VOLUME 11 NOMOR 2 DECEMBER 2024 ISSN 2548 – 611X

JURNAL
BIOTEKNOLOGI & BIOSAINS INDONESIA

Homepage Jurnal: http://ejournal.brin.go.id/JBBI/index

TRANSDERMAL PATCH PILIS FROM TURMERIC RHIZOME AND BLACK SEEDS FOR TREATMENT BASED ON ETHNOPHARMACY

Pilis Patch Transdermal dari Rimpang Kunyit dan Habbatus Sauda untuk Pengobatan Berbasis Etnofarmasi

Nindita Clourisa Amaris Susanto*, Arinda Handiyah Sawitri, Intan Muslimah
Department of Pharmacy, Vocational School, Sebelas Maret University, Surakarta, Central Java 57126, Indonesia
*Email: nindita_clourisa@staff.uns.ac.id

ABSTRACT

Pilis, a traditional product containing various herbal ingredients, is currently less desirable due to its impractical and unfashionable method of application. Pilis is used to treat dizziness, pain, eye fatigue, encephalitis in children, fever, and to aid recovery for mothers after childbirth. However, pilis also carries risks related to uncontrolled dosage and contamination, particularly from chemical or heavy metal pollutants, which may cause toxic reactions. To mitigate these risks, pilis should be used in recommended doses and produced under clean and safe conditions. This research aimed to provide the innovation of patches as an alternative treatment to increase attractiveness and control the active substances released and delivered for a long time. Transdermal patches are made from a combination of turmeric and black seed containing flavonoid active metabolite compounds, namely curcumin, carotenoids, quercetin, kaempferol, and apigenin. The combination has a synergistic effect that can increase total flavonoid levels and the therapeutic effect of pilis. The method used in this research was literature review and data analysis. The results showed the effect of transdermal patch pilis from the combined extracts added to the formula in vitro and in vivo using animal tests. In conclusion, transdermal patch pilis has prospects as a topical treatment based on the combination of an active delivery system with a patch and metered dose system.

***Keywords**: Blackseed, Flavonoid, Patch transdermal, Pilis, Turmeric*

ABSTRAK

Pilis, produk tradisional yang mengandung berbagai bahan herbal, saat ini kurang diminati karena cara penggunaannya yang tidak praktis dan kurang modern. Pilis digunakan untuk mengobati pusing, nyeri, kelelahan mata, ensefalitis pada anak-anak, demam, serta pemulihan ibu pasca melahirkan. Namun, pilis juga memiliki risiko terkait dosis yang tidak terkendali dan kontaminasi, terutama kontaminasi bahan kimia atau logam berat yang dapat menyebabkan reaksi toksik. Untuk menghindari risiko ini, penggunaan pilis harus dalam dosis yang direkomendasikan dan diproduksi dalam kondisi yang bersih dan aman. Penelitian ini bertujuan untuk memberikan inovasi patch sebagai pengobatan alternatif untuk meningkatkan daya tarik dan mengontrol zat aktif yang dilepaskan dan dihantarkan dalam waktu lama. Patch transdermal terbuat dari kombinasi kunyit dan jintan hitam yang mengandung senyawa metabolit aktif flavonoid yaitu kurkumin, karotenoid, quercetin, kaempferol, dan apigenin. Kombinasi tersebut mempunyai efek sinergis yang dapat meningkatkan kadar flavonoid total dan efek terapeutik pilis. Metode yang digunakan dalam penelitian ini adalah tinjauan pustaka dan analisis data. Hasil

***Received**: 22 April 2024* ***Accepted**: 24 November 2024* ***Published**: 30 November 2024*

penelitian menunjukkan efek pilis patch transdermal dari kombinasi ekstrak yang ditambahkan ke formula secara in vitro dan in vivo menggunakan uji pada hewan. Kesimpulannya, patch pilis transdermal memiliki prospek sebagai pengobatan topikal berdasarkan kombinasi sistem penghantaran aktif dengan sistem patch dan dosis terukur.

Kata kunci: Jintan hitam, Flavonoid, Koyo transdermal, Kunyit, Pilis

INTRODUCTION

Traditional medicine (TM) is a significant and often overlooked aspect of healthcare services. In some regions of the world, traditional medicine has benefits to maintain health and prevent and treat several diseases (Liu 2021). One of the traditional medicines is pilis, a traditional Javanese paste made from various herbal ingredients. Pilis is used to cure dizziness, headaches, fever, and tired eyes (Timotius et al. 2023). It is made from a "potion" of a synergistic herbal mixture. Pilis is used by grinding the plant material, flattening it, and finally placing it on the forehead and/or temples. Currently, the use of pilis is less widespread because it is considered less fashionable and impractical, and its quality is not yet standardized. The traditional use of pilis cannot also be controlled in dosage, and its effectiveness and safety are uncertain. Moreover, the possibility of contamination is high in its use, and there has been no definitive testing.

Plants used as pilis include turmeric, aromatic ginger, nutmeg, cloves, ginger, lime, white cumin, and black cumin. The pharmacological effects that must be present in Pilis preparations are anti-inflammatory, analgesic, and antipyretic. Compounds that can be used as anti-inflammatory, analgesic, and antipyretic are flavonoids. Flavonoids are compounds have been experimentally shown to have anti-inflammatory qualities and can prevent the formation of prostaglandins in the cyclooxygenase cycle via an inhibitory mechanism. Furthermore, by blocking lipoxygenase and attaching to free radicals, which can result in inflammation, they have been demonstrated to boost the activity of the cyclooxygenase enzyme and decrease leukotriene formation. Furthermore, flavonoids have been found to act as an antipyretic by inhibiting the COX enzyme and as an analgesic by inhibiting pain receptors (Abdel-Aleem et al. 2019).

The active content of turmeric includes flavonoids, specifically curcuminoids, which are a mixture of curcumin (diferuloylmethane), monodemethoxycurcumin, and bisdemethoxycurcumin. Approximately 90% of the curcuminoids in turmeric are found in the plant (Grover et al. 2021). Among its many biological properties include anti-inflammatory, antioxidant, and antiulcer properties (Bourgou et al. 2008). *Nigella sativa* L's NSSEO, according to Badri et al. (2018), contains a number of main phytochemicals, including as nigellone, p-cymene, α-pinene, thymohydroquinone, dithymoquinone, linoleic acid, and thymoquinone. The flavonoids found in black cumin seeds are linked to the phenolic and flavonoid fractions and may possess antioxidant qualities. Significant levels of primary fatty acids with well-known biological activity, such as linoleic (C18:2), oleic (C18:1), and palmitate (C16:0), are also present in the seeds (Ansary et al. 2022). Therefore, turmeric and black cumin can be combined as a traditional pilis medicine.

Based on the description, the author provides innovation in traditional pilis medicinal preparations in the form of transdermal pilis patches as an alternative treatment to increase attractiveness and control the active substances released that can be used for long periods. The designed transdermal patch combines turmeric rhizomes and black cumin seeds because both have a synergistic effect and can increase total flavonoid levels so that they can increase the therapeutic effect of the transdermal pilis patch created. Transdermal patch pilis is a type of medicinal patch that is attached to the skin's surface using adhesive. They are designed to deliver a precise dose of medication through the skin and into the bloodstream at a predetermined release rate, in

order to effectively reach the body. Currently, the most common transdermal systems on the market are based on a semipermeable membrane called a patch. A transdermal drug delivery system (TDDS), also known as a transdermal or skin patch, is a drug delivery method that delivers therapeutic doses of medication through the patient's skin and bloodstream (Patel and Shah 2018). The percutaneous drug administration route is an alternative route for several drugs. It possesses several advantages, including long-term drug action, constant drug release, ease of patient use, and reduced drug administration frequency (Nurhamidah and Nurrochman 2022).

Research questions

1. How is the safe and effective transdermal patch pilis formulation from a combination of turmeric rhizome and black cumin seeds?
2. How to make a safe and effective transdermal pilis patch?

Objectives

1. To provide innovative traditional medicine preparations in the form of transdermal pilis patches as an alternative treatment to increase attractiveness and control the active substances released that can be used for long periods.
2. To know the formulation and method of making transdermal pilis patches from a safe and effective combination of turmeric rhizomes and black cumin seeds.

Hypothesis

1. Transdermal pilis patch preparations from a combination of turmeric rhizomes and black cumin seeds can reduce headache pain.
2. The transdermal pilis patch preparation from a combination of turmeric rhizomes and black cumin seeds can be effective and safe.

MATERIALS AND METHODS

Research design

The research idea in this study followed the recommendations of the study selection and feasibility criteria. Researchers conducted a systematic search on PubMed and Google Scholar using the keywords *Nigella sativa*, turmeric, pilis, and transdermal, and they were paired with the following words: turmeric content, black cumin content, and uses of transdermal pilis. English-language journals published each piece. Manually searching was done again using the reference lists of earlier meta-analyses, review articles, and original research papers. The quality, applicability, and contribution of the collected literature to the study were evaluated. Studies had to fulfill each of the following requirements in order to be accepted. The following requirements had to be fulfilled for studies to be qualified: (1) A parallel or crossover design randomized controlled trial; (2) using curcumin as the only active treatment intervention; (3) providing available data to determine the beneficial substances of black tea. The analytical parameters are summarized as a reference and summary of current research findings that researchers can rely on to create new procedures and/or refine newly published methods.

RESULT AND DISCUSSION

Table 1. Compound, method, and benefit of several materials from some studies

Material	Compound	Method	Benefits	Citation
Turmeric Extract	Curcumin	To ascertain the impact of turmeric *Curcuma domestica*), mice were used in an in vivo experiment on the number of lymphocytes in mice (*Mus musculus*) and those without turmeric. Administration of turmeric	Antibacterial, antioxidant, anti-inflammatory, and antiviral.	Kartikorini et al. (2023)

Material	Compound	Method	Benefits	Citation
		phytochemical extract increases lymphocyte cell numbers in mice.		
Turmeric	Alkaloids, anthraquinones, curcumin, cyclo-curcumin, glycosides, detox curcumin, bisdemethoxy-curcumin, terpenes, tannins, saponins, steroids, anthocyanins, quinones, dan flavonoid	Literature review	Anti-inflammatory, analgesic, antipyretic, immunomodulator, anti-inflammatory, antioxidant, antimicrobial, anticancer	Uchejeso et al. (2021)
Turmeric methanol extract	Curcumin	The in vivo test on mice was conducted using the tail flick method. The mice were divided into three groups: group 1 Group 1 was given a methanol extract of turmeric extract with intraperitoneally with doses of 300, 200, and 100 mg/kg. Group 2 was assigned sodium salicylate (Sigma) intraperitoneally with a dose of 300 mg/kg. Group 3 was given 5.2% formalin with a volume of 5 microliters subcutaneously	Analgesics	Khani and Ranjbar (2022)
Turmeric extract	Polyphenolic curcuminoid, such as curcumin, bisdemethoxy-curcumin and dimethoxy-curcumin.	The analgesic activity is tested using the Hot Plate technique. Group 1 made use of regular saline. Group 2 utilized normal saline as a positive control and diclofenac sodium pills (100 mg/kgBW). Groups 3, 4, and 5 received extract solutions weighing 200 mg/kg, 400 mg/kg, and 800 mg/kg, in that order. Group B (positive control) had the soles of their hind feet treated with 1% diclofenac sodium gel, while Group A served as the control group. A plethysmometer was used to conduct the anti-inflammatory activity test, and normal saline was the only solution administered. Group 2 received 10 mg/kg of diclofenac sodium as the usual	Anti-inflammatory	Saher et al. (2022)

Material	Compound	Method	Benefits	Citation
		control. Group 3 received an extract dosage of 200 mg/kg. Group 4 received 400 mg/kg of it, whereas Group 5 received 800 mg/kg.		
Turmeric Drink	Curcumin, essential oils, anthocyanins, and Tani	Clinical Trial was done on 2 volunteers. Researchers made turmeric drinks for respondents on the first to third day of menstruation.	Analgesic	Utami et al. (2020)
Turmeric powder	Curcumin	The biochemical test for curcumin content was done by dissolving a fine powder of turmeric rhizomes in 5 ml of 95% alcohol. Then, it was shaken in a rocker for 1 hour, and the volume was made up to 10 ml with 95% alcohol. The mixture obtained was filtered using Whatman filter paper and diluted 20X. Absorbance was measured at 425 nm with a UV-Vis spectrophotometer. A standard curve was obtained using standard solutions of 1 µg/ml to 4 µg/ml. The absorbance of this solution was measured using a UV-Vis spectrophotometer at 425 nm.	Anti-inflammatory, antioxidant, anticancer, antipyretic, protects liver function and digestive tract.	Kumari et al. (2022)
Turmeric extract	Curcumin	In Vivo tests are carried out on test animals. Test animals were grouped into 5, as follows: Normal group (Nor) induced osteoarthritis; the Control group (Con) was given distilled water orally after induced osteoarthritis with MIA; the Indomethacin administration group (Indo) was given oral indomethacin as much as 5 mg/kg body weight after inducing osteoarthritis with MIA; The next was the group that was given a low concentration extract, namely turmeric extract as much as 50 mg/kg body weight after being induced by osteoarthritis with	Anti-inflammatory and Antioxidant	Kim and Kim (2019)

Material	Compound	Method	Benefits	Citation
		MIA; The last group was given a high concentration of turmeric extract of 100 mg/kg body weight orally after inducing osteoarthritis with MIA.		
Turmeric Methanol Extract	Curcumin, flavonoids, saponins, glycosides, terpenoids, alkaloids and tannins.	Phytochemical analysis was done To determine the presence of saponins, a foam test was carried out, terpenoids were tested using the Salkowski test, glycosides were tested using the Borntrager test, tannins were tested using the iron chloride test, and alkaloids were used using the Dragendorff test. The total phenolic content was determined using concentration and absorbance calibration curves obtained from a UV-Vis Spectrophotometer.	Antioxidant, anti-inflammatory, anti-thrombocyte, cholesterol-lowering, antibacterial and anti-fungal	Javed et al. (2020)
Coarse powder of turmeric rhizomes	Curcuminoids are curcumin, demethoxycurcumin and bisdemethoxycurcumin;	The process of isolating curcuminoids involved precisely weighing 20 grams of coarsely ground turmeric rhizome powder and utilizing a Soxhlet Extractor to extract the material for six hours using acetone solvent. after which a rotary evaporator was used to filter and concentrate. Petroleum ether was added after the extract had precipitated. Filtering and vacuum suction drying are the next steps. Thin layer chromatography (TLC) was used to examine the curcumin combination in more detail. The Rf value is used to identify the spots that develop in a mixture of methanol and chloroform (9.5:0.5) as the solvent.	Antimicrobial, anti-malarial, anti-inflammatory, anti-proliferative, anti-angiogenic, anti-tumor, anti-aging, anti-rheumatic, anti-Alzheimer's, hypoglycemic, and antiulcer properties.	Grover et al. (2021)
Turmeric extract	Alkaloids, flavonoids, tannins, saponins, glycosides and phenols	Phytochemical analysis was done with the tannin, alkaloid, flavonoid, saponin, phenol, and glycoside tests (Kellar-Kiliani test).	Antioxidant, anti-inflammatory, analgesic, improves digestion and metabolism nutrition.	Nazir and Chauhan (2019)
Turmeric Extract	Curcumin (diferuloylmethane)	Gas Chromatography-Mass Spectrometry (GC-MS) is	Anti-inflammatory, antioxidant, anti-	Arivoli et al. (2019)

Material	Compound	Method	Benefits	Citation
		using for bioactive compounds test	carcinogenic, wound healing, anti-diabetic, anti-stress, and antiviral properties	
Turmeric Extract	Curcumin	The tail-flick analgesia meter method was used to conduct the in vivo test on Wistar rats. Five groups of test animals were created. Group 1 received 0.5 ml of N/S. Group 2 was provided Syp 30 mg/kg of ibuprofen Group 3 was assigned 100 mg/kg body weight of C. longa crude extract Group 4 was assigned 200 mg/kg body weight of C. longa crude extract Group 5 was assigned 400 mg/kg body weight of C. longa crude extract	Analgesics	Phukan and Das (2020)
Black cumin	Thymoquinone	The test was conducted on Wistar mice. The mice were divided into treatment and control groups. The treatment group would receive thymoquinone, while the control group would receive a placebo or other control.	The therapeutic effect of local pain	Badri et al. (2018)
Black cumin	Thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellimine-N-oxide, nigellicine, nigellidine, alpha-hederinand nigellidine,	In vitro and in vivo studies have been conducted to investigate the pharmacological properties of *Nigella sativa* and its ingredients on both humans and laboratory animals. The results suggest that *Nigella sativa* and its components may have a wide range of pharmacological effects.	Immune enhancement, anti-inflammatory, hypoglycemic, antihypertensive, antiasthmatic, antimicrobial, antiparasitic, antioxidant and anticancer effects.	Aljabre et al. (2015)
Black cumin	Nigelidine	Nigellidine has binding capabilities. suppresses the development of the virus by proteasing the nucleocapsid and N-terminus. A number of additional substances, including α-hederin and thymohydroquinone, bind to the ACE2 receptor and obstruct the communication between the virus and its	Anti-inflammatory, antimicrobial	Hossain et al. (2021)

Material	Compound	Method	Benefits	Citation
		host. The essential oil NS (1.5 mg/ml) is used to isolate nigellidine, which inhibits the synthesis of aflatoxin on (67.4%) and mycelial growth.		
Black Cumin Extract	Flavonoids, Nigellon, Timoquinone	100 g of *Nigella sativa* fine seeds were mixed with 70% ethanol in a Soxhlet extractor. The final extract produced was 32% and then concentrated at low temperature pressure.	Antioxidant, anti-inflammatory, analgesic	Alkhalaf et al. (2020)
Nigella sativa powder	Flavoboid	*Nigella sativa* seeds were collected and ground into powder and stored in a closed bottle at room temperature in a dark place until needed. 200 grams of it was soaked in ethanol. The extract was filtered using Whatman filter paper and thickened by distillation using rotary completely dry to remove any last traces of solvent use. Different concentrations of ethanol extract of *Nigella sativa* bark (NaEE) was prepared using the Hedon-Fleig Solution.	Antioxidant, anti-inflammatory, analgesic	Selvaraju et al. (2019)
Nigella sativa Ethanol Extract	Trimoquinone	Black cumin powder was extracted using methanol, ethanol, diethyl acetate, and water as solvents.	Antioxidant, anti-inflammatory, analgesic	Habib and Choudhry (2021)
Trimoquinone isolate	Thymoquinone	Trimoquinone was isolated and treated with five doses of methanol extract. For black color Seeds, it was found to increase the total white blood cell count [increasing to 1.2104 cells/mm^3]. After receiving black cumin extract, bone marrow cellularity also increased significantly.	Analgesic	Perera et al. (2021)

Table 1 presents studies that detail the compounds, methods, and benefits of the materials used in this research. The findings in Table 1 provide key data relevant to the two primary focus areas of this study: the safety and efficacy of the transdermal patch. Based on this data, we observe indications

of the patch's effectiveness in achieving desired outcomes (e.g., symptom reduction or improvement in specific parameters) among groups receiving the patch compared to control or baseline groups. The effectiveness data may include significant changes in clinical variables measured or meaningful differences in groups using the transdermal patch. Regarding safety, Table 1 also outlines the frequency and types of side effects potentially associated with transdermal patch usage. If the data shows minimal or mild side effects for the majority of users, this supports the conclusion that the transdermal patch has an acceptable safety profile. Conversely, a higher occurrence of serious side effects would indicate the need for further consideration of the patch's safety. By comprehensively analyzing the effectiveness and safety data summarized in Table 1, we can better understand whether this transdermal patch represents a safe and effective method for the study's target population.

Transdermal patch pilis turmeric rhizome and black seed

Based on the literature, Transdermal Pilis, containing turmeric (*Curcuma longa*) as its main ingredient with compounds like curcumin, flavonoids, and phenolics (Figure 1), can act as an anti-inflammatory and analgesic (Verma et al. 2018). When combined with black cumin (*Nigella sativa*), which contains active compounds such as nigellone and thymoquinone, it offers additional pain-relieving and anti-inflammatory effects. These two ingredients can be administered topically or transdermally, providing a sustained therapeutic effect. This aligns with findings by Kooshki et al. (2016), demonstrating the analgesic, antispasmodic, and anti-inflammatory properties of these compounds in both in vivo and in vitro studies. In our study, pilis was applied transdermally to allow direct absorption of active substances into the bloodstream, enhancing the pharmacological effect in pain treatment (Timotius et al. 2015).

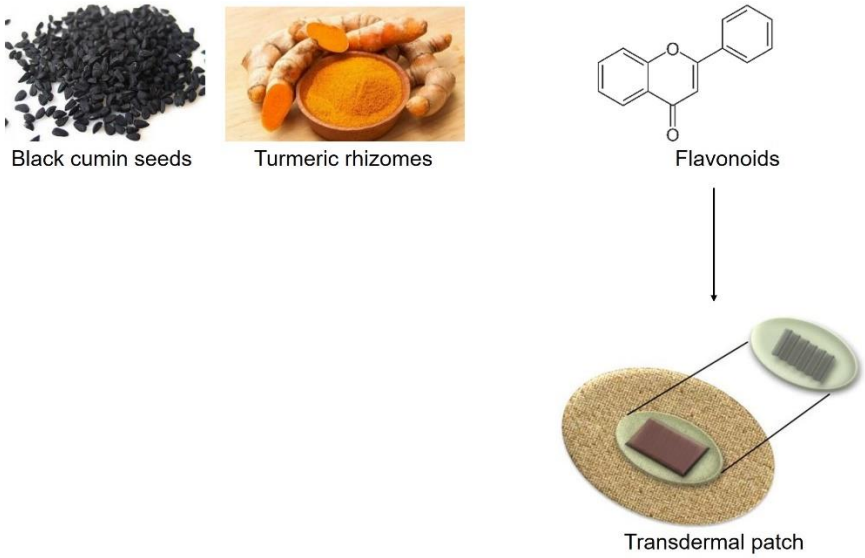

Figure 1. Transdermal Pilis with the main ingredient turmeric

Transdermal patches are advantageous in drug delivery systems because they provide a controlled and sustained release of medication into the bloodstream through the skin. Their primary benefit lies in delivering a consistent dose over time, improving therapeutic outcomes (Hemamalini and Kumar, 2024). However, using skin permeability enhancers can raise concerns regarding potential long-term skin damage or systemic side effects. Despite these considerations, transdermal patches have proven to be effective and safe, depending on factors such as drug properties, patch design, and patient characteristics. Continuous advancements in patch technology and personalized patient care can further optimize their clinical use.

Regarding the mechanism, transdermal drug absorption through the skin involves two primary pathways: transepidermal and transappendageal routes. The transepidermal route allows drugs to penetrate the skin's outermost layer, the stratum corneum, either through intercellular spaces or directly through cells. This pathway is the primary mechanism for transdermal drug delivery due to the large surface area of the stratum corneum. In contrast, the transappendageal route involves drug absorption through skin appendages such as hair follicles and sweat glands. Although this route has high permeability, its role in drug absorption is limited because skin appendages cover only a small fraction of the total skin surface. This secondary pathway is more effective for delivering polar or ionic molecules, which have difficulty penetrating the stratum corneum (Timotius et al. 2015).

Combining turmeric and black cumin in a transdermal patch can enhance therapeutic effects by leveraging these absorption routes for a sustained release of active compounds. Curcumin and thymoquinone, the main active compounds in turmeric and black cumin, act through complementary anti-inflammatory pathways, offering a synergistic effect. Thymoquinone primarily inhibits inflammatory cytokine production, while curcumin suppresses inflammatory mediators such as NF-kB and COX-2, enhancing the body's defense against inflammation and oxidative stress (Amin F. et al. 2015). Together, these compounds strengthen the antioxidant and anti-inflammatory efficacy of the transdermal pilis patch.

Transdermal patch pilis mechanism

Skin is considered the site for transdermal drug absorption. Once the transdermal patch is administered to the skin, the drug is released into the skin. Transdermal drug delivery system can be seen in Figure 2. As shown in Figure 3, drug absorption from the skin occurs via two routes: transepidermal and transappendageal. It is worth noting that the primary absorption route is transepidermal. Due to the stratum corneum's large surface area, medications from the transdermal patch can permeate the skin's surface and enter cells by transcellular or intercellular pathways. The transepidermal pathway can be divided into two subtypes: transcellular and intercellular. During absorption via the transcellular route, the medication diffuses into the stratum corneum cells. As a result, a lipid bilayer membrane must be crossed by the medication. Because lipid interactions in the stratum corneum cell membranes are hydrophobic, hydrophobic medicines generally follow this path. There is an intercellular pathway. Here, the medication needs to permeate the lipid matrix of the keratinocytes' intercellular gaps in the stratum corneum. Small molecules or hydrophilic substances are transported by this pathway to the dermal capillaries. It is commonly known that the main mechanism for medication absorption is the intercellular route. This process is largely influenced by the specific balance of drug molecules, which must be adequately soluble in both fat and water (Ramadon et al. 2022).

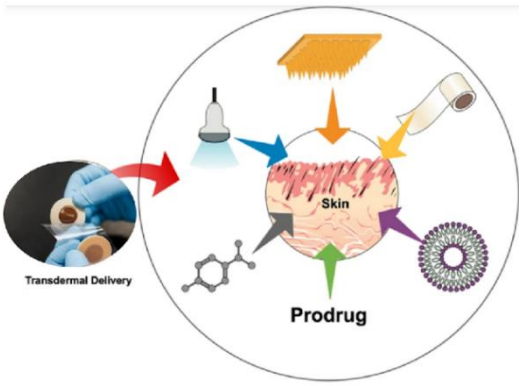

Figure 2. Transdermal drug delivery system

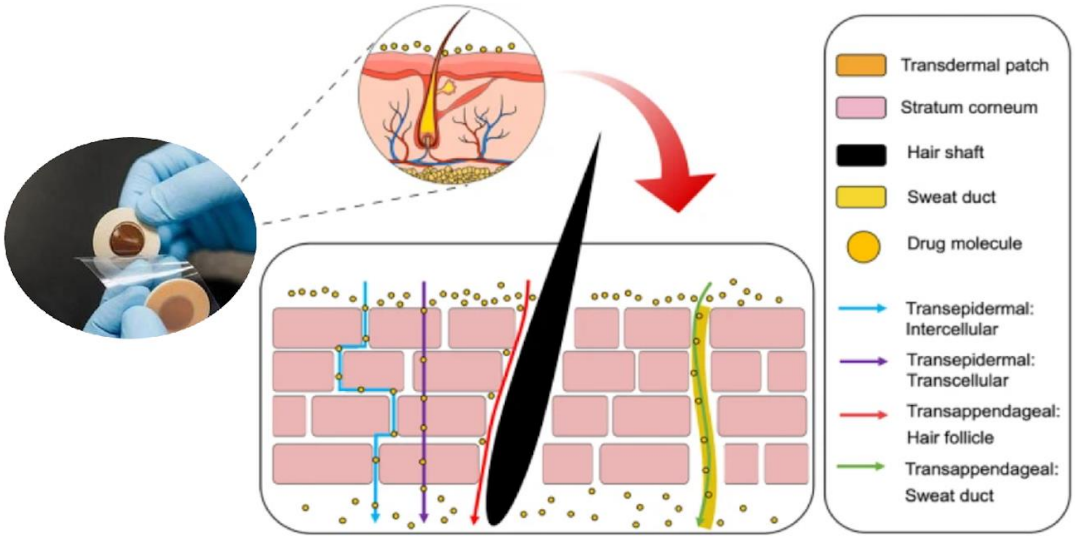

Figure 3. Schematic representation of transdermal drug delivery mechanisms

The combination of turmeric (*Curcuma longa*) and black cumin (*Nigella sativa*) presents a promising synergistic potential in enhancing therapeutic effects. Curcumin, the primary compound in turmeric, exhibits potent anti-inflammatory and antioxidant properties, while thymoquinone from black cumin provides additional anti-inflammatory and antiviral effects. Together, these compounds enhance the body's ability to neutralize free radicals more effectively than when used separately, offering stronger antioxidant and protective effects. This synergistic interaction improves the overall efficacy of the transdermal patch in alleviating pain and inflammation.

The dosage used in this study is 741.36 mg/g for turmeric rhizome and 5.83 mg/g for black cumin seed flavonoids. In the context of pilis, which traditionally contains herbal ingredients like turmeric and betel leaves, these amounts are considered safe when used appropriately. The anti-inflammatory effect of this combination is primarily due to increased antioxidant activity and bioavailability of curcumin. The combination of turmeric and black cumin helps modulate multiple signaling pathways, including the NF-κβ pathway, which plays a crucial role in reducing inflammation. Moreover, combining curcumin with piperine can further enhance its bioavailability, optimizing its therapeutic potential in the patch formulation.

CONCLUSION

In conclusion, this research successfully formulated a safe and effective transdermal pilis patch from a combination of turmeric rhizomes and black cumin seeds. The results demonstrated that the transdermal patch pilis, incorporating the combined extracts, exhibited significant anti-inflammatory and antioxidant effects in vitro and in vivo using animal tests. The synergistic properties of thymoquinone from black cumin and curcumin from turmeric contribute to these therapeutic effects, helping to reduce inflammation and combat oxidative stress. Moreover, studies indicate that the combination of black cumin and turmeric is generally safe when consumed at a dose of 100 mg/kg body weight. Therefore, transdermal patch pilis shows promise as a topical treatment that leverages an active delivery system and a metered dose system for enhanced therapeutic outcomes.

IMPLICATIONS

The research implies that drug research results influence national and international health policies, such as guidelines for drug use by public health institutions and medical associations. Besides, it also increases public awareness of the vital role of research in medical progress and public health. Additionally, it encourages collaboration between academic researchers, pharmaceutical companies, and regulatory

agencies, which can speed up the process of drug development and implementation in clinical practice.

REFERENCES

Abdel-Aleem ER, Attia EZ, Farag FF, Samy MN, Desoukey SY (2019) Total phenolic and flavonoid contents and antioxidant, anti-inflammatory, analgesic, antipyretic and antidiabetic activities of *Cordia myxa* L. leaves. Clin Phytoscience 5:29. doi: 10.1186/s40816-019-0125-z

Aljabre SHM, Alakloby OM, Randhawa MA (2015) Dermatological effects of *Nigella sativa*. J Dermatol Dermatol Surg 19:92-98. doi: 10.1016/j.jdds.2015.04.002

Alkhalaf MI, Hussein RH, Hamza A (2020) Green synthesis of silver nanoparticles by *Nigella sativa* extract alleviates diabetic neuropathy through anti-inflammatory and antioxidant effects. Saudi J Biol Sci 27:2410-2419. doi: 10.1016/j.sjbs.2020.05.005

Amin, F., Islam, N., Anila, N., & Gilani, A. H. (2015). Clinical efficacy of the co-administration of Turmeric and Black seeds (Kalongi) in metabolic syndrome–A double blind randomized controlled trial–TAK-MetS trial. Complementary therapies in medicine, 23(2), 165-174. doi: 10.1016/j.ctim.2015.01.008

Ansary J, Regolo L, Machì M, Salinari A, Cianciosi D (2022) Evaluation of the in vitro bioaccessibility of phenolic compounds of black cumin (BARI-1cumin) methanolic extract. eFood 3:e15. doi: 10.1002/efd2.15

Arivoli S, Tennyson S, Divya S, Rani S, Marin G (2019) GC-MS analysis of bioactive compounds of *Curcuma longa* Linnaeus (Zingiberaceae) rhizome extract. J Pharmacogn Phytochem 8:49-52

Badri W, El Asbahani A, Miladi K, Baraket A, Agusti G, Nazari QA, Errachid A, Fessi H, Elaissari A (2018) Poly (ε-caprolactone) nanoparticles loaded with indomethacin and *Nigella Sativa* L. essential oil for the topical treatment of inflammation. J Drug Deliv Sci Technol 46:234-242. doi: 10.1016/j.jddst.2018.05.022

Bourgou S, Ksouri R, Bellila A, Skandrani I, Falleh H, Marzouk B (2008) Phenolic composition and biological activities of Tunisian *Nigella sativa* L. shoots and roots. C R Biol 331:48-55. doi: 10.1016/j.crvi.2007.11.001

Grover M, Behl T, Sehgal A, Singh S, Sharma N, Virmani T, Rachamalla M, Farasani A, Chigurupati S, Alsubayiel AM, Felemban SG, Sanduja M, Bungau S (2021) In vitro phytochemical screening, cytotoxicity studies of curcuma longa extracts with isolation and characterisation of their isolated compounds. Molecules 26:7509. doi: 10.3390/molecules26247509

Habib N, Choudhry S (2021) HPLC Quantification of thymoquinone extracted from *Nigella sativa* L. (Ranunculaceae) seeds and antibacterial activity of its extracts against Bacillus species. Evid Based Complement Alternat Med 2021:e6645680. doi: 10.1155/2021/6645680

Hemamalini Saravanan, K. L. Senthil Kumar. (2024) Transdermal Patches: Advancements, Challenges And Future Perspectives, Int. J. of Pharm. Sci., Vol 2, Issue 4, 362-373. doi: 10.5281/zenodo.10933536

Hossain MdS, Sharfaraz A, Dutta A, Ahsan A, Masud MdA, Ahmed IA, Goh BH, Urbi Z, Sarker MdMR, Ming LC (2021) A review of ethnobotany, phytochemistry, antimicrobial pharmacology and toxicology of *Nigella sativa* L. Biomed Pharmacother 143:112182. doi: 10.1016/j.biopha.2021.112182

Javed M, Shoaib M, Iqbal Z, Khan MA, Hussain S, Amjad M (2020) Phytochemical and Biological Studies on *Curcuma longa* L. in Pattoki (Kasur), Pakistan: Chemical and Biological studies of *Curcuma longa*. Proc Pak Acad Sci B Life Environ Sci 57:59-66

Kartikorini N, Widyastuti R, Ariana D, Kunsah B, Permata FD (2023) Bioactivity of phytochemicals in *Curcuma domestica* on lymphocyte cell count in mice (*Mus Musculus*). In: Advances in Health Sciences Research. Atlantis Press, pp 108-115

Khani A, Ranjbar A (2022) The analgesic effect of *Curcuma Longa* rhizome methanol extract in male rat. Pars J Med Sci 16:41-48. doi: 10.52547/jmj.16.1.41

Kim YJ, Kim YJ (2019) Effects of *Curcuma longa* rhizoma on MIA-induced osteoarthritis in rat model. J Korean Med 40:35-58. doi: 10.13048/jkm.19026

Kolimi, P., Narala, S., Youssef, A. A. A., Nyavanandi, D., & Dudhipala, N. (2023). A systemic review on development of mesoporous nanoparticles as a vehicle for transdermal drug delivery. Nanotheranostics, 7(1), 70. doi: 10.7150/ntno.77395

Kooshki A, Forouzan R, Rakhshani MH, Mohammadi M (2016) Effect of topical application of Nigella sativa oil and oral acetaminophen on pain in elderly with knee osteoarthritis: A crossover clinical trial. Electron Physician 8:3193-3197. doi: 10.19082/3193

Kumari A, Prasad C, Kumar R (2022) Biochemical studies in different varieties of turmeric (*Curcuma longa* L.). Pharma Innov J 11:1639-1645

Liu C (2021) Overview on development of ASEAN traditional and herbal medicines. Chin Herb Med 13:441-450. doi: 10.1016/j.chmed.2021.09.002

Nazir I, Chauhan RS (2019) Qualitative phytochemical analysis of *Allium sativum* (garlic) and *Curcuma longa* (turmeric). J Entomol Zool Stud 7:545-547

Nurhamidah R, Nurrochman A (2022) Karakterisasi polimer alami sebagai perekat sediaan transdermal patch dengan metode pencampuran. J Ris Farm 125-132. doi: 10.29313/jrf.v2i2.1449

Patel AV, Shah BN (2018) Transdermal drug delivery system: A review. Pharma Sci Monit 9:378-390

Perera W, Liyanage JA, Dissanayake KGC, Chandrasiri WAL, Gunathilaka H (2021) A review on pharmacological activities and anti-microbial properties of *Nigella sativa* and isolated thymoquinone. J Med Plants Stud 9:118-122

Phukan S, Das S (2020) A comparative study of anti-nociceptive activity of *Curcuma Longa* Linn. with that of ibuprofen in experimental animals. Asian J Pharm Clin Res 13:51-53

Ramadon D, McCrudden MTC, Courtenay AJ, Donnelly RF (2022) Enhancement strategies for transdermal drug delivery systems: Current trends and applications. Drug Deliv Transl Res 12:758-791. doi: 10.1007/s13346-021-00909-6

Saher T, Manzoor R, Abbas K, Mudassir J, Wazir MA, Ali E, Ahmad Siddique F, Rasul A, Qadir MI, Aleem A, Qaiser N, Usman A, Romman M, Ali MS (2022) Analgesic and anti-inflammatory properties of two hydrogel formulations comprising polyherbal extract. J Pain Res 15:1203-1219. doi: 10.2147/JPR.S351921

Selvaraju DA, Kaviya S, Dhanraj DKM (2019) Phytochemical analysis and anthelmintic potential of *Nigella sativa* against the trematode, Cotylophoron cotylophorum. J Pharmacogn Phytochem 8:3161-3166

Timotius KH, Sari IN, Santoso AW (2015) Major bioactive compounds of pilis plant materials: A GC-MS analysis. Pharmacogn Commun 5:190-196

Timotius KH, Sudrajat SE, Rahayu I (2023) Bioactive compounds in aqueous extract of pilis, a forehead transdermal herbal medicine. Pharmacogn Commun 13:141-146

Uchejeso OM, Raphael OC, Etukudoh NS, Obiora ER (2021) Use of turmeric against COVID-19 in Nsukka; the need for massive farming. Direct Res J Public Health Environ Technol 6:21-25

Utami RB, Damayanti DF, Rodiah D (2020) The effectiveness of *Curcuma longa* drink in decreasing the intensity of dysmenorrhea. Biomed Pharmacol J 13:2055-2060

Verma RK, Kumari P, Maurya RK, Kumar V, Verma RB, Singh RK (2018) Medicinal properties of turmeric (*Curcuma longa* L.): A review. Int J Chem Stud 6:1354-1357