IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 17, Issue 2 Ser. III (Mar. –Apr. 2022), PP 40-47
www.Iosrjournals.Org

Review of Menthol on Pain Relief Formulations

Fenti Fatmawati[1], Nina Nirmala[1,] Soni Muhsinin[1]
[1](*Faculty of Pharmacy, Bhakti Kencana University, Indonesia)*

Abstract:
Background*: When experiencing pain, pain relievers are always sought after, especially when suffering from persistent pain. Pain relievers that are often used are topical analgesics which are one of the agents used for pain treatment. Topical analgesics have the advantage of reducing pain by systemic absorption by targeting peripheral nerves and soft tissues, have few side effects, are easy to stop dose, and avoid first-pass metabolism. The ingredient that is often used to relieve pain is menthol which is used in various products. Menthol is also a commercial raw material that has been consistently used until now, especially in the pharmaceutical sector. In this review article, information about menthol as a pain reliever is discussed.*
Key Word*: Formulation; Menthol; Pain Relief.*

Date of Submission: 02-04-2022 Date of Acceptance: 14-04-2022

I. Introduction

Pain

Pain is one of the most prominent negative physiological conditions[1]. Pain is a sensory event caused by tissue damage[2]. Pain is a multidimensional sensory event that varies in strength (mild, moderate, severe), quality (blunt, tingling, sharp), duration (temporary, brief, persistent), and range (wide, local)[3]. In addition, pain acts as a defense function that allows immobilization of inflamed and damaged organs, soothes the senses, and promotes healing[4]. Pain is also defined as an unwanted sensory experience caused by tissue injury, tissue damage associated with instant pain due to the release of certain chemical mediators such as prostaglandins and bradykinins that cause pain sensations[5].

The pain tolerance threshold varies from person to person, the degree of pain felt the first time experiencing pain is called the pain threshold[4]. The measurement of pain strength is subjective and individual. At the same strength, the pain felt by two people will be different. Pain intensity is a picture of the strength of pain that occurs in a person. Factors causing pain include gender, culture, age, pain significance, previous experience, attention, anxiety, fatigue, and coping styles[2].

Pain receptors can be stimulated by mechanical, thermal, and chemical stimuli that can cause inflammation, causing pain. A place of pain as well as a pain barrier that can cause vasoconstriction in blood vessels so that ischemia occurs is called muscle spasm[6]. There are several processes in the pain mechanism, namely inflammation, peripheral sensitization, phenotypic changes, central sensitization, ectopic excitability, structural reorganization, and decreased inhibition. In the process of stimulating tissue injury, there are several processes, including transduction, transmission, modulation, and perception[3].

Pain Relief

Analgesic is a drug that can reduce and eliminate pain without losing consciousness[4]. Analgesics are commonly used to reduce symptoms of pain during menstruation, toothache, abdominal pain, headaches, muscle aches, and others. These analgesics are divided into two groups, namely the opioid group (narcotics) which if used repeatedly can cause dependence, and the non-opioid group which if used repeatedly will not cause dependence[7].

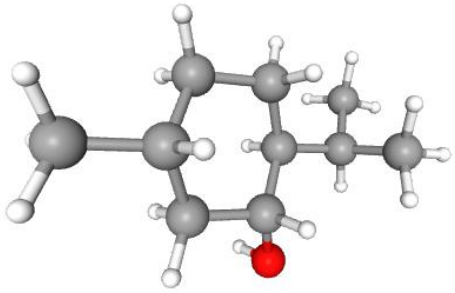
Topical analgesics are one of the agents used in the treatment of pain[8]. The most common topical pain relievers are NSAIDs, local anesthetics such as lidocaine, and counterirritants such as methyl salicylate and camphor. The goal of topical pain relievers is to achieve an analgesic effect comparable to that of oral analgesics and fewer side effects than oral analgesics[9].

Topical preparations are preparations that are administered through mucous membranes and skin that can provide local effects. Topical preparations are given by applying to the skin, mixing the drug with the bathwater, wetting the skin area with the solution, and using a damp bandage. Examples of formulations in topical preparations are gels, lotions, creams, and ointments[10]. The side effect of using topical analgesics is burning or stinging in the area that is applied[11].

Menthol

Menthol has another name 2-Isopropyl-5-methylcyclohexanol.

Menthol is a monoterpenoid organic compound in the form of a clear, waxy crystalline substance that is solid at room temperature and melts at higher temperatures. Naturally, menthol has a (−)-menthol configuration (1R,2S,5R). Menthol can be used as a local anesthetic and counter-irritant and relieves minor throat irritations. The source of menthol is corn, peppermint, or other mint oils.



Menthol

Menthol is the main bioactive agent of peppermint and is slightly polar because menthol is a monoterpene with one phenolic group[12]. Menthol is a cyclic monoterpene alcohol that can be used for various products. Menthol can also act as a skin absorption agent, local anesthetic, topical analgesic, antipyretic, and gastric sedative[13].

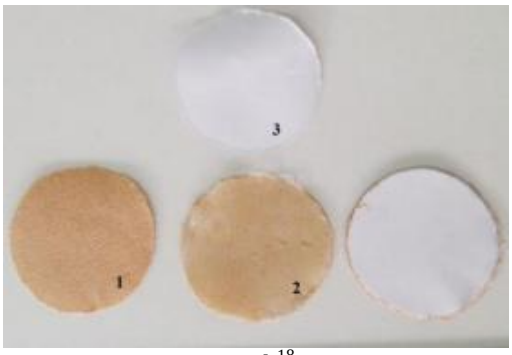
Menthol is a waxy, crystalline, white substance that is solid at room temperature and has a minty, sweet, and refreshing odor[12]. Menthol has a melting point of 41-44°C and solidifies when stored at room temperature (25°C) with a density of 0.890 kg/dm3. Menthol is poorly soluble in water (435.5 mg/L at 25°C) and is soluble in alcohol, diethyl ether, or chloroform. At a wavelength of less than 290 nm, menthol can absorb UV light and its peak absorption is at a wavelength of 220 nm[14].

Menthol Application

The application of menthol comes in several forms, menthol is widely used in the pharmaceutical, cosmetic, kretek cigarettes, and in the food industry such as chocolate and confectionery and soft drinks[15]. In the pharmaceutical field, menthol is used as an additional ingredient in several preparations, such as in balm preparations that contain menthol which functions as a cold sensation enhancer[16]. Menthol is also used as an additive in aromatherapy stick balms[17]. Menthol is also used as an additive, namely as a penetration enhancer in diclofenac potassium patch preparations[18].

Ointment[16]

Balm Stick [17]



Pacth[18]

In addition to the pharmaceutical sector, menthol is also used as an ingredient in several commercial products, as in previous studies, research on toothpaste using menthol as a flavoring material was conducted[19]. Menthol is also used to provide a fresh and cool atmosphere in shampoo products[20]. Menthol is also used as a fragrance in hair tonic products[21].

Shampo[20]

.

Hair tonic [21]

Menthol as a Pain Reliever

Pain is an uncomfortable sensory and emotional experience associated with tissue damage or potential tissue damage[22]. When experiencing pain, pain relief is almost always sought after, especially when suffering from persistent pain. In such situations, pain relief can be the dominant goal[23]. Menthol is one of the topical analgesics of 30-70% peppermint essential oil which is effective in treating minor aches and musculoskeletal pains[24]. Menthol can act as a skin absorption agent, local anesthetic, topical analgesic, antipyretic, and gastric sedative[13]. Menthol used topically can stimulate thermoreceptors, so that they will produce a sensation of cold or warmth, and have an anesthetic effect[25].

Menthol is a chemical derived from natural and semi-synthetic sources. Global use of pure menthol is estimated at more than 20,000 tonnes per year. Its use includes various applications such as flavoring, cooling components, and as a local anesthetic in drug formulations and skin products[26]. Menthol can act as a skin absorption agent, local anesthetic, topical analgesic, antipyretic, and gastric sedative[13].

Mechanism of Menthol as Pain Reliever

Menthol is a natural compound derived from plants and is widely used because of its sensory properties. Menthol is often part of the topical cooling, analgesic, antipyretic, and antiseptic medications available in pharmacies[27]. And for the mechanism of menthol as a pain reliever, see the table below:

Table no 1: Menthol mechanism as Pain Reliever

No	Mechanism	Reference
1.	Blocks Nav1.8, Nav1.9, and Na	27
2.	Activation of TRPM8 which can induce analgesics for acute pain and inflammation.	28
3.	Non-selective TRPM8 agonists may produce a cooling sensation.	29
4.	Stimulation of TRPM8, blocking of neural calcium channels, inhibition of voltage-gated sodium channels in the dilation of blood vessels, and increased local blood flow.	24
5.	Binds to TRPM8 receptors and releases calcium ions that can reduce pain through activation of endogenous opioids.	30

Menthol can produce a cooling sensation through the activation of TRPM8. TRPM8 is a member of the melastatin subfamily of the transient receptor potential ion channel (TRP) superfamily. TRPM8 is expressed in a subpopulation of cold-activated pain and temperature sensory neurons (≤28°C) so that it is chemically bound by refrigerants, thymol, and eucalyptol. At relatively high concentrations (~30%), topical use of menthol can induce cold soreness and hyperalgesia. Gaudioso et al. evaluated the effect of topical menthol application on tetrodotoxin-resistant (TTX) Nav1.8 and Nav1.9 channel subtypes in DRG neurons, and on Na-sensitive TTX+ channels. Their results showed that menthol can selectively block Nav1.8, Nav1.9, and Na channels which are sensitive to TTX+ channels indicating the efficacy of menthol as a topical analgesic compound[27].

In acute pain and inflammation, the use of topical menthol can induce the main analgesic mediator, TRPM8[28]. This TRPM8 receptor is a polymodal receptor that is activated by many stimuli such as cold, membrane depolarization, and chemical ligands[31]. In the study of Liu et al., it was stated that the replacement of L-menthol in analgesic and counterirritant treatment by TRPM8 selective agents such as WS-12 could prevent pro-inflammatory effects and allow for more effective analgesic therapy with reduced side effects[28]. Whereas non-selective TRPM8 agonists can cause a cooling sensation, at higher concentrations, they can cause cold hyperalgesia in normal subjects and paradoxically analgesics in neuropathic patients[29].

Keshavarzian & Shagholian compared the effect of topical application of rosemary and menthol on musculoskeletal pain in hemodialysis patients, and the results of their study showed that topical use of menthol and rosemary could reduce the intensity of musculoskeletal pain in the legs among patients undergoing

hemodialysis. Menthol can reduce pain through stimulation of TRPM8, blocking of neural calcium channels, inhibition of voltage-gated sodium channels in the dorsal horn, dilation of blood vessels, and increased local blood flow. Lack of pain signal is a factor that can reduce pain after the application of menthol[24]. Menthol binds to the TRPM8 receptor and causes calcium ions which are believed to modulate pain through the activation of endogenous opioids[30].

Menthol Formulation in Pain Relief Preparations

Gel

The gel is a preparation for external use that can be applied easily to bind to the skin and allows the drug to heal the affected area, can quickly penetrate the layers of the skin, is easily rinsed off from the site of application, and generally does not irritate the skin[8]. Some pain relief gel preparations contain menthol, such as some of the gel preparations listed in the table no 2 below.

Table no 2: Menthol Formulation in Gel Preparations

No	Formulation	Activity	Function	Reference
1.	Menthol Benzokain Prokain HCl Carbopol 940 Glyserol Trietilenatetramine Aquadest	Analgesic	The active substance in combination with benzocaine and procaine HCL	[8]
2.	Ibuprofen SDIB Carbopol 941 Alcohol Propyleneglycol Isopropyl myristate Phospoliphone 80H Menthol Trietanolamine NaCl Water	Anti-inflammatory and analgesic	Permeation enhancer	[32]
3.	Menthol Thymol Polymethylene carboxy	Analgesic	Active substance	[5]

The study of B. Angelovska et al. aims to present "Russian water" The gel consists of menthol, benzocaine, and procaine HCl as a topical analgesic agent indicated for temporary pain relief. The gel is applied to the skin and during application the gel provides a cooling sensation, relieves pain, rinses off easily with water, and does not cause irritation to the skin. And their results showed that the gel can provide a longer analgesic effect compared to a liquid ethanol solution consisting of the same components[8].

The second gel formulation in the table above has analgesic and anti-inflammatory activity which contains menthol which acts as a permeation enhancer. This study showed that the drug release in solid dispersion of ibuprofen with menthol (SDIBM5%) resulted in a value of 98.21% and the transdermal delivery of ibuprofen made it a potentially ideal drug delivery system to produce analgesic and anti-inflammatory effects thereby reducing systemic side effects[32].

The study of Jafri et al. aims to determine the test of dermal irritant and central analgesic effect of a topical drug with the application of seven different formulations where there is a formula containing menthol as the active substance. In this study, an analgesic activity test was carried out with a tail-flick test and the test results showed that all the test gel samples had an analgesic effect at 15, 30, and 60 minutes after sample application[5].

Menthol Formulation in Emulgel Preparations

Emulgel is an emulsion of W/O or O/W type which is gelled with the help of one or more gelling agents, the gel consists of two parts, namely the emulsion and the gel[33]. Some pain reliever emulgel preparations contain menthol, such as some of the emulgel preparations listed in the table no 3 below

Table no 3: Menthol Formulation in Emulgel Preparations

No	Formulation	Activity	Function	Reference
1.	Meloxicam Carbopol 934 Menthol Triethanolamine Liquid paraffin	Antirheumatic	Drug release enhancer and rubefacient	[34]

	Propylene glycol Tween-20 Span-20 Aquadest			
2.	Dexibuprofen Capsaicin Carbopol 940 Liquid paraffin Ethanol Tween 80 Span 80 Propylene glycol Methylparaben Menthol Propylparaben Distilled water Triethanolamine	Anti-inflammatory and analgesic	Permeation enhancer	33
3.	Meloxicam CMC Na VCO Na Lauryl sulfate Cetostearyl alcohol Propylene glycol Menthol Triethanolamine Methyl paraben Aquadest	Anti-inflammatory	Penetrant enhancer	35

The study of Mwangi et al. aimed to formulate and evaluate meloxicam emulgel as a potential alternative topical treatment for rheumatism. The emulgel formulation contains menthol which acts as a drug release enhancer and rubefacient. The results of this study indicate that emulgel with high concentrations of menthol can cause high drug release and the optimized meloxicam emulsions show high pharmaceutical quality and are pharmacologically active[34].

The study of Burki et al. aimed to formulate and characterize a dexibuprofen-capsaicin emulsion for transdermal drug delivery with enhanced anti-inflammatory and analgesic effects. In this emulgel formulation containing menthol which acts as an enhancer of skin permeation, in this study an ex vivo permeation study was carried out which aimed to see the effect of menthol as a permeation enhancer using Franz diffusion cells and the results showed that the addition of menthol into the emulgel preparation resulted in an increase in transdermal drug flux. compared to the usual formulation[33].

Falahi et al., added enhancers to increase permeation, and the enhancers used were propylene glycol 10% and menthol 3%. The addition of these enhancers can provide differences in the anti-inflammatory effects of the meloxicam emulgel. The results of the addition of enhancers indicate that emulgel with the addition of menthol is more effective in delivering meloxicam because menthol can be distributed into the intercellular space of the stratum corneum which then reversibly disrupts the lipid domain between cells so that the active substance will shift towards the main group of the bilayer contained. in the stratum corneum[35].

Menthol Formulation in Ointment Preparations

The ointment is a semi-solid preparation that is used as an external drug on mucous membranes and skin, is easy to apply, and has a soft texture[36]. Some pain relief ointment preparations contain menthol, such as some of the ointment formulations listed in the table no 4 below.

Table no 4: Menthol Formulation in Ointment Preparations

No	Formulation	Activity	Function	Reference
1.	Camphor Menthol White soft paraffin Lanolin Paraffin wax Cetosteryl alcohol Methyl paraben Propyl paraben	Muscle spasm	Active substance (in combination with Camphora)	37
2.	Champor Menthol Solid Paraffin Liquid Paraffin Vaselin album Essensial oil	Analgesic (reduce muscle aches)	Cool sensation	16

Anusha, compared the preparation of hydrophilic and hydrophobic base ointment to relieve muscle spasms. In the manufacture of the ointment using a combination of camphora and menthol which has analgesic activity. From the results of this comparison, it shows that the hydrophobic base ointment shows better results and is comparable to the preparations on the market and the hydrophobic ointment formulation shows good analgesic activity[37]. In the study of Warditiani et al., a topical balm was made in which this balm is an ointment-like preparation, and the formulation contains menthol which acts as a cold sensation enhancer. In topical products, menthol has efficacy as an analgesic and can provide a cold sensation on the skin and can overcome local pain[16].

Menthol Formulation in Eezpain Spray and OFCMT

Eezpain spray is a preparation consisting of natural ingredients and has been clinically proven for its analgesic and anti-inflammatory activity[38]. OFCMT is a combination of three active ingredients (champora, menthol and thymol) which are emulsified[39]. Some pain relief preparations contain menthol, such as the formulations in Eezpain Spray and OFCMT, which are listed in the table no 5 below.

Table no 5: Menthol Formulation in Eezpain Spray and OFCMT

No	Formulation	Preparations	Activity	Function	Reference
1.	Gaultheria Eucalyptus Oil Turpentine Oil Clove Oil Menthol Champora Propylene glycol PEG Benzyl Alcohol	*Eezpain Spray*	Muscle pain reliever	Active substance	[38]
2.	Camphor Menthol Thymol Tween 80 Cyclodextrin Dimethyl sulfoxide Turpentine oil Distilled water	OFCMT	Anti-inflammatory and analgesic	Active substance	[39]

He study by Nawaz et al., tested the efficacy of the eezpain spray formulation to reduce muscle pain. In this eezpain spray formulation, it contains menthol which acts as an active substance. The eezpain spray is applied to the knee and wrist joints, back of the neck and shoulders, forearms, and lower back. And from the results of research conducted statistically, shows that this eezpain spray can reduce pain, inflammation, pain and provide a calming effect. The results of applying eezpain spray three times a day, shows maximum efficacy in curing pain symptoms[38].

The study of Ghori et al. aimed to determine the analgesic and anti-inflammatory activity of an oily formulation containing camphor, menthol, and thymol. This OFCMT preparation contains menthol which acts as the active substance, and to determine its analgesic activity, a test was carried out using the hot plate method with diclofenac sodium as the standard. The results of these tests indicate that the formulation with a dose (100 mg/kg & 200 mg/kg) produces a significant analgesic effect while the formulation with a dose (250 mg/kg & 500 mg/kg) shows an anti-inflammatory effect[39].

References

[1]. Hein G, Engelmann JB, Tobler PN. Pain relief provided by an outgroup member enhances analgesia. *Proc R Soc B Biol Sci*. 2018;285(1887):1-9. doi:10.1098/rspb.2018.0501

[2]. Astutik P, Kurlinawati E. Pengaruh Relaksasi Genggam Jari Terhadap Penurunan Nyeri Pada Pasien Post Operasi Sectio Caesarea Di Ruang Delima RSUD Kertosono. *Str J Ilm Kesehat*. 2017;6(2):30-37.

[3]. Bahrudin M. Patofisiologi nyeri (PAIN). *Saintika Med J Ilmu Kesehat dan Kedokt Kel*. 2017;13(1):7-13.

[4]. Olii ADC, Bodhi W, Edi HJ. UJI EFEK ANALGESIK EKSTRAK ETANOL DAUN KEJI BELING (Strobilanthes crispus L) PADA TIKUS PUTIH GALUR WISTAR (Rattus norvegicus). *Pharmacon*. 2020;9(2):170. doi:10.35799/pha.9.2020.29267

[5]. Jafri R, Imran H, Ahmed A, Sohail T, Ahmed I, Yaqeen Z. Formulation and screening of analgesic activity of different analgesic gel preparations. *Pak J Pharm Sci*. 2019;32(5):2149-2153.

[6]. Romadhon AJ. Stimulasi Magnetik Lebih Meningkatkan Kemampuan Fungsional pada Pasien Nyeri Punggung Bawah Dibanding Stimulasi Elektris. *J Keterapian Fis*. 2020;5(1):21-27. doi:10.37341/jkf.v5i1.169

[7]. Sipahutar LRB, Ompusunggu HES, Napitupulu RRJ. Gambaran Penggunaan Obat Analgetik Secara Rasional Dalam Swamedikasi Pada Masyarakat PKS Balam, Desa Balai Jaya KM. 31 Kecamatan Balam Sempurna, Kabupaten Rokan Hilir, Riau. *Nommensen J Med*. 2021;6(2):53-57. doi:10.36655/njm.v6i2.265

[8]. B. Angelovska, S. Maleska-Stojadinovikj, E, Drakalska and B. Gjorgjeska. Production of Gel with Menthol, Benzocaine and Procaine HCl for Topical Application in Rheumatoid Arthritis Patients. *J Pharm Pharmacol*. 2017;5(5):245-248. doi:10.17265/2328-2150/2017.05.003

[9]. Murthykumar K, Varghese S. Analgesic efficacy and safety of transdermal and oral diclofenac in postoperative pain management following periodontal flap surgery. *Drug Invent Today*. 2019;11(162):652-656.

[10]. Irma A, Ningsih F, Adisaputra H. Uji Sifat Fisik Sediaan Gel Ekstrak Etanol 70 % Biji Kelengkeng (Euphoria Longan). *J Ilmu Kesehat Dan Farm*. 2021;9(1):18-21.

[11]. Anggraini SN, Yanti NF. Nyeri Sendi Lansia Dengan Arthritis Gout Di Panti Sosial Tresna Werda Khusnul Khotimah Pekanbaru. *Heal Care J Kesehat*. 2019;7(2):69-76.

[12]. Ishaque S, Arshad A, Haider M, Fatima F. Biological and Clinical Sciences Research Journal. *Biol Clin Sci Res J*. Published online 2021:1-9.

[13]. Umezu T. Identification of novel target molecules of l-menthol. *Heliyon*. 2021;7(6). doi:10.1016/j.heliyon.2021.e07329

[14]. Kamatou GPP, Vermaak I, Viljoen AM, Lawrence BM. Phytochemistry Menthol : A simple monoterpene with remarkable biological properties. *Phytochemistry*. Published online 2013:1-11. doi:10.1016/j.phytochem.2013.08.005

[15]. Trisilawati O, Pribadi ER, Rizal M, Suhirman S. PENGARUH PEMUPUKAN N, P DAN K TERHADAP PRODUKTIVITAS DAN MUTU MINYAK Mentha arvensis Effect of N, P and K fertilizer to the yield and quality of Mentha arvensis oil Octivia Trisilawati*, Ekwasita Rini Pribadi, Molide Rizal, Sintha Suhirman. *J Agronida*. 2020;6:2407-9111.

[16]. Warditiani N, Arisanti C, Swastini D, Wirasuta I. Analisa Kesukaan Produk Balsem Aroma Bunga. *J Farm Udayana*. 2020;9(1):62. doi:10.24843/jfu.2020.v09.i01.p09

[17]. Purba O. PEMBUATAN SEDIAAN BALSEM STICK DARI SEREH (Cymbopogon citratus (DC.) Stapf) SEBAGAI AROMATERAPI. *J Penelit Farm Herb*. 2020;3(1):75-81. doi:10.36656/jpfh.v3i1.326

[18]. Purnamasari N, Alatas F, Gozali D. Formulasi Dan Evaluasi Transdermal Patch Kalium Diklofenak. *Kartika J Ilm Farm*. 2019;7(1):43. doi:10.26874/kjif.v7i1.209

[19]. Jagtap AM, Kaulage SR, Kanse SS, et al. Preparation and Evaluation of Toothpaste. *Asian J Pharm Anal*. 2018;8(4):191. doi:10.5958/2231-5675.2018.00035.2

[20]. Permadi YW, Mugiyanto E. Formulasi Dan Evaluasi Sifat Fisik Shampo Anti Ketombe Ekstrak Daun Teh Hijau. *J Farm Sains dan Prakt*. 2018;4(2):62-66. doi:10.31603/pharmacy.v4i2.2324

[21]. Diana, W WM. Penggunaan Ekstrak Buah Alpukat dan Madu Sebagai Bahan Aktif Hair Tonic Untuk Rambut Rontok. *e-Journal*. 2014;03(01):226-235.

[22]. Broto W, Busalim F, Prasetsyowati A, Suryaningsih N. APLIKASI TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION (TENS) SEBAGAI TERAPI PEMULIHAN Prosiding Seminar Nasional Teknik Elektro Volume 4 Tahun 2019. *Pros Semin Nas Tek Elektro*. 2019;4:341-346.

[23]. Becker S, Schakib-Ekbatan K, Wroblewski D, Schweiker M. Perception of repeated pain relief with controllable and uncontrollable pain. *Eur J Pain (United Kingdom)*. 2021;25(8):1702-1711. doi:10.1002/ejp.1775

[24]. Keshavarzian S, Shahgholian N. Comparison of the effect of topical application of rosemary and menthol for musculoskeletal pain in hemodialysis patients. *Iran J Nurs Midwifery Res*. 2017;22(6):436-441. doi:10.4103/ijnmr.IJNMR_163_16

[25]. Lai PM, Collaku A, Reed K. Efficacy and safety of topical diclofenac/menthol gel for ankle sprain: A randomized, double-blind, placebo- and active-controlled trial. *J Int Med Res*. 2017;45(2):647-661. doi:10.1177/0300060517700322

[26]. Klumpp DA, Sobel RM, Kokkinidou SG, et al. Synthesis of Menthol Glycinates and Their Potential as Cooling Agents. *ACS Omega*. 2020;5(8):4043-4049. doi:10.1021/acsomega.9b03624

[27]. Gaudioso C, Hao J, Martin-Eauclaire MF, Gabriac M, Delmas P. Menthol pain relief through cumulative inactivation of voltage-gated sodium channels. *Pain*. 2012;153(2):473-484. doi:10.1016/j.pain.2011.11.014

[28]. Liu B, Fan L, Balakrishna S, Sui A, Morris JB JS. TRPM8 is the Principal Mediator of Menthol-induced Analgesia of Acute and Inflammatory Pain. *Bone*. 2013;154(10):2169-2177. doi:10.1016/j.pain.2013.06.043.TRPM8

[29]. Patel R, Gonçalves L, Leveridge M, et al. Anti-hyperalgesic effects of a novel TRPM8 agonist in neuropathic rats: A comparison with topical menthol. *Pain*. 2014;155(10):2097-2107. doi:10.1016/j.pain.2014.07.022

[30]. Gillis DJ, Vellante A, Gallo JA, D'Amico AP. Influence of Menthol on Recovery From Exercise-Induced Muscle Damage. *J strength Cond Res*. 2020;34(2):451-462. doi:10.1519/JSC.0000000000002833

[31]. Xu L, Han Y, Chen X, et al. Molecular mechanisms underlying menthol binding and activation of TRPM8 ion channel. *Nat Commun*. 2020;11(1). doi:10.1038/s41467-020-17582-x

[32]. Lakshmi, PK, Kumar, MK, Sridharan, A., & Bhaskaran S. Research Article FORMULATION AND EVALUATION OF IBUPROFEN TOPICAL GEL : A NOVEL APPROACH FOR PENETRATION. *Int J Appl Pharm*. 2011;3(3).

[33]. Burki IK, Khan MK, Khan BA, Uzair B, Braga VA, Jamil QA. Formulation Development, Characterization, and Evaluation of a Novel Dexibuprofen-Capsaicin Skin Emulgel with Improved In Vivo Anti-inflammatory and Analgesic Effects. *AAPS PharmSciTech*. 2020;21(6):1-14. doi:10.1208/s12249-020-01760-7

[34]. Mwangi AN, Njogu PM, Maru SM, et al. Meloxicam emulgels for topical management of rheumatism: Formulation development, in vitro and in vivo characterization. *Saudi Pharm J*. 2021;29(4):351-360. doi:10.1016/j.jsps.2021.03.005

[35]. Falahi A, Azizah SN, Indriani E, Indah C. Pengaruh Propilen Glikol Dan Menthol Sebagai Enhancer Terhadap Sifat dan stabilitas Fisik Serta Efektifitas anti Inflamasi Emulgel Meloksikam. *J Curr Pharm Sci*. 2020;3(2):219-223.

[36]. Hasrawati A, Famir Y, Aztriana A, Mursyid AM. FORMULASI DAN EVALUASI SALEP EKSTRAK DAUN GULMA SIAM (Chromolaena odorata L.) DENGAN VARIASI BASIS SALEP. *J Ilm As-Syifaa*. 2019;11(1):55-60. doi:10.33096/jifa.v11i1.514

[37]. Anusha P. Formulation and Comparative Evaluation Of Semisolid Dosage Forms Of Natural Agents (Camphor and Menthol) for Muscle Spasms. *Am J PharmTech Res*. 2019;9(6):24-42. doi:10.46624/ajptr.2019.v9.i6.002

[38]. Nawaz A, Sheikh ZA, Feroz M, Alam K, Nazar H, Usmanghani K. Clinical efficacy of polyherbal formulation Eezpain spray for muscular pain relief. *Pak J Pharm Sci*. 2015;28(1):43-47.

[39]. Ghori SS, Ahmed MI, Arifuddin M, Khateeb MS. Evaluation of analgesic and anti-inflammatory activities of formulation containing camphor, menthol and thymol. *Int J Pharm Pharm Sci*. 2016;8(1):271-274.

Fenti Fatmawati, et. al. "Review of Menthol on Pain Relief Formulations." *IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS)*, 17(2), (2022): pp. 40-47.