BIOASSAYS OF INFLAMMATION PATHWAYS FROM COMBINATION OF *Moringa oleifera*, CAPSAICIN AND MENTHOL

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DEDICATION

This thesis is dedicated to my father, who taught me that the best kind of knowledge to have is that which is learned for its own sake. It is also dedicated to my mother, who taught me that even the largest task can be accomplished if it is done one step at a time.

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ABSTRACT

Moringa oleifera is a multi-purpose plant native to Africa and Asia. Many studies have shown the medicinal value of its edible leaves, pods and seeds in treating inflammation and various diseases. The leaf is the most investigated part of this plant for its rich secondary metabolites, vitamins and minerals and has been incorporated in various herbal-based products. Herbal-based formulation to treat the inflammation is popular in the market. However, the effectiveness of anti-inflammatory and antioxidant of *M. oleifera* leaves extract-based formulation with capsaicin and menthol has not been determined. Hence, this study was focused on determining the anti-inflammatory and antioxidant potential of *M. oleifera* leaves extract-based formulation with a combination of capsaicin and menthol. In this study, methanolic extract of oven-dried *M. oleifera* leaves (OME) produced the highest yield (38.49 ± 0.24%), total phenolic content (3.2182 ± 0.1144 mg GAE/g) and total flavonoid content (2.2017 ± 0.1168 mg QCE/g) with promising ferric reducing antioxidant power (FRAP) (5.8456 ± 0.2446 mM Fe^{2+}) and 2,2-diphenyl-1-picrylhydrazyl (DPPH) scavenging (88.90 ± 0.38%) activities compared to fresh leaves and ethanolic extracts. Hence, the OME of *M. oleifera* leaves was chosen as the main ingredient in the cream formulation. Four formulations were made with different concentrations of capsaicin (0.03, 0.075, 0.1 and 0.2%) and menthol (2.8, 2.9, 2.925 and 2.97%). F1 which had the highest capsaicin concentration showed the strongest antioxidant capacities among all the formulations. EC_{50} of F1 in FRAP and DPPH assays were 49.85 ± 0.17 mg/mL and 6.84 ± 0.08 mg/mL, respectively. Also, F1 had the most promising proteinase (IC_{50} = 2.16 ± 0.03%) and lipoxygenase inhibition activities. The results indicated that the combination of *M. oleifera*, capsaicin and menthol in F1 formulation was a more promising anti-inflammatory and antioxidant compared to herbal-based formulation alone due to the synergic effect of the mixture. HPLC analysis of capsaicin and GC determination of menthol gave retention times at around 4.7 and 5.6 minutes, respectively, by referring to the standard. In conclusion, the combination of OME of *M. oleifera* leaves with capsaicin and menthol has the potential to be used as a medicinal formulation to relieve inflammation conditions.

ABSTRAK

Moringa oleifera merupakan tumbuhan pelbagai guna yang berasal dari Afrika dan Asia. Banyak kajian menunjukkan nilai perubatan bahagian tumbuhan ini seperti daun, buah dan benih dalam merawat keradangan dan pelbagai penyakit. Daun tumbuhan ini mendapat perhatian dalam banyak kajian disebabkan kaya dengan metabolit sekunder, vitamin dan galian dan telah digunakan dalam pelbagai produk berasaskan herbal. Formulasi yang berasaskan herba untuk marawat keradangan amat popular di pasaran. Namun, keberkesanan anti-radang dan antioksidan krim formulasi yang dibuat daripada ekstrak daun *M. oleifera* masih belum ditentukan. Oleh itu, kajian ini memfokuskan potensi anti-keradangan dan anti-oksidan formulasi krim yang dibuat daripada ekstrak daun *M. oleifera* bersama dengan kapsaicin dan mentol. Dalam kajian ini, daun *M. oleifera* yang dikeringkan dengan ketuhar dan diekstrak dengan methanol (OME) memberikan hasil (38.49 $\pm$ 0.24%), jumlah kandungan fenolik (3.2182 $\pm$ 0.1144 mg GAE/g) dan jumlah kandungan flavonoid (2.2017 $\pm$ 0.1168 mg QCE/g) tertinggi dengan aktiviti kuasa antioksidan penurunan ion ferik (FRAP) (5.8456 $\pm$ 0.2446 mM Fe^{2+}) dan perencatan radikal bebas 2,2-difenill-1-pikrilhidrazill (DPPH) (88.90 $\pm$ 0.38%) yang amat memuaskan. Lantaran itu, OME daun *M. oleifera* telah dipilih sebagai kandungan utama krim formulasi. Empat jenis formulasi disediakan dengan perbezaan dalam jumlah kandungan kapsaicin (0.03, 0.075, 0.1 dan 0.2%) dan mentol (2.8, 2.9, 2.925 dan 2.97%). F1 yang mempunyai kandungan kapsaicin tertinggi memberikan aktiviti antioksidan terkuat antara semua formulasi yang disediakan. EC_{50} bagi FRAP dan DPPH adalah 49.85 $\pm$ 0.17 mg/mL dan 6.84 $\pm$ 0.08 mg/mL. F1 juga menunjukkan aktiviti perencatan protinase (IC_{50} = 2.16 $\pm$ 0.03%) dan lipoksigenase yang amat memuaskan. Hasil menunjukkan bahawa kombinasi *M. oleifera*, kapsaicin dan mentol dalam formulasi F1 mempunyai aktiviti anti-keradangan dan antioksidan yang amat memuaskan berbanding dengan formulasi yang berasaskan herba sahaja disebabkan kesan sinergi komponen di dalam campuran. Kapsaicin dan mentol yang dianalisa dengan menggunakan HPLC dan GC masing-masing menunjukkan masa rentesi pada 4.7 dan 5.6 minit. Kesimpulannya, kombinasi OME daun *M. oleifera* dengan kapsaicin dan mentol berpotensi untuk digunakan sebagai formulasi ubatan untuk melegakan keradangan.

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CHAPTER 1

INTRODUCTION

1.1 Background

Inflammation is a complex biological defence response of vascular tissues to harmful stimuli which cause tissue injury and pain. Physical trauma, stress, microbial agent and noxious chemicals are the factors that trigger the inflammatory response. It always associates with the increase of vascular permeability, membrane alteration and increase of protein denaturation (Gunathilake *et al*., 2018). Acute inflammation is an initial response of the body where the interaction between cellular and molecular efficiently minimizes impending infection. An uncontrolled acute inflammatory response will contribute to chronic inflammatory diseases. (Chen *et al*., 2018; Gunathilake *et al*., 2018). There are various kind of drugs in the market for relieving and suppressing inflammatory crisis. Steroids, non-steroid anti-inflammatory drugs and immunosuppressant are the most common practice examples of therapy which are associated with adverse side effect (Ghasemian and Owlia, 2015). Therefore, herbal-based drugs are gradually promoted in the anti-inflammatory therapy. Alternative, complementary and traditional medicines are the central source of herbal medication guidance. The anti-inflammatory effect of the medicine herb is the outcome of plenty of metabolites combination and might also be due to their synergistic effect (Ghasemian, Owlia and Owlia, 2016).

Moringa oleifera, sole genus under the family of Moringacea, a native plant from Africa and Asia. *M. oleifera* has been characterized by 13 species from dicotyledonous tropical and subtropical climates. It is commonly known as the drumstick tree or multi-purpose tree which is popularly used in culinary and herbal medicine products. *M. oleifera* is grown for its edible leaves, nutritious pods and flowers that can be processed as medicine, food, cosmetic or forage for livestock (Vergara-Jimenez *et al*., 2017). It has been utilized for the treatment of different illness such as malaria, diabetes and hypertension in the domestic system of medicine

(Suryadevara *et al*., 2018; Vergara-Jimenez *et al*., 2017). *M. oleifera* leaves are the most investigated parts of the plant as it contains a rich concentration of multi-vitamins, flavonoids, carotenoids, alkaloids, polyphenols, tannins, phenolic acid and saponins. A variety of studies, *in vitro* and *in vivo*, have confirmed on its medicinal uses, for example, anti-inflammatory, antimicrobial, antioxidant, anticancer and antidiabetic (Natsir *et al*., 2019; Ali *et al*., 2018; Natarajan *et* al., 2018; Vergara-Jimenez *et al*., 2017; Saini *et al*., 2016). The extract of *M. oleifera* leaves is being known to have the potential to inhibit human macrophage cytokine production (interleukin-6 [IL-6] and tumour necrosis factor-alpha [TNF-α]). Phytochemicals in *M. oleifera* leaves such as isothiocyanates and quercetin involve in the reduction of the inflammatory process by inhibiting the release and action of inflammatory markers (Kooltheat *et al*., 2014; Waterman *et al*., 2014; Das *et al*., 2012). *M. oleifera* leaves extract can induce the production of serum immunoglobulins and neutrophils through both cellular and humoral immune response (Sudha *et al*., 2010; Gupta *et al*., 2010).

In recent years, a new trend of the cosmetic market reveals innovative formulation based on multifunctional ingredients (Nizioł-Łukaszewska *et* al., 2018). The plant-based cream formulation for topical application is made available (Pashmforosh *et* al., 2018; Suryadevara *et al*., 2018). Cream formulations are mostly preferred as its transdermal delivery advantage in the drug administration. It expresses and attractive alternative to oral delivery of the drug by reducing the risk of systemic side effects from oral therapy. Cream formulations can minimize the plasma concentration and providing sustained release of drug at the topical site. Besides, transdermal drug delivery helps to avoid the disturbance associated with the absorption of the drug from the gastrointestinal tract (Leppert *et al*., 2018; Manimaran *et al*., 2014; Prajapeti et al., 2011; Prausnitz and Langer, 2008). In the field of topical application, capsaicin and menthol always play an important role. Capsaicin is the active compound of chilli pepper extract with analgesic properties and will evokes burning sensations which change cold perception in our skin. Menthol has been applied as non-opioid pain reliver since ancient times which can provide cooling sensation and reduce heat pain (Pergolizzi *et al*., 2018; Anderson *et al*., 2014). Based on the study from Anderson *et al*. (2014), the nociceptive behaviours occur when capsaicin and menthol were applied alone but the response had been reduced with the application of both

compounds. In order to have more understanding of the efficacy of herbal-based cream formulation on anti-inflammatory response, this study was carried out to produce and analyse the cream formulation with *M. oleifera*-based and the combination of optimized concentration of capsaicin and menthol.

1.2 Problem Statement

Steroidal and non-steroidal anti-inflammatory drugs (NSAIDs) are ordinarily implemented in relieving inflammation conditions. These agents required a long-term administration for the management of chronic inflammatory conditions (Mittal *et al*., 2017). However, they possess a variety of adverse side effects, for example, gastric ulcers due to gastric irritation, generation of reactive oxygen species causing inflammation, ageing cancer and coronary heart disease (Gunathilake *et al*., 2018). Ideally drugs would be those that could strengthen the remedial effects of inflammation, at the same time control its harmful and destructive complications (Mittal *et al*., 2017). Hence, the interest on natural compounds extracted from the medicinal herbs with anti-inflammatory activity has considerably increased in recent years as they are authenticated as an alternative against chemical-based medicines (Tamrat *et* al., 2017; Ghasemian *et al*., 2016; Karthikeyan *et al*., 2016). Medicinal plants are rich sources of phytochemical constituents which have therapeutically important in disease treatment. These compounds can serve as a template for the synthesis of novel anti-inflammatory drugs with minimal toxicity and greater therapeutic value (Suryadevara *et al*., 2018).

Since the inflammatory response is always associated with pain, ingredients for pain relief should also be included in the formulation of cream. Capsaicin and menthol are the most common pain reliever being added in the topical cream formulation. Capsaicin has been medicinally used for centuries due to its pharmacological properties such as anti-inflammatory, analgesic and anti-oxidant. (Zhang *et al*., 2019; Basith *et* al., 2016). Capsaicin-containing creams have been implemented in medical fields for decades to relieve chronic neuropathic pain disorders. The appropriate concentration of capsaicin has been proved to be potent in

the treatment of myofascial pain syndrome, arthritis-related disorders, muscle strain and other pain disorders (Romero *et al*., 2019; Basith *et al*., 2016). Menthol is a topical non-opioid pain reliever which exhibits an anaesthetic effect and enhances the skin penetration of analgesics agents when applied topically (Pergolizzi *et al*., 2018; Lai *et al*., 2017). It may produce cold allodynia at high concentrations which will increase the sensitivity to normal non-painful cool temperatures (Pergollizzi *et al*., 2017). Capsaicin diminishes heat pain thresholds while menthol increase cold pain thresholds when they are applied alone. There was a study reported the combination of capsaicin and menthol can reduce certain nociceptive behaviours (Anderson *et al*., 2014). The concentration of each ingredient plays a vital role when comes into a formulation of anti-inflammatory cream. However, the suitable concentration of capsaicin and menthol in enhancing the anti-inflammatory capacity of *M. oleifera* leaves extract are also remain unknown. The efficacy of the formulation in reducing the inflammatory condition is very much unascertained, leaving a knowledge gap to be addressed. It is possible that the anti-inflammatory efficacy of *M. oleifera* leaves extract being weaken or enhanced by the capsaicin and menthol in the formulation, Therefore, it is tremendously significant to analyze the effectiveness of the formulation with this three combination on the anti-inflammatory response.

1.3 Research Objectives

The objectives of the research are:

(a)! To determine the phenolic content and antioxidant activities of *M. oleifera* leaves extract prepared by different extraction method.

(b)! To optimize the concentration of capsaicin and menthol in combination with *M. oleifera* leaves extract in the cream formulation.

(c)! To analyse the anti-oxidant and anti-inflammatory activities of the cream formulation.

(d)! To analyse the compounds in the cream formulation through HPLC and GC method.

1.4 Significance of Research

Most commercially available analgesic and anti-inflammatory cream formulations will have capsaicin or menthol in their composition. Phytochemicals in *M. oleifera* leaves also have significant pharmacological properties in anti-inflammatory and anti-oxidant activities. It would be interesting to find out the combination of this herb with capsaicin and menthol in the treatment of inflammation condition. The development of cream formulations from *M. oleifera* leaves with a combination of capsaicin and menthol in this study provide great potential as commercial medical formulations to serve as drugs in the treatment of diseases associated with oxidative damage associated with free radicals as well as any inflammation needs.

1.5 Scope of Work

Firstly, one batch of the *M. oleifera* leaves was oven-dried and pulverized by using a blender. The other batch of leaves was made into powder with liquid nitrogen grinding. Methanol and ethanol were used as extraction solvent. The extracts were tested on total phenolic content (TPC), total flavonoid content (TFC), ferric reducing ability of plasma (FRAP) assay and DPPH (1,1-diphenyl-2-picrylhydrazyl) scavenging assay. The *M. oleifera* leaves that was processed with oven-dried and methanol had the highest yield of phenolic content and antioxidant activities. It was selected as the main ingredient of the cream formulation and combined with active ingredients (capsaicin and menthol). Four different modified formulations were tested on anti-inflammatory and antioxidant activities. The formulation with the most promising activities had been chosen for the HPLC and GC determination.

REFERENCES

Abd Rani, N. Z., Husain, K. and Kumolosasi, E. (2018). Moringa genus: A review of phytochemistry and pharmacology. *Frontiers in Pharmacology*, 9(108), 1-26.

Adedapo, A. A., Falayi, O. O. and Oyagbemi, A. A. (2015). Evaluation of the analgesic, anti-inflammatory, anti-oxidant, phytochemical and toxicological properties of the methanolic leaf extract of commercially processed Moringa oleifera in some laboratory animals. *Journal of Basic and Clinical Physiology and Pharmacology*, 26(5), 491-499.

Adhikari, D., Panthi, V. K., Pangeni, R., Kin, H. J. and Park, J. W. (2017). Preparation, Characterization, and Biological Activities of Topical Anti-Aging Ingredients in a Citrus Junos Callus Extract. *Molecules*, 22(12), 2198.

Alam, M. A., Syazwanie, N. F., Mahmod, N. H., Badaluddin, N. A., Mustafa, K. A., Alias, N., Aslani, F. and Prodhan, M. A. (2018). Evaluation of antioxidant compounds, antioxidant activities and capsaicinoid compounds of Chili (Capsicum sp.) germplasms available in Malaysia. *Journal of Applied Research on Medicinal and Aromatic Plants*, 9(2018): 46-54.

Al-Bakheit, A., Abu-Romman, S., Sharab, A. and Al Shhab, M. (2017). Anti-inflammatory effect of Varthemia iphionoides extracts against prostate cancer in vitro. *European Journal of Inflammation*, 15(1), 8-14.

Al_Husnan, L. A. and Alkahtani, M. D. F. (2016). Impact of Moringa aqueous extract on pathogenic bacteria and fungi in vitro. *Annals of Agricultural Science*, 61(2016), 247-250.

Ali, A., Akhtar, N., Khan, M. S., Rasool, F., Iqbal, F. M., Khan, M. T., Din, M. U. and Elahi, E. (2013) Moisturizing effect of cream containing Moringa oleifera (Sohajana) leaf extract by biophysical techniques: In vivo evaluation. *Journal of Medicinal Plants Research*, 7(8), 386-391.

Ali, M. A., Yusof, Y. A., Chin, N. L., Ibrahim, M. N. and Muneer, S. (2018). Development and standardization of Moringa oleifera leaves as a natural dietary supplement. *Journal of Dietary Supplements*, 16(1), 66-85.

Al-Owaisi, M., Al-Hadiwi, N. and Khan, S. A. (2014). GC-MS analysis, determination of total phenolics, flavonoid content and free radical scavenging activities of

various crude extracts of Moringa peregrine (Forssk.) Fiori leaves. *Asian Pacific Journal of Tropical Biomedicine*, 4(12), 964-970.

Altemimi, A., Lakhssassi, N., Baharlouei, A., Watson, D. G. and Lightfoot, D. A. (2017). Phytochemicals: Extraction, isolation, and identification of bioactive compounds from plant extracts. *Plants*, 6(4), 42.

Amadesi, S., Nie, J., Vergnolle, N., Cottrell, G. S., Grady, E. F., Trevisani, M., Manni, C., Geppetti, P., McRoberts, J. A., Ennes, H., Davis, J. B., Mayer, E. A. and Bunnett. (2004). Protease-activated receptor 2 sensitized the capsaicin receptor transient receptor potential vanilloid receptor 1 to induce hyperalgesia. *The Journal of Neuroscience*, 24(18), 4300-4312.

Amri, O., Zekhnini, A., Bouhaimi, A., Tahrouch, S. and Hatimi, A. (2018). Anti-inflammatory activity of methanolic extract from Pistacia atlantica Desf. leaves. *Pharmacognosy Journal*, 10(1), 71-76.

Anand, P. and Bley, K. (2011). Topical capsaicin for pain management: Therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch. *British Journal of Anaesthesia*, 107(4), 490 -502.

Anderson, E. M., Jenkins, A. C., Caudle, R. M. and Neubert, J. K. (2014). The effects of a co-application of menthol and capsaicin on nociceptive behaviors of the rat on the operant orofacial pain assessment device. *PLOS One*, 9(2), e89137.

Arévalo-Híjar, L., Aguilar-Luis, M. A., Caballero-García, S., Gonzáles-Soto, N. and Valle-Mendoza, J. D. (2018). Antibacterial and cytotoxic effects of Moringa oleifera (Moringa) and Azadirachta indica (Neem) methanolic extracts against strains of Enterococcus faecalis. *International Journla of Dentistry*, 2018(3), 1-5.

Arulselvan, P., Tan, W. S., Gothai, S., Muniandy, K., Fakurazi, S., Esa, N. M., Alarfaj, A. A. and Kumar, S. S. (2016). Anti-inflammatory potential of ethyl acetate fraction of Moringa oleifera in downregulating the NF-κβ signalling pathway in lipopolysaccharide-stimulated macrophages. *Molecules*, 21(11), 1425.

Baba, S. A. and Malik, S. A. (2015). Determination of total phenolic and flavonoid content, antimicrobial and antioxidant activity of a root extract of Arisaema jacquemontii Blume. *Journal of Taibah University for Science*, 9(2015), 449-454.

Bachir Raho, G. and Abouni, B. (2015). *Escherichia coli and Staphylococcus aureus most common source of infection*, in Méndez-Vilas (ed.) *The battle against*

microbial pathogens: basic science, technological advance and educational programs. Spain, pp. 637-648.

Basith, S., Cui, M., Hong, S. and Choi, S. (2016). Harnessing the therapeutic potential of capsaicin and its analogues in pain and other diseases. *Molecules*, 21(8), 966.

Bassetti, M., Vena, A., Croxatto, A., Righi, E. and Guery, B. (2018). How to manage *Pseudomonas aeruginosa infections*. *Drug in Context*.

Basso, L. and Altier, C. (2017). Transient receptor potential channels in neuropathic pain. *Current Opinion in Pharmacology*, 32, 9-15.

Benabdallah, A., Boumendjel, M., Aissi, O., Rahmoune, C., Boussaid, M. and Messaoud. (2018). Chemical composition, antioxidant activity and acetylcholinesterase inhibitory of wild Mentha species from northeastern Algeria. *Sounth African Journal of Botany*, 116, 131-139.

Bernstein, N., Akram, M., Daniyal, M., Koltai, H., Fridlender, M. and Gorelick, J. (2018). Antiinflammatory potential of medicinal plants: A source for therapeutic secondary metabolites. *Advances in Agronomy*, 150, 131-183.

Bhagawan, W. S., Dwi Atmaja, R. R. and Zakiyyah Ramlee, N. A. (2017). Optimization and quercetin release test of Moringa leaf extract (Moringa oleifera) in gel-microemulsion preparation. *Journal of Islamic Pharmacy*, 2(2): 34.

Biswas, S. K. (2016). Does the interdependence between oxidative stress and inflammation explain the antioxidant paradox? *Oxidative Medicine and Cellular Longevity*, 2016(12), 1-9.

Chekalina, N., Burmak, Y., Petrov, Y., Borisova, Z., Manusha, Y., Kazakov, Y. and Kaidashev, I. (2018). Quercetin reduces the transcriptional activity of NF-kb in stable coronary artery disease. *Indian Heart Journal*, 70(5): 593-597.

Chelombitko, M. A. (2018). Role of reactive oxygen species in inflammation: A minireview. *Moscow University Biological Sciences Bulletin*, 73(4), 199-202.

Chen, L. Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X. and Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget*, 9(6), 7204-7218.

Chen, M. X., Alexander, K. S. and Baki, G. (2016). Formulation and evaluation of antibacterial creams and gels containing metal ions for topical application. *Journal of Pharmaceutics*, 2016.

Choi, E., Debnath, T., Tang, Y., Ryu, Y., Moon, S. and Kim, E. (2016). Topical application of Moringa oleifera leaf extract ameliorates experimentally induced atopic dermatitis by the regulation of Th1/Th2/Th17 balance. *Biomedicine & Pharmacotherapy*, 84(2016), 870-877.

Dadi, D. W., Emire, S. A., Hagos, A. D. and Assamo, F. T. (2018). Influences of different drying methods and extraction solvents on total phenolic and flavonoids and antioxidant capacity of Moringa stenopetala leaves. *Journal of Pharmacognosy Phytochemistry*, 7(1), 962-967.

Das, N., Sikder, K., Ghosh, S., Fromenty, B. and Dey, S. (2012). Moringa oleifera Lam. leaf extract prevents early liver injury and restores antioxidant status in mice fed with high-fat diet. *Indian Journal of Experimental Biology*, 50(6), 404-412.

Das, P. K ., Siddika, M. A., Asha, S. Y., Aktar, S., Islam, F., Khanam, J. A. and Rakib, M. A. (2019). Investigation of phytochemicals and antioxidant activities in the leaves methanolic extract from Moringa oleifera plants grown in Bangladesh. *Journal of Pharmacognosy and Phytochemistry*, 8(4), 2502-2508.

de Araújo, E. R. D., Félix-Silva, J., Xavier-Santos, J. B., Fernandes, J. M., Guerra, G. C. B., de Araújo, A. A., Araújo, D. F. S., de Santis Ferreira, L., da Silva Júnior, A. A., Fernandes-Pedrosa, M. F. and Zucolotto, S. M. (2019). Local anti-inflammatory activity: Topical formulation containing Kalanchoe brasiliensis and Kalanchoe pinnata leaf aqueous extract. *Biomedicine & Pharmacotherapy*, 113(2019).

Do, Q. D., Angkawijaya, A. E., Tran-Nguyen, P. L., Huynh, L. H., Soetaredjo, F. E., Ismadji, S. and Ju, Y. (2014). Effect of extraction solvent on total phenol content, total flavonoids content, and antioxidant activity of Limnophila aromatica. *Journal of Food and Drug Analysis*, 22(3), 296-302.

Dragicevic, N.; Maibach, H.I. Percutaneous Penetration Enhancers Drug Penetration Into/Through the Skin; Springer: Berlin/Heidelberg, Germany, 2017; ISBN 978-3-662-53268-3.

Elgamily, H., Moussa, A., Elboraey, A., EL-Sayed, H., Al-Moghazy, M. and Abdalla, A. (2016). Microbiological assessment of Moringa oleifera extracts and its incorporation in novel dental remedies against some oral pathogens. *Open Access Macedonian Journal of Medical Sciences*, 4(4), 585-590.

Ervianingsih, Mursyid, M., Annisa, R. N., Zahran, I., Langkong, J. and Kamaruddin, I. (2019). Antimicrobial activity of moringa leaf (Moringa oleifera L.) extract against the growth of Staphylococcus epidermidis. *Conference Series: Earth and Environmental Science*, 343(2019) 012145.

Espinosa-Leal, C. A. and García-Lara, S. (2019). Current Methods for the Discovery of New Active Ingredients from Natural Products for Cosmeceutical Applications. *Planta Medica*, 85(7), 535-551.

Falowo, A. B., Muchenje, V., Hugo, A., Aiyegoro, O. A. and Fayemi, P. O. (2016). Antioxidant activities of Moringa oleifera L. and Bidens pilosa L. leaf extracts and their effects on oxidative stability of ground raw beef during refrigeration storage. *CyTA-Journal of Food*, 15(2), 249-256.

Fatima, S., Zaman, R., Halder, N., Shamsi, S. and Alam, A. (2017). Design and development of Unani anti-inflammatory cream. *Journal of Ayurveda and Integrative Medicine*, 8(3), 140-144.

Fattori, V., Hohmann, M. S. N., Rossaneis, A. C., Pinho-Ribeiro, F. A. and Verri Jr, W. A. (2016). Capsaicin: Current understanding of its mechanisms and therapy of pain and other pre-clinical and clinical uses. *Molecules*, 21(844).

Ferreira, O. and Pinho, S. P. (2012). Solubility of flavonoids in pure solvents. *Industrial & Engineering Chemistry Research*, 51(18): 6586-6590.

Foreeseter, S. J., Kikuchi, D. S., Hernandes, M. S., Xu, Q. and Griendling, K. K. (2018). Reactive oxygen species in metabolic and inflammatory signalling. *Circulation Research*, 122(6), 877-902.

Formagio, A. S. N., Volobuff, C. R. F., Santiago, M., Cardoso, C. A. L., do Carmo Vieira, M. and Pereira, Z. V. (2014). Evaluation of antioxidant activity, total flavonoids, tannins and phenolic compounds in Psychotria leaf extracts. *Antioxidants*, 3, 745-757.

Fouad, E. A., Abu Einaga, A. S. M. and Kandil, M. M. (2019). Antibacterial efficacy of Moringa oleifera leaf extract against pyogenic bacteria isolated from a dromedary camel (Camelus dromedaries) abscess. *Veterinary World*, 12(6), 802-808.

Gangabhagirathi, R and Joshi, R. (2015). Antioxidant activity of capsaicin on radiation-induced oxidation of murine hepatic mitochondrial membrane preparation. *Research and Reports in Biochemistry*, 2015(5): 163-171.

Ghasemian, M., Owlia, M. B. (2015) A different look at pulsed glucocorticoid protocols; is high dose oral prednisolone really necessary just after initiation of pulse therapy? *Journal of Case Reports in Practice*, 3(1): 1-3.

Ghasemian, M. Owlia, S. and Owlia, M. B. (2016). Review of Anti-inflammatory Herbal Medicines. *Advances In Pharmacological Sciences*, 2016(1).

Ghiasi, Z., Esmaeli, F., Aghajani, M., Ghazi-Khansari, M., Faramarzi, M. A. and Amani, A. (2019). Enhancing analgesic and anti-inflammatory effects of capsaicin when loaded into olive oil nanoemulsion: An in vivo study. *International Journal of Pharmaceutics*, 559(2019), 341-347.

Golan, Y. (2019). Current treatment options for acute skin and skin-structure infections. *Clinical Infectious Diseases*, 68(3), 206-212.

Gopalakrishnan, L., Doriya, K. and Kumar, D. S. (2016). Moringa oleifera: A review on nutritive importance and its medicinal application. *Food Science and Human Wellness*, 5(2), 49-56.

Gopi, A. and Jisho, M. (2018). Evaluation of anti-lipoxygenase activity of Cassia fistula linn leaves using in vitro method. *International Journal of Basic & Clinical Pharmocology*, 7(9).

Gunathilake, K. D. P. P., Ranaweera, K. K. D. S. and Vasantha Rupasinghe, H. P. (2018). In vitro anti-inflammatory properties of selected green leafy vegetables. *Biomedicines*, 6(4), 107.

Guo, Y., Sun, L. and Zhuang, Y. (2019). UPLC-Q-Orbitrap-MS^2 analysis of Moringa oleifera leaf extract and its antioxidant, antibacterial and anti-inflammatory activities. *Natural Product Research*.

Gupta, A., Gautam, M., Singh, R. K., Kumar, M. V., Rao, V. C., Goel, R. K. and Anupurba, S. (2010). Immunomodulatory effect of Moringa oleifera Lam. extract on cyclophosphamide induce toxicity in mice. *Indian Journal of Experimental Biology*, 48(11), 1157-1160.

Hendrawati, Nur Azizah, Y. and Hapsari, N. K. (2020). Facial mask formulation enriched with Moringa leaves (Moringa oleifera) extract and their activity as antioxidants and antibacterials. *Jurnal Kimia Valensi*, 6(2), 198-207.

Hung, L., Tse, L., Cheng, H., Chen, J., Ko, C., Siu, W., Zhou, X., Fung, C., Pang, S., Cheng, K., Wong, C. and Leung, P. (2015). Old-technique – New evidence: Topical agents for musculoskeletal injuries. *Journal of Nature and Science*, 1(3), 51.

Hunter, A. M., Grigson, C. and Wade, A. (2018). Influence of topically applied menthol cooling gel on soft tissue thermodynamics and arterial and cutaneous blood flow at rest. *The International Journal of Sports Physical Therapy*, 13(3), 483-492.

Hussain, T., Tan, B., Yin, Y., Blachier, F., Tossou, M. C. B. and Rahu, N. (2016). Oxidative stress and inflammation: What polyphenols can do for us? *Oxidative Medicine and Cellular Longevity*, 2016.

Ilomuanya, M. O., Akhimien, T., Aghaizu, C., Adeyinka, O. and Ajayi, T. (2018). Polyherbal antioxidant topical preparation comprising ethanol extract of Tetracarpidium conophorum and Ocimum gratissimum: Formulation and evaluation. *Dhaka University Journal of Pharmaceutical Sciences*, 17(2): 213-219.

Isitua, C. C., Ibeh, I. N. and Olayinka, J. N. (2016). Antibacterial activity of Moringa oleifera Lam leaves on enteric human pathogens. *Indian Journal of Applied Research*, 6(8), 553-557.

Iqbal, S. and Bhanger, M. I. (2006). Effect of season and production location on antioxidant activity of Moringa oleifera leaves grown in Pakistan. *Jounal of Food Composition and Analysis*, 19, 544-551.

Jamadar, M. J. and Shaikh, R. H. (2017). Preparation and evaluation of herbal gel formulation. *Journal of Pharmaceutical Research & Education*, 1(2), 201-224.

Jepps, O. G., Dancik, Y., Anissimov, Y. G. and Roberts, M. S. (2013). Modelling the human skin barrier – towards a better understanding of dermal absorption. *Advanced Drug Delivery Reviews*, 65, 152-168.

Jimmy, E. O. and Okon, E. S. (2018). Moringa oleifera leaves extract has same anti-inflammatory potentials as nonsteroidal anti-inflammatory drugs (ibuprofen). *International Journal of Herbal Medicine*, 6(6), 40-42.

Johar, P. Grover, V. Topp, R., and Behm, D. (2012). A comparison of topical menthol to ice on pain, evoked tetanic and voluntary force during delayed onset muscle soreness. *International Journal of Sports Physical Therapy*, 7(3), 314-322.

Kadam, A. S., Ratnaparkhi, M. P. and Chaudhary, S. P. (2014). Transdermal drug delivery: An overview. *International Journal of Research and Development in Pharmacy and Life Sciences*, 3(4), 1042-1053.

Kambizi, L., Bakare-Odunola, M. T., Oladiji, A. T., Kola-Mustapha, A. T., Amusa, T. O., Atolani, O., Njinga, N, S. and Quadri, A. L. (2017). Proteinase inhibition,

membrane stabilization, antioxidant and phutochemical evaluations of leaves, seeds, and calyces of four selected edible medicinal plant. *Cogent Chemistry*, 3(1).

Kansy, M., Senner, F. and Gubernator, K. (1998). Physicochemical high throughput screening: parallel artificial membrane permeation assay in the description of passive absorption processes. *Journal of Medicinal Chemistry*, 41(7), 1007-1010.

Karthikeyan, V., Sundaram, V., Maniyan, R. P. and Balasundaram, S. (2016). Formulation of herbal emulsion based anti-inflammatory cream for skin diseases. *International Journal of Pharmaceutical Science And Research*, 40(2), 215-220.

Keshavarzian, S. and Shahgholian, N. (2017). Comparison of the effect of topical application of rosemary and menthol for musculoskeletal pain in hemodialysis patients. *Iranian Journal of Nursing and Midwifery Research*, 22(6), 436-441.

Ko, S. G. (2014) Plant-derived anti-inflammatory compounds: Hopes and dissapointments regarding the translation of preclinical knowledge into clinical progress. *Mediators of Inflammation*, 2014.

Köllmer, M., Mossahebi, P., Sacharow, E., Gorissen, S., Gräfe, N., Evers, D. H. and Herbig, M. E. (2019). Investigation of the Compatibility of the Skin PAMPA Model with Topical Formulation and Acceptor Media Additives Using Different Assay Setups. *AAPS PharmSciTech*, 2019(20), 89.

Kooltheat, N., Sranujit, R. P., Chumark, P., Potup, P., Laytragoon-Lewin, N. and Usuwanthim, K. (2014). An ethyl acetate fraction of Moringa oleifera Lam. inhibits human macrophage cytokine production induced by cigarette smoke. *Nutrients*, 6(2), 697-710.

Lai, P. M., Collaku, A. and Reed, K. (2017). Efficacy and safety of topical diclofenac/menthol gel for ankle sprain: A randomized, double-blind, placebo- and active-controlled trial. *Journal of International Medical Research,* 0(0), 1-15.

Lasanen, R., Juljunen, P., Airaksinen, O. and Töyräs, J. (2015). Menthol concentration in topical cold gel does not have significant effect on skin cooling. *Skin Research and Technology*, 22, 40-45.

Lavorgna, M.,Orlo, E., Nugnes, R., Piscitelli, C., Russo, C. and Isidori, M. (2019). Capsaicin in hot chili peppers: In vitro evaluation of its radical,

antiproliferative and apoptotic activities. *Plants Foof for Human Nutrition*, 74: 164-170.

Leppert, W., Malec-Milewska, M., Zajaczkowska, R. and Wordliczek, J. (2018). Transdermal and topical drug administration in the treatment of pain. *Molecules*, 23(3), 681.

Leung, P., Ko, C. Siu, W., Pang, S. and Lau, B. (2016). Selected topical agents used in traditional Chinese medicine in the treatment of minor injuries-A review. *Frontiers in Pharmacology*, 7(16), 1-5.

Liu, Y. Chen, Y., Wang, Y., Chen, J., Huang, Y., Yan, Y., Li, L., Li, Z., Ren Y. and Xiao, Y. (2020). Total phenolics, capsaicinoids, antioxidant activity, and α-glucosidase inhibitory activity of three varieties of pepper seeds. *International Journal of Food Properties*, 23(1), 1016-1035.

Luetragoon, T., Sranujit, R. P., Noysang, C., Thongsri, Y., Potup, P., Suphrom, N., Nuengchamnong, N. and Usuwanthim, K. (2020). Bioactive compounds in Moringa oleifera Lam. leaves inhibit the pro-inflammatory mediators in lipopolysaccharide-induced human monocyte-derived macrophages. *Molecules*, 25(1), 191.

Mahajan, A. and Tandon, V. R. (2004). Antioxidants and rheumatoid arthritis. *Indian Journal of Rheumatology*, 12, 139-142.

Mahdi, H. J., Yousif, E. M., Khan, N. A. K., Mahmud, R., Murugaiyah, V. and Asmawi, M. Z. (2016). Optimizing extraction conditions of Moringa oleifera Lam leaf for percent yield, total phenolics content, total flavonoids content and total radical scavenging activity. *International Journal of Advanced Research*, 4(11), 682-695.

Manimaran, S., Nithya and Praveen, T. K. (2014). Development and screening of topical herbal cream formulations for antimicrobial and wound healing activity. *International Journal of Biological & Pharmaceutical Research*, 5(5), 383-388.

Manjunatha, H. and Srinivasan, K. (2006). Protective effect of dietary curcumin and capsaicin on induced oxidation of low-density lipoprotein, iron-induced hepatotoxicity and carrageenan-induced inflammation in experimental rats. *The FEBS Journal*, 273(19), 4528-4537.

Martínez-González, C., Martínez, L., Martínez-Ortiz, E. J., González-Trujano, M. E., Déciga-Campos, M., Ventura-Martínez, R. and Díaz-Reval, I. (2017). Moringa

oleifera, a species with potential analgesic and anti-inflammatory activities. *Biomedicine & Pharmacotherapy*, 87, 482-488.

Mirel, S., Colobatiu, L., Mirel, M. and Pop, S. (2017). Topical patches as treatments for the measurement of patient musculoskeletal and neuropathic pain. *Balneo Research Journal*, 8(1), 21-25.

Mittal, A., Sharma, M., David, A., Vishwakarma, P., Saini, M., Goel, M. and Saxena, K. K. (2017). An experimental study to evaluate the anti-inflammatory effect of Moringa oleifera leaves in animal models. *International Journal of Basic & Clincal Pharmacology*, 6(2), 452-457.

Mittal, M., Siddiqui, M. R., Tram K., Reddy, S. P. and Malik, A. B. (2014). Reactive oxygen species in inflammation and tissue injury. *Antioxidants & Redox Signaling*, 20(7), 1126-1167.

Moldovan, B., Filip, A., Clichici, S., Suharoschi, R., Bolfa, P. and David, L. (2016). Antioxidant activity of Comelian cherry (Cornus mas L.) fruits extract and the in vivo evaluation of its anti-inflammatory effects. *Journal of Functional Foods*, 26(2016), 77-87.

Morales-Del-Rio, J. A., Gutiérrez-Lomelí, M., Robles-García, M. A., Aguilar, J. A., Lugo-Cervantes, E., Guerrero-Medina, P. J., Ruiz-Cruz, S., Cinco-Moroyoqui, F. J., Wong-Corral, F. J. and Del-Toro-Sánchez, C. L. (2015). Anti-inflammatory activity and changes in antioxidant properties of leaf and stem extracts from Vitex mollis Kunth during in vitro digestion. *Evidence-Based Complementary and Alternative Medicine*, 2015.

Muhamad, N., Muhmed, S. A., Yusoff, M. and Gimbun, J. (2014). Influenece of solvent polarity and conditions on extraction of antioxidant, flavonoids and phenolic content from Averrhoa bilimbi. *Journal of Food Science and Engineering*, 4(2012): 255-260.

Muller, K. (1994). 5-lipoxygenase and 12-lipoxygenase: attractive targets for the development of novel antipsoriatic drugs. *Archiv der Pharmazie*, 327(1), 3-19.

Nagoba Shivappa, N., Shinde Nishiganda, G., Sakhare Ram, S., Wadulkar Raghumath, D. and Deshmukh Aditye, Y. (2019). Formulation and evaluation of herbal gel containing Punica granatum. *International Journal of Innovative Science, Engineering & Technology*, 6(7), 36-51.

Natarajan, S. B., Das, S. K., Chandran, S. P., Oo, A. M., Kanneppady, S. S., Entezarian, M. and Lwin, O. M. (2018). Moringa oleifera leaf extract loaded hydrogel for diabetic wound healing. *Malaysian Journal of Medical Research*, 2(2).

Natsir, H., Wahab, A. W., Budi, P., Arif, A. R., Arfah, R. A., Djakad, S. R. and Fajriani, N. (2019) Phytochemical and antioxidant analysis of methanol extract of moringa and celery leaves. *Journal of Physics: Conference Series*, 1341(2019).

Nawarathne, N. W., Wijesekera, K., Wijayaratne, W. M. D. G. B. and Napagoda, M. (2019). Development of novel topical cosmeceutical formulations from *Nigella sativa* L. with antimicrobial activity against acne-causing microorganisms. *The Scientific World Journal*, 2019.

Naz, R., Ayub, H., Nawaz, S., Islam, Z. U., Yasmin, T., Bano, A., Wakeel, A., Zia, S., and Roberts, T. H. (2017). Antimicrobial activity, toxicity and anti-inflammatory potential of methanolic extracts of four ethanomedicinal plant species from Punjab, Pakistan. *BMC Complementary Medicine and Therapies*, 17: 302.

Ng, S. P., Marcant, M. and Davis, A. F. (2019). In vitro human skin concentrations following topical application of 2% tranexamic acid in co-enhancer cream and branded cream formulations. *Journal of Cosmetic Dermatology*, 00, 1-7.

Nizioł-Łukaszewska, Z., Furman-Toczek, D., Bujak, T. and Wasilewski, T. (2018). Moringa oleifera L. extracts as bioactive ingredients that increasing safety of body wash cosmetics. *Preprints* 2018.

Nobossé, P., Fombang, E. N. and Mbofung, C. M. F. (2018). Effects of age and extraction solvent on phytochemical content and antioxidant activity of fresh Moringa oleifera L. leaves. *Food Science and Nutrition*, 6(8), 2188-2198.

Nwidu, L. L., Elmorsy, E., Aprioku, J. S., Siminialayi, I. and Carter, W. G. (2018). In vitro anti-cholinesterase and antioxidant activity of extracts of Moringa oleifera plants from rivers state, Niger Delta, Nigeria. *Medicines*, 5(71).

Oboh, G., Ademiluyi, A. O., Ademosun, A. O., Olasehinde, T. A., Oyeleye, S. I., Boligon, A. A. and Athayde, M. L. (2015) Phenolic extract from Moringa oleifera leaves inhibits key enzymes linked to erctile dysfunction and oxidative stree in rat's penile tissues. *Biochemistry Research International*, 2015(6).

Oguntibeju, O. O. (2018). Medicinal plants with anti-inflammatory activities from selected countries and regions of Africa. *Journal of Inflammation Research*, 2018(11), 307-317.

Ondua, M., Njoya, E. M., Abdalla, M. A. and McGaw, L. J. (2018). Anti-inflammatory and antioxidant properties of leaf extracts of eleven South African medicinal plants used traditionally to treat inflammation. *Journal of Ethnopharmacology*, 234, 27-35.

Padmalochana, K. (2018). Anti-inflammatory activity and phytochemical analysis of Moringa oleifera ethanol and acetone leaves extract. *Journal of Drug Delivery and Therapeutics*, 8(6), 269-273.

Parameswari, P., Devika, R. and Vijayaraghavan, P. (2018). In vitro anti-inflammatory and antimicrobial potential of leaf extract from Artemisia nilagirica (Clarke) pamp. *Saudi Journal of Biological Sciences*, 26(3), 460-463.

Pashmforosh, M., Vardanjani, H. R., Vardanjani, H. R., Pashmforosh, M. and Khodayar, M. J. (2018). Topical anti-inflammatory and analgesic activities of Citrullus colocynthis extract cream in rats. *Medicine*, 54(4), 51.

Patzelt, A., Richter, H., Knorr, F., Schäfer, U., Lehr, C. M., Dähne, L., Sterry, W. and Lademann, J. (2011). Selective follicular targeting by modification of the particle sizes. *Journal of Controlled Release*, 150, 45-48.

Paun, G., Neagu, E., Moroeanu, V., Albu, C., Ursu, T. M., Zanfirescu, A., Negres, S., Chirita, C. and Radu, G. L. (2018). Anti-inflammatory and antioxidant activities of the Impatiens noli-tangere and Stachys officinalis polyphenolic-rich extracts. *Brazilian Journal of Pharmacognosy*, 28(1), 57-64.

Pawar, P. M., Solanki, K. P. and Mandali, V. A. (2018). Recent advancements in Transdermal Drug Delivery System. *International Journal of Pharmaceutical and Clinical Research*, 10(3), 65-73.

Peixoto, J. R. O., Silva, G. C., Costa, R. A., de Sousa Fontenelle, J. L., Vieira, G. H. F., Filho, A. A. F. and dos Fernandes Vieira, R. H. S. (2011). In vitro antibacterial effect of aqueous and ethanolic Moringa leaf extracts. *Asian Pacific Journal of Tropical Medicine*, (2011), 201-204.

Pergolizzi, J. V., Taylor, R., LeQuang, J. A. and Raffa, R. B. (2018). The role of mechanism of action of menthol in topical analgesic products. *Journal of Clinical Pharmacy and Therapeutics*, 43(3), 313-319.

Perkins, N. D. (2000). The Rel/ NF-κβ family: friend and foe. *Trends in Biochemical Sciences*, 25(9), 434-440.

Petit, C., Bujard, A., Skalicka-Woźniak, K., Cretton, S., Houriet, J., Christen, P., Carrupt, P. A. and Wolfender, J. L. (2016). Prediction of the Passive Intestinal

Absorption of Medicinal Plant Extract Constituents with the Parallel Artificial Membrane Permeability Assay (PAMPA). *Planta Medica*, 82(5), 424-431.

Poljsak, B., Šuput, D. and Milisav, I. (2013). Achieving the balance between ROS and antioxidants: When to use the synthetic antioxidants. *Oxidative Medicine and Cellular Longevity*, 2013.

Povolo, C. Extraction and characterization of chemicals from vegetal matrices and assessment of their properties for nutraceutical and cosmetic applications. Università Degli Studi Di Padova; 2018.

Prajapati, S. T., Patel, C. G. and Patel, C. N. (2011). Formulation and evaluation of transdermal patch of repaglinide. *International Scholarly Research Network*, 2011.

Prausnitz, M. R. and Langer, R. (2008). Transdermal drug delivery. *Nature Biotechnology*, 26(11), 1261-1268.

Priya, E. S., Selvan, P. S. and Ajay, B. (2017). Tannin rich fraction from Terminalia chebula fruits as anti-inflammatory agent. *Journal of Herbs, Spices & Medicinal Plants*, 24(2), 1-13.

Pulido, R., Bravo, L. and Saura-Calixto, F. (2000). Antioxidant activity of dietary polyphenols as determined by a modified ferric reducing/antioxidant power assay. *Journal of Agricultural and Food Chemistry*, 48(8), 3396-3402.

Rai, P., Poudyl, A. P. and Das, S. (2019). Pharmaceutical creams and their use in wound healing: A review. *Journal of Drug Delivery & Therapeutics*, 9(3), 907-912.

Ranjan, A., Shaik, S., Nandanwar, N., Hussain, A., Tiwari, S. K., Semmler, T., Jadhav, S., Wieler, L. H., Alam, M., Colwall, R. R. and Ahmed, N. (2017). Comparative genomics of Escherichia coli isolated from skin and soft tissue and other extraintestinal infections. *mBio*, 8(4), 1070-1017.

Romero, V., Lara, J. R., Otero-Espinar, F., Salgado, M. H., Modolo, N, S, P. and Moreira de Barros, G. A. (2019). Capsaicin topical cream (8%) for the treatment of myofascial pain syndrome. *Bazilian Journal of Anesthesiology*, 69(5), 432-438.

Saini, R. K., Sivanesan, I. and Keum, Y. S. (2016). Phytochemicals of Moringa oleifera: A review of their nutritional, therapeutic and industrial significance. *3 Biotech*, 6(2), 203.

Roshanak, S., Rahimmalek, M. and Hossein Goli, S. A. (2016). Evaluation of seven different drying treatments in respect to total flavonoid, phenolic, vitamin C content, chlorophyll, antioxidant activity and color of gree tea (Camellia sinensis or C. assamica) leaves. *Journal of Food Science Technology*, 53(1), 721-729.

Safdar, M. N., Kausar, T., Jabbar, S., Mumtaz, A., Ahad, K. and Saddozai, A. A. (2016). Extraction and quantification of polyphenols from kinnow (Citrus reticulate L.) peel using ultrasound and maceration technique. *Journal of Food And Drug Analysis*, 25(3), 488-500.

Saleem, A., Saleem, M. and Akhtar, M. F. (2020). Antioxidant, anti-inflammatory and antiarthritic potential of Moringa oleifera Lam,: An ethnomedicinal plant of Moringaceae family. South African Journal of Botany, 128, 246-256.

Sanchez-Moreno, C., Larrauri, J. A. and Saura-Calixto, F. (1998). A procedure to measure the antiradical efficiency of polyphenols. *Journal of Science of Food and Agriculture*, 79, 270-276.

Santos-Sánchez, N. F., Salas-Coronado, R., Villanueva-Cañongo, C. and Hernández-Carlos, B. (2019). Antioxidant compounds and their antioxidant mechanism. *Antioxidant*.

Sarveswaran, R., Jayasuriya, W. J. A. B. N. and Suresh, T. S. (2017). In vitro assays to investigate the anti-inflammatory activity of herbal extracts: A review. *World Journal of Pharmaceutical Research*, 6(17), 131-141.

Shahtalebi, M. A., Asghari, G. R., Rahmani, F., Shafiee, F. and Najafabadi, A. J. (2018). Formulation of herbal gel of Antirrhinum majus extract and evaluation of its anti-*propionibacterium acne* effects. *Advanced Biomedical Research*.

Shanmugavel, G., Prabakaran, K. and George, B. (2018). Evaluation of phytochemical constituents of Moringa oleifera (Lam.) leaves collected from Puducherry region, South India. *International Journal of Zoology and Applied Biosciences*, 3(1), 1-8.

Shawai, R. S. and Singh, R. (2016). Phytochemical screening, antioxidant and antimicrobial activity of Moringa oleifera leaf extract. *International Journal of Innovation Sciences and Research*, 5(6), 778-785.

Sherwani, N., Mahroqi, K. A. and Farooq, S. A. (2021). Evaluation of phytochemical, antioxidant and anti-inflammatory properties of near endemic Aloe dhufarensis. *Asian Journal of Plant Sciences*, 20(2): 332-343.

Siddhuraju, P. and Becker, K. (2003). Antioxidant properties of various solvent extracts of total phenolic constituents from three different agroclimatic origins of drumstick tree (Moringa oleifera Lam.) leaves. *Journal of Agricultural and Food Chemistry*, 51, 2144-2156.

Sinkó, B., Pálfi, M., Béni, S., Kökösi, J. and Takács-Novák, K. (2010). Synthesis and characterization of long-chain tartaric acid diamides as novel ceramide-like compounds. *Molecules*, 15, 824-833.

Skumar, S., Navas, M., Silki, T. S., Anju, S., Bhagyasree, G. and Fathimathul Mubashira, M. (2018). A review on transdermal patches. *World Journal of Pharmacy and Pharmaceutical Sciences*, 7(7), 511-523.

Srivastava, P., Vyas, V. K., Variya, B., Patel, P., Qureshi, G. and Ghate, M. (2016). Synthesis, anti-inflammatory, analgesic, 5-lipoxygenase (5-LOX) inhibition activities, and molecular docking study of 7-substituted coumarin derivatives. *Bioorganic Chemistry*, 67, 130-138.

Sudha, P., Asdag, S. M., Dhamingi, S. S. and Chandrakala, G. K. (2010). Immunomodulatory activity of methanolic leaf extract of Moringa oleifera in animals. *Indian Journal of Physiology And Pharmacology*, 54(2), 133-140.

Sugihartini, N. and Nuryanti, E. (2017). Formulation cream of extract Moringa oleifera leaves as antiaging. *Periodical of Dermatology and Venereology*, 29(1).

Sultana, B., Anwar, F. and Ashraf, M. (2009). Effect of extraction solvent/technique on the antioxidant activity of selected medicinal plant extracts. *Molecules*, 14, 2167-2180.

Suryadevara, V., Doppalapudi, S., Reddivallam, S. L. C., Anne, R. and Mudda, M. (2018). Formulation and evaluation of anti-inflammatory cream by using Moringa oleifera seed oil. *Pharmacognosy Research*, 10(2), 195-204.

Tambewagh, U. U., Kandhare, A. D., Honmore, V. S., Kadam, P. P., Khedkar, V. M., Bodhankar, S. L. and Rojatkar, S. R. (2017). Anti-inflammatory and antioxidant potential of guaianolide isolated from cyathocline purpurea: role of COX-2 inhibition. *International Immunopharmacology*, 52, 110-118.

Tamrat, Y., Nedi, T., Assefa, S., Teklehaymanot, T. and Shibeshi, W. (2017). Anti-inflammatory and analgesic activities of solvent fractions of the leaves of Moringa stenopetala Bak. (Moringaceae) in mice models. *BMC Complementary Medicine and Therapies*, 17, 473.

Thangam, E. B., Jemima, E. A., Singh, H., Baig, M. S., Khan, M., Mathias, C. B., Church, M. K. and Saluja, R. (2018). The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. *Frontiers in Immunology*, 2018(9), 1873.

Truong, D. H., Nguyen, D. H., Ta, N. T. A., Bui, A. V., Do, T. H. and Nguyen, H. C. (2019). Evaluation of the use of different solvents for phytochemical constituents, antioxidants and *in vitro* anti-inflammatory activities of Severinia buxifolia. *Journal of Food Quality*, 2019(1), 1-9.

Tubon, I., Zannoni, A., Bernardini, C., Salaroli, R., Bertocchi, M., Mandrioli, R., Vinueza, D., Antogoni, F. and Forni, M. (2019). In vitro anti-inflammatory effect of Salvia sagittata ethanolic extract on primary cultures of porcine aortic endothelial cells. *Oxidative Medicine And Cellular Longevity*, 2019(3), 1-11.

Udeogu, C., Ejiofor, C. C. and Nwakulite, A. (2019). Effects of Moringa oleifera leaves methanolic extract on alloxan-induced diabetic albino rats. *Asian Journal of Research in Medical and Pharmaceutical Science*, 7(2), 1-8.

Vanti, G., Bani, D., Salvatici, M. C., Bergonzi, M. C. and Bilia, A. R. (2019). Development and Percutaneous Permeation Study of Escinosomes, Escin-Based Nanovesicles Loaded with Berberine Chloride. *Pharmaceutics*, 11(12), 682.

Vergara-Jimenez, M., Almatrafi, M. M. and Fernandez, M. L. (2017). Bioactive compounds in Moringa oleifera leaves protect against chronic disease. *Antioxidants*, 6(4), 91.

Vongsak, B., Sithisarn, P., Mangmool, S., Thongpraditchote, S., Wongkrajang, Y. and Gritsanapan, W. (2013). Maximizing total phenolics, total flavonoids contents and antioxidant activity of Moringa oleifera leaf extract by the appropriate extraction method. *Industrial Crops and Products*, 44, 566-571.

Wakeel, A., Jan, S. A., Ullah, I., Shinwari, Z. K. and Xu, M. (2019). Solvent polarity mediates phytochemical yield and antioxidant capacity of Isatis tinctoria. *PeerJ*, 7.

Waterman, C., Cheng, M., Rojas-Silva, P., Poulev, A., Dreifus, J., Lila, M. A. and Raskin, I. (2014). Stable, water extractable isothiocyanates from Moringa oleifera leaves attenuate inflammation *in vitro*. *Phytochemistry*, 103, 114-122.

Welch, R. H. and Tietje, A. H. (2017). Investigation of Moringa oleifera leaf extract and its cancer-selective antiproliferative properties. *Journal of the South Carolina Academy of Science*, 15(2), 8-13.

Wortley, M. A., Birrell, M. A. and Belvisi, M. G. (2016). Drugs affecting TRP channels. *Handbook of Experimental Pharmacology*, 237, 213-241.

Wright, R. J., Lee, K. S., Hyacinth, H. I., Hibbert, J. M., Reid, M. E., Wheatley, A. O. and Asemota, H. N. (2017). An investigation of the antioxidant capacity in extracts from Moringa oleifera plants grown in Jamaica. *Plants*, 6(48).

Xiao, X., Wang, J., Meng, C., Liang, W., Wang, T., Zhou, B., Wang, Y., Luo, X., Gao, L. and Zhang, L. (2020). Moringa oleifera La and its therapeutic effects in immune disorders. *Frontiers in Pharmacology*, 11.

Xu, Y. B., Chen, G. L. and Guo, M. Q. (2019). Antioxidant and anti-inflammatory activities of the crude extracts of Moringa oleifera from Kenya and their correlations with flavonoids. *Antioxidants*, 8(8), 296.

Yong, Y. L., Tan, L. T., Ming, L. C., Chan, K., Lee, L., Goh, B. and Khan, T. M. (2017). The effectiveness and safety of topical capsaicin in postherpetic neuralgia: A systematic review and meta-analysis. *Frontiers in Pharmacology*, 7(538).

Zhang, S., Wang, D., Huang, J., Hu, Y. and Xu, Y. (2019). Application of capsaicin as a potential new therapeutic drug in human cancers. *Journal of Clinical Pharmacy and Therapeutics*, 45(1), 1-13.

LIST OF PUBLICATIONS

Non-Indexed Journal

1. **Lee, Y.H**., Rahmat, Z. and Chris, L. (2021). Anti-inflammatory potential of optimized Moringa oleifea leaf extract. International Academic Journal of Applied Bio-Medical Sciences, 2(5), 9-16. 10.47310/iajabms.2021.v02i05.002

Non-Indexed Conference Proceedings

1. **Lee, Y.H**., Rahmat, Z. and Chris, L. (2021). Comparison between methanolic and ethanolic extracts on antioxidant activity of Moringa oleifera. In *1st International Virtual Conference on Integrative Medicine 2021* (ICIM 2021) *in conjunction with the 4th International Biohealth Science Conference.*