used in cooking and traditional medicine. MC is locally referred to as bitter melon, karela, balsam pear or bitter gourd[5, 6].

Previous studies have reported the healing properties of MC such as antidiabetic, antioxidative, antiviral, anti-inflammatory and cholesterol-lowering effects[6]. The phenolic compounds found in MC may have antioxidative and antimutagenic properties[7, 8]. In traditional practice, almost all parts of MC such as fruits, stems, leaves and roots are used in the treatment of various human diseases like hyperlipidaemia, digestive disorders, microbial infection and menstrual problems[9]. Most studies done on the effects of MC pertain to diabetes mellitus in humans. There were also studies performed among adult subjects where metabolic syndrome incidence rate was decreased with MC supplementation[10].

Several animal studies have demonstrated the analgesic response of MC[11, 12, 13], including one conducted by Patel and Ullah *et al*, which revealed that ethanolic MC extract had significantly reduced acetic acid-induced writhing as well as offered significant protection in tail-immersion test in mice[12, 13]. Acetic acid-induced writhing method is an effective approach to assess analgesics that are peripherally active; agents that successfully decrease the writhing count most possibly demonstrated its analgesic activity via peripheral mechanism by inhibition of prostaglandin synthesis. The pain reduction of MC extract may be led by its activity in inhibiting the production of prostaglandin[12,13], which is involved in causing inflammatory pain in knee OA. None of such studies have been carried out in the human population. Therefore, this study is done to assess the analgesic effect of MC supplement among primary knee OA patients.

3.4 METHODOLOGY

This is a single-blinded randomized controlled study. This study has been conducted in Hospital Universiti Sains Malaysia from October 2015 until October 2016. Study protocols had been approved by the Universiti Sains Malaysia (USM) Research Ethics Committee (Human) and was conducted according to the principles of the Declaration of Helsinki. All patients were required to sign an informed consent form before participation in the trial. Each patient was included in the trial for 3 months.

Eighty primary knee osteoarthritis (OA) patients who attended our orthopaedic clinic and who fulfill the inclusion criteria were recruited. To be eligible, the patients had to be confirmed as primary unilateral or bilateral knee osteoarthritis patients with the diagnosis made according to the clinical and radiological criteria of the American College of Rheumatology[14]; and OA grade between I and III, determined based on knee radiograph with the Kellgren-Lawrence classification[15]. Patients with debilitating medical conditions such as severe hematologic disorders or renal and liver disease, patients having grade IV knee OA, secondary knee OA, or who have been planned for surgical intervention were not included in this study. Using an online randomization list generator, the patients were randomized 1:1 into 2 groups: MC or placebo, with 40 patients in each arm. Patients had no knowledge of which arm of the trial they were allocated to.

Commercially available MC capsules were obtained from a local manufacturer (CCM Duopharma Sdn Bhd). Similar-looking capsules of placebo containing inactive excipients were also prepared accordingly by a local manufacturer (Skinfix Technologies Sdn Bhd). Both manufacturers are GMP-certified (Good Manufacturing Practice-certified), and except

for supplying MC and placebo capsules, they were not involved in any part of this study. Both manufacturers also did not make any therapeutic claims of their products based on the findings of this study. The MC capsules are products registered with the National Pharmaceutical Regulatory Agency of the Malaysian Health Ministry. Both the MC and placebo were 500mg/capsule, with 60 capsules in each unlabeled identical bottle. The patient had no way of determining whether they were on MC supplement or placebo.

Three capsules of MC or placebo were taken thrice daily post-meal for a 3-month supplementation period, resulting in a total of 4500mg consumption of MC supplementation or placebo per day. Current medications were continued as usual, patients were allowed to take rescue analgesia as required; but consumption of analgesia was to be recorded in an analgesia diary. Within supplementation period, all patients were asked to avoid intake of any MC-related foodstuff, corticosteroids and hyaluronic acid injections, and procedures such as arthroscopic surgery. Patients found to have violated the protocol was excluded.

On the first visit, social demographic data, medical history, current medications and knee OA history were recorded for each participant. Baseline body weight, height and body mass index (BMI) were measured while blood was drawn for total cholesterol (TC), triglyceride (TG) and fasting blood sugar (FBS) measurements. The severity of knee pain and symptoms for each patient was quantified using the Knee Injury and Osteoarthritis Outcome Score (KOOS) and EQ-5D-3L Health questionnaires. Patients were then supplied with either MC or placebo capsules based on a randomization list and advised to follow the study procedure accordingly. During the second visit (one week after initiation), patients were assessed to evaluate compliance and safety of supplementation. Symptoms like nausea, vomiting, diarrhoea, discomfort or other side effects experienced by the patients after taking the trial medications

were recorded and further actions such as prescribing rescue analgesia were taken accordingly. For rescue analgesia, patients were prescribed tablet acetaminophen 1 gram stat for mild to moderate pain; and capsule celecoxib 200 milligram stat for severe pain (or tablet tramadol 50 milligram if unable to tolerate celecoxib). In addition, patients were provided with a medication diary to record the number and frquency of analgesia they had consumed. Change to other form of analgesia was not allowed except if they had informed the investigators beforehand. All patients were reassessed at first, second and third month of the supplementation period. Side effects of the supplementation and compliance were evaluated, and the medication diary collected. Compliance was measured based on the return of unused capsules by patients using this formula:

Compliance = (no. of capsules taken/no. of capsules should have been taken) x 100

Any patients taking less than 80% of capsules are considered non-compliant. Evaluation of pain, symptoms, quality of life and other related parameters was also performed using KOOS and EQ-5D-3L questionnaires while measurements of body weight, BMI, TC, TG and FBS were repeated after the 3-month supplementation period.

Physical and biochemical measurements were performed at baseline and after the 3 months supplementation period. Weight and height were measured in standing position using a digital weighing scale with an attached measuring rod. BMI was calculated as weight in kg divided by height in m^2 (kg/m^2). Fasting peripheral blood was withdrawn and sent to our laboratory for TC, TG and FBS measurements. KOOS is a widely used questionnaire in clinical trials to assess the patient's pain, stiffness and physical function in relation to afflictions of the knee joints such as osteoarthritis. It has five subscales; Pain, Symptoms,

Function-Activities of Daily Living (ADL), Function-Sport and Recreation Activities (Sport/Rec), and knee-related Quality of Life (QOL). The previous week is the time frame considered each time the questionnaire is answered. For each item in the 5 subscales of the KOOS questionnaire, standardized answer options are given (5 Likert boxes) and each question was assigned a score from 0 to 4. A higher score for each subscale indicates better condition among patients[16].

The EQ-5D-3L questionnaire is a descriptive system that captures health-related quality of life. There are 2 parts in this validated questionnaire - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-3L descriptive system comprises of 5 dimensions: Mobility, Self-care, Usual Activities, Pain/Discomfort and Anxiety/Depression. Each dimension has 3 levels of severity: no problems, some problems and extreme problems; a lower score indicates less problems. The EQ VAS documents the patient's self-rated health on a vertical, visual analogue scale. The scale has endpoints labelled 'Best imaginable health state' (highest) on one spectrum and 'Worst imaginable health state' (lowest) on the other. The EQ VAS is a quantitative measure of health outcome as perceived by the individual patients[17]. KOOS and EQ-5D-3L were measured at baseline and first, second and third months of the supplementation period. Analgesia intake was documented in the analgesia diary, including the type, date, and dosage of tablets taken. Score 1 was given for each tab acetaminophen 1 gram taken while score 2 was given for capsule celecoxib 200 milligram or tab tramadol 50 milligram. A lower score indicates less intake of analgesia. The analgesic score was recorded at each month of the supplementation period.

Sample size calculation was done using Power and Sample Size Calculation software[18]. Power analysis ($\alpha = 0.05$; Power = 0.8) determined that a sample size of 36 patients in each

arm was required for a detectable difference (δ) of 9.3 in total pain score using KOOS score between MC and placebo group. Based on the study by Giordano et al, the standard deviation (σ) was 13.9[19]. Forty patients were enrolled per group to allow for 10% dropouts; therefore total sample size calculated was 80.

The data was analyzed using Statistical Package for the Social Sciences (SPSS). All data were expressed as mean and standard deviation(SD). Within and between group changes for physical and biochemistry parameters were analysed using paired and independent *t*-test respectively. Changes of the analgesic score, KOOS and EQ-5D-3L in each and between the group throughout 3 months supplementation were analysed using repeated measures ANOVA (RMA). Significant change was indicated by p-value < 0.05.

3.5 RESULTS

Of the eighty patients recruited, 2 patients from MC group and 3 patients from placebo group (all females) were withdrawn from the study, leaving 38 patients in MC group (15 males, 23 females) and 37 patients in placebo group (9 males, 28 females) who had completed the study. Of the five drop-outs, three patients had mild allergic reaction (1 in MC group, 2 in placebo group) and two patients had defaulted follow-up (both 1 patient in each group) (Figure 1).

Of the 75 participants who had completed the trial, 58.67% had Grade 2 OA (n=44), 33.33% Grade 3 OA (n=25) and 8% Grade 1 OA (n=6). There was no significant difference in age, OA grade and baseline value of body weight, BMI, TC and FBS between MC and placebo groups except for TG where placebo group showed higher TG. TG levels after the supplementation period in placebo group was also significantly higher compared to MC group. However, the mean values for baseline and post-TG were still within the recommended normal range (0.5-1.8 mmol/L). Interestingly, after a 3-month supplementation, body weight, BMI and FBS were reduced significantly in MC group when compared to the baseline, but no significant changes were seen in placebo group (Table 1).

Throughout the 3-month MC supplementation, the analgesic score was significantly reduced and all subscales in KOOS questionnaire showed significant increase in its score. Except for the self-care dimension score, other dimensions score in EQ-5D-3L questionnaire were significantly decreased. Meanwhile, the EQ VAS score showed significant increase at the end of the supplementation period (Table 2).

Significant changes were also noted in the placebo group. However, in contrast to the MC group, the analgesic score in this group was increased. Scores in KOOS' subscales namely pain, sport/rec and QOL were also increased. Similar to the MC group, scores of all dimensions in EQ-5D-3L questionnaire except self-care were reduced while EQ VAS was increased (Table 3).

In addition, mean comparison between groups throughout the supplementation period only differ significantly in the analgesic score. It was also found that, there was a different trend in analgesic score between both groups where the MC group demonstrated a reduced trend whereas the placebo group showed an increased trend throughout the 3 months supplementation period (Figure 2). Also, no side effects were experienced by the 75 patients during supplementation period. .

3.6 DISCUSSION

In the present study, baseline and post-TG were higher in placebo compared to the MC group, but still in normal range while post-body weight, BMI and FBS were reduced in MC group compared to the baseline. MC supplementation for 3 months offers significant improvement in pain management and quality of life among primary knee OA patients. Most importantly, these beneficial effects were achieved with the reduced consumption of analgesics. Surprisingly, patients receiving placebo had also shown significant improvement in their pain management and quality of life. However, this could partly be attributed to the increased intake of analgesia.

In our study, MC supplementation did not show any adverse side effects. Only one patient claimed to have mild allergic reaction (nausea and giddiness) and was withdrawn from the study. An acute toxicity study in mice revealed that no toxic effects were seen with 2000mg/kg oral administration of MC whereas further observation also recorded no mortality among the mice[13]. In their study, Patel *et al* had estimated LD_{50} for MC extract was more than 5000mg/kg[12]. Moreover, Tsai *et al*. used a dosage of 4.5-5.0g/day of MC as the supplementation dose in their study among adult Taiwanese and only two subjects were withdrawn due to dizziness and headache[10].

The reduction of body weight after MC consumption has been reported previously in animal studies[20, 21, 22]. In fact, MC supplementation has been reported to prevent and reduce adiposity caused by high fat diet in rats[22, 23]. The possible mechanism on how MC lowers the body weight and thus BMI, could lie in the increased lipolysis activity and this can be supported by the increased concentration of serum free fatty acid in studied animals[23]. Higher activity of

lipolysis may occur due to the need to sustain energy efficiency which is influenced by the hypoglycaemic effect of MC.

Albeit the hypoglycaemic effect of MC has been in the centre of attention in discussing the medical potential of MC, majority of clinical studies involving MC hypoglycaemic effects have been performed with improper control, small sample size and suffered from poor methodologies without baseline characterisations[24]. Nevertheless, previous clinical trials and case studies have reported the reduction of blood glucose in diabetes patients after MC consumption[25, 26, 27, 28, 29]. The anti-diabetic effect of MC and its modes of action have been extensively reviewed previously[6, 30]. MC has been proposed to reduce blood glucose through various biochemical and physiological processes. These consist of increased glucose utilisation by skeletal muscle and peripheral cells, stimulation of pentose phosphate pathway key enzymes, stimulation of insulin secretion and glucose metabolism; with a concurrent inhibition in intestinal glucose uptake and hexokinase activity as well as suppression of some key gluconeogenic enzymes. Furthermore, MC also promotes preservation of pancreatic B cells and their functions[6, 30].

We found that with MC supplementation, our patients experienced less knee pain, symptoms and had reduced their intake of analgesia, while their daily activities and quality of life have improved. Our findings were in accordance with reports from previous animal studies where it was demonstrated that the methanol extract of MC seeds had manifested a significant analgesic response in rats and mice[31]. In addition, studies by Patel and Ullah *et al* revealed that ethanolic MC extract had significantly reduced acetic acid-induced writhing as well as offered significant protection in tail-immersion test in mice[12, 13]. Taken together, MC extracts had exhibited analgesic activity in animal models. Unfortunately, no studies had been carried

out in human subjects to explore the analgesic potential of MC, especially in pain-related diseases such as primary knee OA. Thus, the mechanism on how MC reduces pain in human remains unclear.

However, based on previous animal studies by Patel and Ullah *et al*, the pain reduction of MC extract may be peripherally mediated, led by its activity in inhibiting prostaglandin synthesis[12, 13]. Acetic acid-induced writhing method is an effective approach to assess analgesics that are peripherally active; agents that successfully decrease the writhing count most possibly demonstrated its analgesic activity via peripheral mechanism by inhibition of prostaglandin synthesis[32]. In this method, localised inflammation response was triggered, resulting in increased levels of prostaglandin E2 (PGE2) and prostaglandin F2α (PGF2α) in peritoneal fluid[33]. PGE2 is well known for its role in contributing to inflammatory pain[34]. Nonetheless, the consumption of ethanolic MC extract has reduced the writhing count significantly and it can be due to the inhibitory activity of MC extract on peripheral PGE2 synthesis.. An increased level of PGE2 as well as cyclooxygenase-2 (COX-2) has been found in human OA tissue[35]. Furthermore, abundant data had suggested that PGE2 is often produced via COX-2 dependent pathway[36] while COX-2 inhibition by dexamethasone, indomethacin or COX-2-selective inhibitor resulted in inhibition of PGE2 production in OA-affected cartilage and also showed significant pain relief among knee OA patients[37, 38].

In the tail immersion method which was used to assess centrally acting analgesics[39], higher reaction time in MC treated mice indicated that the analgesic activity of MC may also be centrally mediated. Four subtypes of PGE2 receptors, namely EP1, EP2, EP3 and EP4 may be present in sensory neurons and mediate the peripheral and/or spinal PGE2-induced

nociceptive process[34, 40], but according to the report by Ullah in 2012, the involvement of prostaglandin may be minimised in this model[13].

Phytochemical examination of MC extract has found the presence of alkaloids, saponin, glycosides, steroids, sterol and phenolic compounds[12, 13]. Phenolic compound such as flavonoid has been found to effectively inhibit PGE2 production and COX-2 expression as well as down-regulated inducible microsomal prostaglandin E synthase-1 (mPGES-1) expression[41]. The antinociceptive activity of plant-isolated flavonoid as well as another phenolic compound, tannin, was also reported by other researchers previously[42, 43]. Therefore, the presence of these phytochemical compounds in MC might contribute to the pain reduction after consumption of MC.

According to the study by Ullah *et al*, 500 mg/kg MC per oral in rats, edema induced by carrageenan was significantly reduced by 42.10 %[13]. Therefore, based on the formula by Reagan-Shaw *et al*, 2008 which is used to determine the human effective dose (HED) from animal study[44], the HED for adult human with 60 kg body weight is 4.9g daily. For this study, the treatment group had consumed 3 capsules of MC thrice daily, giving a total dosage of 4.5g daily.

Surprisingly, the placebo group had also shown significant reduction in pain and symptom; with improved daily activity and quality of life. However, there was significant increase of analgesia intake throughout the study period. Mean analgesic score throughout study period in the placebo group was significantly different compared to the MC group which showed decreased intake of analgesia. Hence, it can be postulated that, improvement in pain,

symptom, daily activity as well as quality of life in the placebo group could be due to the increased intake of analgesia throughout study period.

This study offers early understanding regarding the analgesic effects of MC, in particular among primary OA patients. Randomisation and blinding reduce bias among patients on supplementation they received. However, this study did not measure levels of pain-related cytokines such as COX-2 and PGE2 levels, thus the analgesic pathway of MC cannot be clearly delineated. Moreover, as the MC capsules used in this trial are made up of entire bitter melon fruits, the specific components that possess analgesic properties cannot be determined. In addition, the use of questionnaires to evaluate pain and symptoms of OA may be inaccurate and subjective. The intake of analgesia could be affected because some subjects have concurrent co-morbidities such as cervical spondylosis and spinal stenosis requiring painkillers. Pain relief by other alternatives such as physiotherapy or local ointments area also not accounted for.

3.7 CONCLUSION

Our study has shed light on the potential analgesic effects of MC in humans. With MC supplementation, there was significant pain reduction, improvement of symptoms, daily activities and quality of life. In addition, it reduced the intake of analgesia and there were no major side effects reported. Therefore, it can be conceived that, *Momordica charantia* supplementation offers a safe alternative in reducing pain and improving symptoms among primary knee OA patients, while reducing the need for analgesia consumption. These beneficial effects can be seen as early as 3 months of supplementation.