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Developing transdermal patch from *Momordica charantia* L. fruit using polyvinyl alcohol and ethyl cellulose potentially as anti-inflammatory dosage form

Teti Indrawati [1,*], Zainur Rahman Hakim [2] and Fiqi Fatimah [1]

[1] *Department of Pharmacy, Faculty of Pharmacy, National Institute of Science and Technology, Moch. Kahfi II St., Bhumi Srengseng Indah No.13, Jagakarsa, South Jakarta, Indonesia 12630.*
[2] *Pharmacognosy and Phytochemistry Laboratory, Faculty of Pharmacy, Universitas Pancasila, Srengseng Sawah, Jagakarsa, South Jakarta, Indonesia 12640.*

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Abstract

Introduction: Anti-inflammatory medication is currently sufficiently developed for the ease of application and effectiveness of therapy. Development of natural ingredients that are applied through the skin is needed to get a profitable product. This study aimed to develop bitter melon (*Momordica charantia* L.) fruit as an anti-inflammatory agent using transdermal patch preparations.

Materials and Methods: Dried bitter melon powder was macerated using 96% ethanol, followed by evaporation until a viscous extract was obtained. Bitter melon fruit extract (BMFE) 30% was prepared into three patch transdermal preparations using combinations of polyvinyl alcohol (PVA) and ethyl cellulose (EC) as bases. A mixture of BMFE, propylene glycol, and glycerin was added to the bases and mixed until homogeneous. The entire mass was poured into a mold, coated with aluminum foil, allowed to stand for 24 h, and dried in an oven at 40 °C for 30 min. All preparations of the transdermal patch were evaluated for their physical and chemical characteristics as well as their anti-inflammatory effects

Results: All transdermal patch preparations had solid form, visible brown, weight 0.424 -0.432 g, thickness 0.344 – 0.320 mm, folding endurance of more than 300, pH 4.84 – 4.87, and hygroscopicity 6.50 - 6.99 %. All preparations showed a decrease in the diameter of the edema, but this was not significant; after the 90th minute, the edema diameter was significantly reduced.

Conclusion: This study showed that BMFE can be used for anti-inflammatory patch preparation and has the potential to be developed as a transdermal anti-inflammatory dosage form.

Keywords: Anti-inflammation; Bitter melon; Characterization; Transdermal patch

1 Introduction

Inflammation is an immune response to tissue damage and infections. Treatment with anti-inflammatory drugs, both steroids and nonsteroidal agents, has significant side effects such as gastric ulcers, anemia, muscle atrophy, and decreased immunity to infection[1]. The use of traditional and alternative medicines is increasing in Indonesia. This traditional treatment uses natural ingredients because they are easy to obtain, safer, and have fewer side effects than synthetic ingredients[2]. Bitter melon (*Momordica charantia* L.) is a naturally healthy vegetable [3]. Bitter melon fruit

* Corresponding author: Teti Indrawati

(BMF) has a bitter taste and is traditionally used to treat several skin problems, such as burns and inflammation, which are also commonly used for dysentery, colic, fever, and pain during menstruation[4,5].

BMF can improve inflammatory responses in mice with reduced inflammation markers/indicators and pro-inflammation in the body[6]. BMF is an important medicinal plant that has been explored previously[7,8]. The major chemical constituents of BMF are flavonoids, sterols, saponins, cucurbitane-type triterpene glycosides, cucurbitane-type triterpenoids, phenolic acids, essential oils, fatty acids, amino acids, and some proteins[3,9]. The chemical constituents of BMF can be developed into novel drugs with anti-inflammatory[6], and anticancer activities[10]. BMF has antipyretic[5], antidiabetic[11–13], antimicrobial and antiviral activities[14]. The bitter melon fruit extract (BMFE) showed an anti-inflammatory effect of 67.18% at a dose of 150 mg/kg BW[5]. Topical application of olive oil macerate of bitter melon (*Momordica charantia* L.) promotes the healing of excisional and incisional wounds in rat buccal mucosa[15].

Inflammation can be treated by systemic and topical administration of anti-inflammatory drugs. Topical and transdermal drug delivery can be used on the skin for local and systemic effects[16]. Topical drug delivery systems are easy and painless for patients[17]. Patches are the most efficient and effective medical treatment method, particularly for loading drugs such as anti-inflammation, tissue regeneration, antibacterial, and hemostatic drug[18]. Transdermal patches are polymeric-based patches containing dispersed bioactive ingredients that deliver therapeutic agents at a constant rate through the human skin surface[19]. Transdermal patches have been proven to be effective for drug delivery in children[18]. Transdermal patches are also effective in carrying eplerenone, which is used to control the patient's blood pressure[20]. Currently, many transdermal patch products have been produced and marketed, such as Catapres-TTS® (clonidine) to control blood pressure, Minitran® (nitroglycerin) for angina pectoris, Qutenza®(capsaicin) to relieve neuropathic pain, and the most popular patch in Indonesia Salonpas® (menthol/methylsalicylate) to relieve muscle and joint pain[21].

Currently, polyvinyl alcohol (PVA) is a biomaterial for drug delivery systems that uses biocompatible water-soluble polymers on a large scale[22]. Selective permittivity and sensor membranes using polyvinyl alcohol (PVA) hydrogel bases have been successfully used in biomedical and biotechnological applications. This base can be used to control macroscopic properties and regulate drug release during transdermal drug delivery[22–24]. Increasing the number of hydrophilic polymers, such as ethyl cellulose (EC), tends to increase the cumulative amount of drug released due to its high hydrophilicity, resulting in increased drug release. The combination use of polyvinyl alcohol (PVA) and ethyl cellulose (EC) (5:5) resulted in the amount of drug that penetrated more by 262.75 ± 16.97 µg/cm2/hour[25].

Increasing the hydrophilic polymer content tends to increase drug release owing to its high hydrophilicity, resulting in increased drug release. To date, there have been no medical products, especially transdermal products, using BMFE; therefore, this research aimed to study the preparation and evaluation of a transdermal drug delivery system from BMFE, which is more profitable than vegetables and waste. This study was conducted using a transdermal anti-inflammatory patch of BMFE (150 mg/kg BW) with polyvinyl alcohol (PVA) and ethyl cellulose (EC) as bases.

2 Material and methods

2.1 Materials

The material used in this study was bitter melon fruit (*Momordica charantia* L.) from Cipayung, Depok, Indonesia, which was obtained from the Herbarium Bogorinese Biology Research Center, Cibinong, Bogor, West Java, Indonesia, with specimen No.2503/IPH.1.01/If.07/XI/2018. The results of the determination showed that the plant used in this study was *Momordica charantia* L. (Cucurbitaceae), Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP), Ethylcellulose, PEG 400, Propylene glycol and Ethanol 96% (Brataco Chemika, Indonesia), Bye-bye fever (PT. Hisamitsu, Indonesia), yeast instant powder (Fermipan, Lesaffre, France), and Ketoplast® ketoprofen patch (Zuventus Healthcare Ltd., India).

2.2 Animals

A total of 60 white male mice *Mus musculus* 20-30 g at 28-day age were used to determine the anti-inflammatory effect of the approved research protocol (No. B/1396/V/2019/KEPK) of the Health Research Ethics Commission of "Veteran" National Development University, Jakarta.

2.3 Preparation of extract

Bitter melon (*Momordica charantia* L.) fruits weighing as much as 40 kg were sorted, attached to the simplicia, and cleaned off the seeds for further cutting. The samples were then dried in an oven at 60 °C, and dry sorting was performed.

Dried pulp was separated from the damaged flesh by heating, mashing, and sieving through an appropriate sieve. Simplicia powder (*Momordica charantia* L.) was macerated using 96% ethanol at a ratio of the extract to 1:10 solvent, soaked for 1 × 24 h with occasional stirring in a glass container, and protected from light. Maceration was repeated 2 times with a new solvent. The maceration results were filtered using a filter paper, and the filtrate was collected. The filtrate was evaporated and the viscous extract was collected.

2.4 Identification of Alkaloid

A total (0.5 g) was moistened with 5 ml of 25% ammonia, and then chloroform was added until the mass was immersed, stirred, heated over a water bath, and then filtered. The residue was poured into a tube, and three drops of 2N HCl were added, shaken, and left to 2 layers form. A clear layer was formed and inserted into tube 3 in the same amount. Mayer's reagent (Bouchardart) was added. There were white deposits in the Mayer reagent and brown deposits in the Bouchardat reagent[26].

2.5 Identification of Flavonoids

A total of 0.5 g of BMFE added 1-2 ml of 95% ethanol, add 0.5 g of Mg or Zinc powder plus hydrochloric acid 5 drops, if there is a change in red-orange to red-purple indicates a flavonoid [26].

2.6 Identification of Saponin

The saponin test was made by dissolving 0.5 g BMFE with hot water 10 ml hot then the solution was filtered, and the solution was shaken for 10 seconds. Positive results were obtained if the foam was formed as high as 1-10 cm which was stable for not less than 10 min [23].

2.7 Identification of Tannins

2 g of BMFE are added with hot water 100 ml, boiled for 5 minutes then the solution is filtered. Five milliliters of the filtrate were placed into a test tube, and 1% iron (III) chloride reagent was added if green-purple or black appeared, and then tannin was positive [26].

2.8 Identification of Steroids and Terpenoids

BMFE (2 g) was macerated with ether (20 ml, left to stand for 2 h, and then filtered and dipped in an evaporative cup until the residue was obtained, after the residue added 2 drops of anhydrous acetate and 2 ml of chloroform were added, and then transferred to a test tube. Slowly add concentrated H_2SO_4 1 ml (*Lieberman Buchard*) through the tube wall. A ring layer is formed. Triterpenoids are indicated by purple and steroid-green colors[26] [23].

2.9 Preparation of BMFE transdermal patch

Bitter melon fruit extract (BMFE), PVA, EC, PEG 400, propylene glycol, and glycerin were weighed (Table 1). The patch bases were prepared by dissolving PVA in water (Mixture 1). Propylene glycol, glycerin, and BMFE were mixed until homogeneous (mixture 2). Mixtures 1 and 2 were mixed until homogeneous. The entire mass was poured into a mold, coated with aluminum foil, allowed to stand for 24 h, and dried in an oven at 40 °C for 30 min[24].

Table 1 Anti-inflammation BMFE transdermal patch

Materials	**Amount (%)**		
	F1	**F1**	**F3**
BMFE	30.00	30.00	30.00
Polyvinyl Alcohol (PVA)	12.00	16.00	20.00
Ethyl cellulose (EC)	4.00	4.00	4.00
Propylene glycol	30.00	30.00	30.00
Glycerin	15.00	15.00	15.00
Water ad	100	100	100

2.10 Physical and chemical characterization of BMFE transdermal patch [27]

The organoleptic test is a visual examination of the shape, color, and smell. Weight test This test was performed by weighing each formula. Five patch preparations were randomly selected, weighing each patch, and the average weight of the patches in each formulation was calculated. The resulting patch thickness was measured using a micrometer with an accuracy of 0.01 mm Micrometer. The measurements were performed for five different preparations. The folding resistance test was performed manually by folding the patch repeatedly on the same line until it broke or folded up to 300 times. A surface pH test was performed using a tolerable pH (4.5 - 6.5) indicator to avoid skin irritation. The patch preparation was dissolved in 5 ml of Aqua Dest. Then enter the pH of the stick for 1 min. Physical stability of patches under high humidity conditions by hygroscopic testing. The weighed patch was placed in a desiccator with silica gel for 24 h and weighed, and the moisture content and percentage of water absorption were calculated.

$$Hygroscopic\ test = \frac{(\text{final weight} - \text{initial weight})}{\text{initial weight}} \text{x} 100$$

2.11 Evaluation of the antipyretic effectiveness test of BMFE transdermal patch

The effectiveness test used 30 healthy *Mus musculus* mice with weights ranging from to 20-35 g. All the mice were adapted in the laboratory for 2 weeks and grouped into 5 groups and weighed, given a certain mark as in Table 2. All the feet of mice were injected intraplanar with 0.3 ml of 1% carrageenan suspension in physiological NaCl solution then after 1 hour the edema in the feet was measured using a digital scrub micrometer and recorded as initial edema. The next step was to attach the patch to the edema site, as shown in Table 2. Edema of the mouse feet at o, 60, 90, 120, 150, and 180 min and percent edema and percent inhibition were calculated[5].

Table 2 Treatment group BMFE transdermal patch

Group	Mice Number	Treatment
Negative control	5	No treatment
Positive control	5	Keratoplasty
BMFE 1	5	F 1
BMFE 2	5	F 2
BMFE 3	5	F 3

3 Results and discussion

A thick extract of 108 g was obtained from 733.45 g BMF powder with a yield of 14.73%. This yield value is related to the amount of bioactive content in the plants; the higher the yield value, the more bioactive the content[9]. The quality of the resulting extract is inversely proportional to the yield. The higher the yield value, the lower quality obtained[4,28]. The evaluation of BMFE showed that it has a viscous liquid shape, dark brown color, bitter melon smell, pH 5.84, and is alcohol-free.

Table 3 Phytochemical screening BMFE

No	Chemical content	Result
1	Alkaloid	+
2	Flavonoid	+
3	Saponin	+
4	Tannin	-
5	Terpenoid and steroid	-

The phytochemical screening results for bitter melon powder and its extracts are presented in Table 3. Bitter melon contains flavonoids, alkaloids, and saponins but has negative effects on tannins, steroids, and terpenoids. Phytochemical

screening of bitter melon powder and extract showed that bitter melon extract contains flavonoids and saponins, which have anti-inflammatory effects[11].

The results of the organoleptic evaluation of all formula transdermal patch preparations showed a solid form that was previously in liquid form, and there were also visible brown spots due to the oven drying process, which caused a decrease in the solubility of one of the dissolved ingredients. The resulting patch also had a flexible texture owing to the addition of glycerin 15% as the plasticizer. It is brown in color and has a burning smell from the thick extract of bitter melon which is dark brown in color and also smells like burning. Based on the organoleptic examination results, the addition of PVA as a base did not affect the shape, color, or odor of the transdermal patch preparation.

Patch weight was affected by the cutting technique of each patch after printing. The test was carried out to determine the uniformity of the patch weight because the heavier the patch, the more uncomfortable it will be when used, and will affect the weight of the active substance dissolved in it will affect the effect. Patches that are too heavy contain many solvents, which affect the stability of the patch during storage, making it easier for the mold to grow and become soft, which affects the quality of patch preparation. The weight of the transdermal patch of BMFE in this study was almost the same, which showed that the cutting of each patch was performed equally well[25,29]. The results of the resulting patch have similarities with other studies because of the decrease in weight that is expected with the results due to the loss of solvent in the drying process[30].

Table 4 shows that the film weight, thickness, and folding endurance of the patches are uniform. The thickness of the transdermal patch of BMFE in this study was almost the same, indicating that the pouring of the patch solution on the mold was relatively even, and during the drying process, it was placed on a flat base. The patch had a fairly thin film thickness and was almost the same; therefore, it was expected to effectively release active ingredients. Patches that are too thick can slow down the process of drug entry into the skin so the expected effect will be longer, which will affect the quality of patch preparation[25]. In another study using a 15% glycerin plasticizer, it had a good folding resistance of more than 300 times, and the patch was still in good condition and not torn[31]. All formulas have almost the same hygroscopic average, which is 6.50 - 6.99%. The amount of water from the polymer contained in the patch affects the release of the drug and the stability of the preparation. If the water content is too high, contamination by microorganisms can occur, thereby reducing the stability of the preparation will be reduced. The percentage of water content is influenced by several factors, including the primary molecular mass, contact time between the polymer and mucosa, and the average polymer expansion index.

The results of this test showed that 15% glycerin plasticizer could function well in increasing the elasticity of the patch to avoid damage to the patch when combined with different base concentrations. All the formulas had a folding endurance of more than 300 times, indicating that they had strong folding endurance. Therefore, the results of the resulting patch were similar to those of other studies because of the expected decrease in weight owing to the loss of solvent during the drying process[32].

The results of the surface-pH tests are presented in Table 4. The three formulas had average pH of 4.8. In another study, a pH of 5.73 was also obtained because the active ingredient used piroxicam had a pH of 5.7, desired surface pH is 4.5-6.5, which is the skin surface pH [31], and it does not irritate during application[23]. This indicates that the resulting preparation meets the criteria for a pH range that can be tolerated by the skin surface; therefore, it is safe for use.

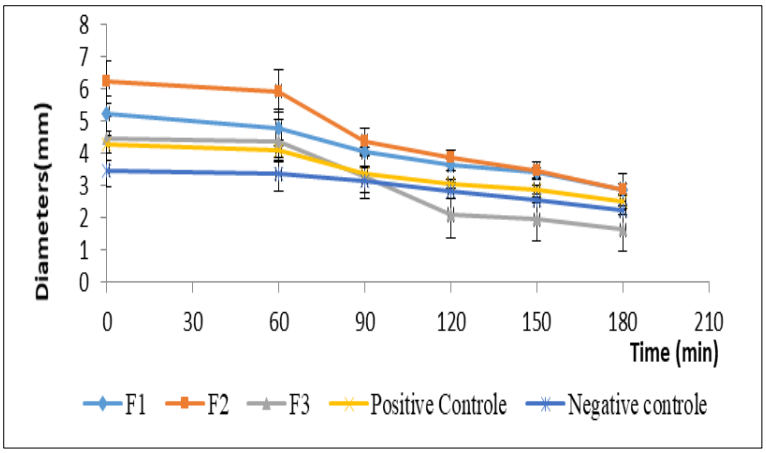
Table 4 Evaluation Result of BMFE Patch

No	Formula	Weight (g)	Thick (mm)	Folding endurance	pH	hygroscopicity (%)
1	F1	0.432 ± 0.069	0.344 ± 0.052	>300	4.87± 0.01	6.50 ± 0.071
2	F2	0.464 ± 0.080	0.314 ± 0.041	>300	4.82± 0.01	6.62 ± 0.056
3	F3	0.424 ± 0.037	0.320 ± 0.067	>300	4.84± 0.01	6.99 ± 0.067

Results are expressed as mean±SD, n=3

All formulas have almost the same hygroscopic average, which is 6.50 - 6.99%. The amount of water from the polymer contained in the patch affects the release of the drug and the stability of the preparation. If the water content is too high, contamination by microorganisms can occur, thereby reducing the stability of the preparation will be reduced[31]. The percentage of water content is influenced by several factors, namely the primary molecular mass, contact time between the polymer and mucosa, and the average polymer expansion index[27]. The results of measuring the diameter of edema on the soles of the mice are shown in Fig. 2 and Fig. 3. At the 60th minute, treatment groups F1, F2, and F3

experienced a decrease in edema diameter; however, this was not statistically significant. This was attributed to the presence of saponins and flavonoids in BMFE. At the 90th minute, the mice treated with F1, F2, F3, and the positive control began to experience a reduction in edema diameter. However, in the negative control group, there was no significant decrease in edema diameter, even though there was a decrease in the diameter of edema (Figure 1).



Results are expressed as mean±SD, n=3

Figure 1 Effectiveness of BMFE anti-inflammatory patch

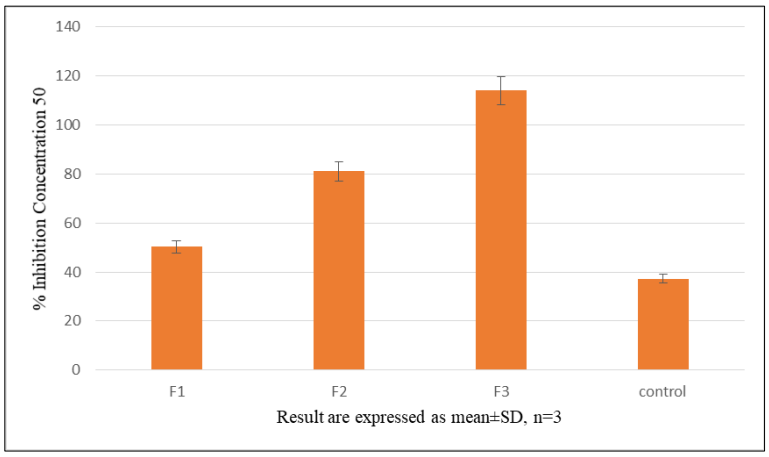


Figure 2 Inhibition profile of edema

The results of measuring the diameter of the edema on the soles of the mice are shown in Fig. 1 and Fig 2. At the 60th minute, treatment groups F1, F2, and F3 experienced a decrease in edema diameter, but this was not statistically significant. This was due to the presence of saponins and flavonoids in BMFE. At the 90th minute, the mice treated with F1, F2, F3, and the positive control began to experience a reduction in edema diameter. However, in the negative control group, there was no significant decrease in edema diameter, even though there was a decrease in edema diameter. This shows that the PVA base can accelerate the release of secondary metabolites from the bitter melon extract. It was also observed in F3 that there was a significant decrease compared to F1, F2, and the positive control at 120 min, because the concentration of PVA: EC (5:1) accelerated the penetration of bitter melon extract, reducing the diameter of edema. In addition, it is necessary to conduct further research on the addition of enhancers such as limonene, cineol, beta-cyclodextrin, and oleic acid, which will increase the ability to penetrate the skin and maximize drug releases, such as limonene, cineol, beta-cyclodextrin, and oleic acid [32].

4 Conclusion

From this study, it was concluded that BMFE can be prepared into a patch with an optimum anti-inflammatory effect using PVA and ethyl cellulose as the base of the patch. BMFE has great potential for production on a factory scale as an anti-inflammatory transdermal patch.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

The research was ethically approved by the Health Research Ethics Commission of "Veteran" National Development University, Jakarta, Indonesia.

References

[1] Chuncharunee A, Khosuk P, Naovarat R, Kaliyadan F, Sreekanth GP. ASPP 092, a phenolic diarylheptanoid from *Curcuma comosa* suppresses experimentally-induced inflammatory ear edema in mice. Saudi J Biol Sci. 2021;28(10):5937–46. https://doi.org/10.1016/j.sjbs.2021.06.056

[2] Ariyati L, Muhtadi. Anti-inflammatory activity of a combination of snakehead fish (*Channa striata*) and ethanol extract of bitter melon fruit (*Momordica charantia* L.) against carrageenan-induced male Wistar rats. 5Th Urecol Proceeding. 2017;(February):50–8.

[3] Saeed F, Afzaal M, Niaz B, Arshad MU, Tufail T, Hussain MB, et al. Bitter melon (*Momordica charantia*): a natural healthy vegetable. Int J Food Prop. 2018;21(1):1270–90. https://doi.org/10.1080/10942912.2018.1446023

[4] Boy HIA, Rutilla AJH, Santos KA, Ty AMT, Yu AI, Mahboob T, et al. Recommended Medicinal Plants as Source of Natural Products: A Review. Digit Chinese Med. 2018;1(2):131–42. https://doi.org/10.1016/S2589-3777(19)30018-7

[5] Parawansah, Wahyuni, Mahmudah Z. Antipyretic and anti-Inflammatory effects assays of bitter melon (*Momordica charantia* L.) ethanolic extract on male mice. J Medula (Jurnal Ilm Fak Kedokt Halu Oleo). 2016;4(1):309–15.

[6] Chao CY, Sung PJ, Wang WH, Kuo YH. Anti-inflammatory effect of *Momordica charantia* in sepsis mice. Molecules. 2014;19(8):12777–88. https://doi.org/10.3390/molecules190812777

[7] Kumar SR, Ashish J, Satish N. *Momordica charantia* Linn. : A Mini Review. Int J Biomed Res. 2011;2(11):579–87. Available from: https://ssjournals.com/index.php/ijbr/article/view/685/681

[8] Gupta M, Sharma S, Gautam AK, Bhadauria R. *Momordica charantia* Linn.(Karela): Nature's silent healer. Int J Pharm Sci Res IJPSR. 2011;11(1):32–7.

[9] Perez JL, Jayaprakasha GK, Patil BS. Metabolite profiling and in vitro biological activities of two commercial bitter melon (*Momordica charantia* Linn.) cultivars. Food Chem. 2019;288(March):178–86. https://doi.org/10.1016/j.foodchem.2019.02.120

[10] Dandawate PR, Subramaniam D, Padhye SB, Anant S. Bitter melon: A panacea for inflammation and cancer. Chin J Nat Med. 2016;14(2):81–100. https://doi.org/10.1016/S1875-5364(16)60002-X

[11] Puspitasari V, Choerunisa N. A Systematic Review: Antidiabetic effect of bitter melon fruit (*Momordica charantia* Linn.) on blood glucose levels in alloxan induced mice. Generics J Res Pharm. 2021;1(2):2774–9967.

[12] Muhtadi A, Irenka Y, Ayu WC, Hendriani R, Zuhrotun A. Hypoglycemic activity of 10 medicinal plants extract in glucose induced mice. Asian J Pharm Clin Res. 2017; https://doi.org/10.22159/ajpcr.2017.v10s2.19473

[13] Reyes BAS, Bautista ND, Tanquilut NC, Anunciado R V, Leung AB, Sanchez GC, et al. Anti-diabetic potentials of *Momordica charantia* and *Andrographis paniculata* and their effects on estrous cyclicity of alloxan-induced diabetic rats. J Ethnopharmacol. 2006; https://doi.org/10.1016/j.jep.2005.10.018

[14] Costa JGM, Nascimento EMM, Campos AR, Rodrigues FFG. Antibacterial activity of *Momordica charantia* (Curcubitaceae) extracts and fractions. J basic Clin Pharm. 2010;2(1):45–51.

[15] Ilhan M, Bolat IE, Süntar I, Kutluay Köklü H, Uɻar Çankal DA, Keleş H, et al. Topical application of olive oil macerate of *Momordica charantia* L. promotes healing of excisional and incisional wounds in rat buccal mucosa. Arch Oral Biol. 2015;60(12):1708–13. https://doi.org/10.1016/j.archoralbio.2015.09.006

[16] McConville A, Atchison J, Roddy A, Davis J. A wireless smart patch for the controlled repetitive transdermal administration of therapeutic agents. Sensors Actuators, B Chem. 2019;294:24–31. https://doi.org/10.1016/j.snb.2019.05.023

[17] Jain S, Patel N, Shah MK, Khatri P, Vora N. Recent Advances in Lipid-Based Vesicles and Particulate Carriers for Topical and Transdermal Application. J Pharm Sci. 2017;106(2):423–45. https://doi.org/10.1016/j.xphs.2016.10.001

[18] Delgado ME, Haza AI, Arranz N, Garcia A, Morales P. Dietary polyphenols protect against N -nitrosamines and benzo (a) pyrene- induced DNA damage (strand breaks and oxidized purines / pyrimidines) in HepG2 human hepatoma cells. Eur J Nutr. 2008;47(2008):479–90. https://doi.org/10.1007/s00394-008-0751-6

[19] Shariatinia Z, Barzegari A. Polysaccharide hydrogel films/membranes for transdermal delivery of therapeutics. Polysaccharide Carriers for Drug Delivery. Elsevier Ltd.; 2019. 639–684 p. https://doi.org/10.1016/B978-0-08-102553-6.00022-2

[20] Shinde R, Velraj M. Formulation, Optimization, and Characterization of Transdermal Drug Delivery Systems Containing Eplerenone. Int J Appl Pharm. 2022;14(1):198–207. https://doi.org/10.22159/ijap.2022v14i1.42827

[21] Kumar CA, Ashwini J, Archana GL, Laxmi SV, Garige AK, Chandupatla V, et al. Transdermal Patches for the Treatment of Angina Pectoris: an Effective Drug Delivery System-a Review. Int J Appl Pharm. 2022;14(4):115–25. https://doi.org/10.22159/ijap.2022v14i4.44623

[22] Sivaraman A, Ganti SS, Nguyen HX, Birk G, Wieber A, Lubda D, et al. Development and evaluation of a polyvinyl alcohol based topical gel. J Drug Deliv Sci Technol. 2017;39:210–6. https://doi.org/10.1016/j.jddst.2017.03.021

[23] Malaiya MK, Jain A, Pooja H, Jain A, Jain D. Controlled delivery of rivastigmine using transdermal patch for effective management of alzheimer's disease. J Drug Deliv Sci Technol. 2018;45:408–14. https://doi.org/10.1016/j.jddst.2018.03.030

[24] Sa'adon S, Abd Razak SI, Ismail AE, Fakhruddin K. Fabrication of Dual Layer Polyvinyl Alcohol Transdermal Patch: Effect of Freezing-Thawing Cycles on Morphological and Swelling Ability. Procedia Comput Sci. 2019;158:51–7. https://doi.org/10.1016/j.procs.2019.09.027

[25] Windriyati YN, Sholikhah A, Muliawati F. Development of Matrix-Type Diltiazem HCl Transdermal Film with a Combination of Polyvinyl Alcohol and Ethyl Cellulose Polymers and PEG 400 Penetration Enhancer. J Ilmu Farm &Farmasi Klin. 2016;13(1):21–6.

[26] Jia S, Shen M, Zhang F, Xie J. Recent advances in *Momordica charantia*: Functional components and biological activities. Int J Mol Sci. 2017;18(12). https://doi.org/10.3390/ijms18122555

[27] Chauhan MK, Sharma PK. Optimization and characterization of rivastigmine nanolipid carrier loaded transdermal patches for the treatment of dementia. Chem Phys Lipids. 2019;224:104794. https://doi.org/10.1016/j.chemphyslip.2019.104794

[28] Cultivars L, Perez JL, Jayaprakasha GK, Patil BS. Metabolite profiling and in vitro biological activities of two commercial bitter melon (*Momordica charantia* Linn.) cultivars vegetable and fruit improvement center, Department of Horticultural Sciences,. Food Chemistry. Elsevier Ltd; 2019. https://doi.org/10.1016/j.foodchem.2019.02.120

[29] Ameen D, Michniak-Kohn B. Development and in vitro evaluation of pressure sensitive adhesive patch for the transdermal delivery of galantamine: Effect of penetration enhancers and crystallization inhibition. Eur J Pharm Biopharm. 2019;139:262–71. https://doi.org/10.1016/j.ejpb.2019.04.008

[30] Pan-On S, Rujivipat S, Ounaroon A, Kongkaew C, Tiyaboonchai W. Development, characterization and skin irritation of mangosteen peel extract solid dispersion containing clay facial mask. Int J Appl Pharm. 2018;10(5):202–8. https://doi.org/10.22159/ijap.2018v10i5.28247

[31] Saryanti D, Setiawan I, Safitri RA. Optimization of the oil in water (O/W) cream formulation from kepok banana peel (*Musa acuminata* L.) extract. J Ris kefarmasian Indones. 2019;1(3):225–37.

[32] Sethi B, Mazumder R. Comparison of effect of penetration enhancer on different polymers for drug delivery. Int J Appl Pharm. 2019;11(1):89–93. https://doi.org/10.22159/ijap.2019v11i1.29082