International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Design, Development and Evaluation of Herbal Transdermal Patch for the Treatment of Rheumatoid Arthritis

Ms. Pranjal M. Dabhade[1], Prof. Sharda S. Kulkarni[2], Dr. Sanjay R. Arote[3]

[1]Student, IVM's Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune, Maharashtra – 410507
[2]Assistant Professor, Department of Pharmaceutics, IVM's Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune, Maharashtra – 410507
[3]Principal, IVM's Krishnarao Bhegade Institute of Pharmaceutical Education & Research, Talegaon Dabhade, Pune, Maharashtra – 410507

ABSTRACT
This study aimed to develop a novel polyherbal transdermal patch for managing Rheumatoid Arthritis (RA), using plant-based anti-inflammatory agents such as eucalyptus oil, camphor, ginger, methyl salicylate, and nicotine from *Nicotiana tabacum*. The patch was formulated using the solvent casting method with HPMC and PVP as polymers and evaluated for physicochemical properties. Among the formulations, F3 exhibited optimal characteristics in flexibility and moisture content. A patient survey revealed strong interest and openness toward herbal-based transdermal therapies. These findings suggest that such patches may offer a patient-friendly alternative to conventional RA treatments with fewer systemic side effects.

Keywords: Eucalyptus oil, Ginger, Methyl salicylate, Nicotine, Rheumatoid Arthritis, Transdermal Patch

1. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by inflammation of synovial joints, cartilage damage, and bone erosion. The disease, associated with genetic and environmental factors such as smoking and microbiota imbalance, affects more women than men and is prevalent especially after the age of 40 [1,2].

Figure 1: RA patient's hand

Conventional treatments include NSAIDs, glucocorticoids, DMARDs, and biologics, which offer relief but are associated with side effects and high costs [3,4]. Transdermal Drug Delivery Systems (TDDS) present a promising alternative, offering sustained drug release, bypassing first-pass metabolism, and improving patient compliance [5-7].

This study explores the development of a transdermal patch combining multiple herbal agents known for their anti-inflammatory and analgesic effects.

2. MATERIALS AND METHODS

2.1 Materials

Eucalyptus oil, camphor, ginger powder, and *Nicotiana tabacum* leaves were sourced from local markets. Nicotine was extracted using isopropyl alcohol. HPMC, PVP, ethanol, and other analytical reagents were used from institutional labs.

- **Eucalyptus Oil**

Eucalyptus oil, derived from the leaves of *Eucalyptus globulus* (family Myrtaceae), is widely used for its biological properties. It primarily consists of eucalyptol (1,8-cineole), a monocyclic monoterpene ether that makes up 70–90% of the essential oil. Minor components include α-pinene, α-phellandrene, p-cymene, cuminaldehyde, limonene, terpinen-4-ol, and trans-pinocarveol [8]. Clinical trials have explored its potential in treating muscle soreness, hypertension, migraines, COVID-19, tick bites, gingivitis, and dental plaque [9].

Uses of eucalyptus oil

It possesses anti-inflammatory properties that aid in alleviating pain and inflammation linked to rheumatoid arthritis. Additionally, some studies have demonstrated its antioxidant properties [8].

Figure 2: Eucalyptus oil

- **Nicotine**

Nicotine is an alkaloid obtained from *Nicotiana tabacum* (tobacco), a plant belonging to the Solanaceae family. Beyond its use in cigarettes, tobacco has gained attention for applications in organic fertilizers, biopesticides, biomaterials, food, feed, and medicine. Tobacco contains around 5,700 chemical compounds, including carbohydrates, alkaloids, and phenolics. Nicotine ($C_{10}H_{14}N_2$), a pyridine and pyrrole alkaloid, makes up about 5% of the plant's weight and 90%–95% of its total alkaloid content [10,11].

Uses of nicotine

Nicotine has demonstrated positive effects on neurodegenerative diseases, reducing inflammation, and promoting weight loss. Extracts of *Nicotiana tabacum* have been found to exhibit anti-arthritic activity [11,12].

Figure 3: Tobacco powder

- **Methyl salicylate**

Methyl salicylate, the primary organic compound in natural wintergreen oil and is derived from the leaves of the wintergreen plant *Gaultheria procumbens* L. belonging to the family Ericaceae [13]. Salicylic acid methyl ester, synthesized by several plant species, acts as a rubefacient that enhances blood circulation and provides a topical analgesic effect, making it commonly used in topical applications such as gels, creams, or patches. [14,15].

Uses of methyl salicylate

Methyl salicylate possesses anti-inflammatory, pain-relieving, digestion-boosting, antibacterial, and antioxidant effects. It effectively reduces inflammation in rheumatoid arthritis and inflammatory skin disorders, such as psoriasis [13].

Figure 4: Methyl salicylate

- **Ginger**

Zingiber officinale, commonly known as ginger, is a member of the Zingiberaceae family and is widely recognized for its association with relieving inflammatory symptoms [5]. Ginger rhizomes contain carbohydrates, fatty oils, proteins, fiber, and volatile oils rich in sesquiterpenes and monoterpenes. Key bioactive compounds include gingerols, shogaols, paradols, and zingerone [16].

Uses of ginger

Ginger has been widely utilized as a food, spice, supplement, flavoring agent, and a key component in traditional medicines. It is used to treat various diseases and symptoms, including colds, headaches, nausea, upset stomach, diarrhea, arthritis, and rheumatism. Also, it acts as a carminative, antiflatulent, and digestive aid [16].

Figure 5: Ginger powder

- **Camphor**

Camphor is a terpene ketone obtained either from the wood of *Cinnamomum camphora* or through synthetic production using turpentine [17]. Synthetic camphor, commonly known as Karpura, is burned during puja ceremonies and religious rituals in temples across India and is valued for its distinctive aromatic fragrance. The chemical structure of camphor is 1,7,7-trimethylbicyclo[2.2.1]heptanone and a molecular formula of $C_{10}H_{16}O$. It is a waxy, white, or translucent solid that emits a strong, aromatic odour [18].

Uses of camphor

Camphor is utilized in the treatment of inflammation-related ailments, including rheumatism, sprains, bronchitis, asthma, indigestion, muscle pain, and infestations caused by *Lasioderma serricorne*. It exhibits a range of biological properties, including antimicrobial, antibacterial, antiviral, and antitussive effects, as well as anti-mutagenic and anticancer activities. Camphor is commonly used to alleviate ailments like eye diseases, ear pain, joint and muscular pain, chest congestion, and headaches [17,18].

Figure 6: Camphor

2.2 Extraction of Nicotine from *Nicotiana tabacum* leaves

The *Nicotiana tabacum* leaves were dried using a tray dryer at 60 ◦C for 20 mins. After drying, the leaves were ground into a fine powder. A quantity of 30 gm of the powdered leaves was subjected to percolation in 140 ml of isopropyl alcohol at room temperature (25 ± 2 ◦C) for 24 hrs using the conical percolator. After completion of the percolation process, the extract was collected and filtered to remove plant residues. The nicotine-rich extract was then stored in an amber-colored container for the further use in the formulation of the transdermal patch.

Figure 7: Tray dryer, tobacco powder, isopropyl alcohol, conical percolator and nicotine extract

2.3 Preparation of Herbal Transdermal Patch

The transdermal patches were prepared using the solvent casting method. Based on the solubility of ingredients, they were dissolved in their respective phases- aqueous or oil- and stirred continuously to form water-in-oil (W/O) emulsion. Once the emulsion was stable, the extracted nicotine was gradually incorporated into the emulsion with continuous stirring to ensure uniform distribution.

In a separate step, the polymeric components were dissolved in an appropriate solvent to form a clear solution. The prepared W/O emulsion was then slowly added to the polymer solution while maintaining constant stirring, resulting in a homogenous blend. The final solution was poured into a flat glass petri dish and allowed to dry at room temperature for 24 hrs. After drying, patches were carefully peeled off and stored in a desiccator.

Figure 8: Prepared formulations

Table 1: Formulation table

Sr.no.	Ingredients	F1	F2	F3	Role of Ingredient
1	Eucalyptus oil	3%	5%	4%	Anti-inflammatory, analgesic
2	Nicotine extract	6%	6%	6%	Anti-arthritic, anti-inflammatory
3	Methyl salicylate	2.5 ml	2.5 ml	2.5 ml	Anti-inflammatory, analgesic
4	Ginger powder	0.2 gm	0.2 gm	0.2 gm	Anti-inflammatory
5	Camphor	0.2 gm	0.2 gm	0.2 gm	Anti-inflammatory, analgesic
6	Oleic acid	2.5 ml	2.5 ml	2.5 ml	Permeation enhancer
7	Aloe vera gel	0.5 gm	0.5 gm	0.5 gm	Permeation enhancer
8	HPMC	2 gm	1.5 gm	1 gm	Polymer
9	PVP	2 gm	1.5 gm	1 gm	Polymer
10	Water	10 ml	10 ml	10 ml	Solvent
11	Ethanol	10 ml	10 ml	10 ml	Solvent

Figure 9: Combination of ingredients

2.4 EVALUATION OF TRANSDERMAL PATCHES

1. Physical Appearance and Sensitivity test:

All the formulated patches were examined visually to assess their colour, clarity, presence of air bubbles, flexibility, surface smoothness and sensitivity and irritation [19].

2. Thickness:

The thickness of each patch was determined using a screw gauge at five distinct points on the patch, and the average value was then calculated [20,21].

Figure 10: Screw gauge

3. Weight Variation:

Patches with a radius of 2 cm were cut. The weights of five individual patches were measured, and the weight variation was calculated [20].

Figure 11: Analytical balance

4. Flatness:

Longitudinal strips were cut from each formulation patch—one from the centre and one from the edge. The length of each strip was measured to assess variation due to non-uniform flatness. A 0% constriction was considered as indicating 100% flatness. Flatness was then calculated using the specified formula [19].

$$\%\text{Constriction} = \frac{\text{Initial length of each strip} - \text{Cutted film length}}{\text{Cutted film length}} \times 100$$

5. Folding endurance:

Folding endurance was evaluated by repeatedly folding a small strip of the patch approximately 2 × 2 cm at the same spot until it broke. The number of times the patch could be folded at the same location without breaking was noted as the folding endurance value [19].

6. Percentage moisture content:

The prepared transdermal films were individually weighed and placed in a desiccator containing fused calcium chloride at room temperature for 24 hours. After the 24-hour period, the films were reweighed, and the percentage moisture content was calculated using the following formula [21].

$$\text{Percentage Moisture Content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Figure 12: Dessicator

3. RESULTS OF PATCH EVALUATION

1. Physical Appearance:

All patches were clear, smooth, uniform, flexible, and yellowish-green in colour. No air bubbles or surface imperfections were observed. Also no irritation or skin sensitivity reaction was observed.

Figure 13: Herbal patch applied on volunteer's hand and leg

2. Thickness:

The thickness of the formulated patches was found to be in the range of 0.138± 0.006 to 0.152± 0.007 mm, indicating good uniformity across all batches with minimal variation.

3. Weight Variation:

The weight of the transdermal patches ranged from 750±0.002 to 950± 0.001 mg, showing slight variation among the formulations, which may be due to differences in polymer and active ingredient concentrations.

4. Flatness:

All formulated patches showed 100% flatness, indicating no visible folds or constrictions, and confirmi

ng uniform surface and flexibility.

5. Folding endurance:

The folding endurance of the patches ranged from approximately 111± 2.6 to 125± 2.6 folds, indicating satisfactory mechanical strength and flexibility across all formulations.

6. Percentage moisture content:

The moisture content of the patches ranged from 4.99% to 7.05%, falling within the ideal range of 2–10% for transdermal drug delivery systems. F3 exhibited 7.05% moisture content, which contributed to enhanced flexibility and potential drug permeation without compromising physical stability.

Table 2: Evaluation of transdermal patches

Formulation	Thickness (mm) ± S.D	Weight variation (mg) ±S.D	Flatness (%)	Folding endurance ± S.D	Percentage moisture content ± S.D
F1	0.152 ± 0.007	950± 0.001	100	125± 2.6	4.99 ± 0.221
F2	0.143 ± 0.005	830±0.001	100	117± 2.7	6.32 ± 0.300
F3	0.138 ± 0.006	750±0.002	100	111± 2.6	7.05 ± 0.427

All patches were clear, smooth, yellowish-green, flexible, and showed no irritation. Thickness varied between 0.138 mm to 0.152 mm, with minimal weight variation. All patches showed 100% flatness and adequate folding endurance (111–125 folds). Moisture content ranged from 4.99% to 7.05%, with F3 being the most flexible.

4. PATIENT SURVEY ON RA EXPERIENCE AND TREATMENT:

A structured online survey was conducted to gather real-world insights into the experiences, treatment patterns, and challenges faced by patients with Rheumatoid Arthritis (RA). It included both multiple-choice and open-ended questions covering disease history, medication use, lifestyle impact, and pain management. The primary objective was to assess awareness of RA, current treatments, and the willingness of patients to try herbal transdermal patches.

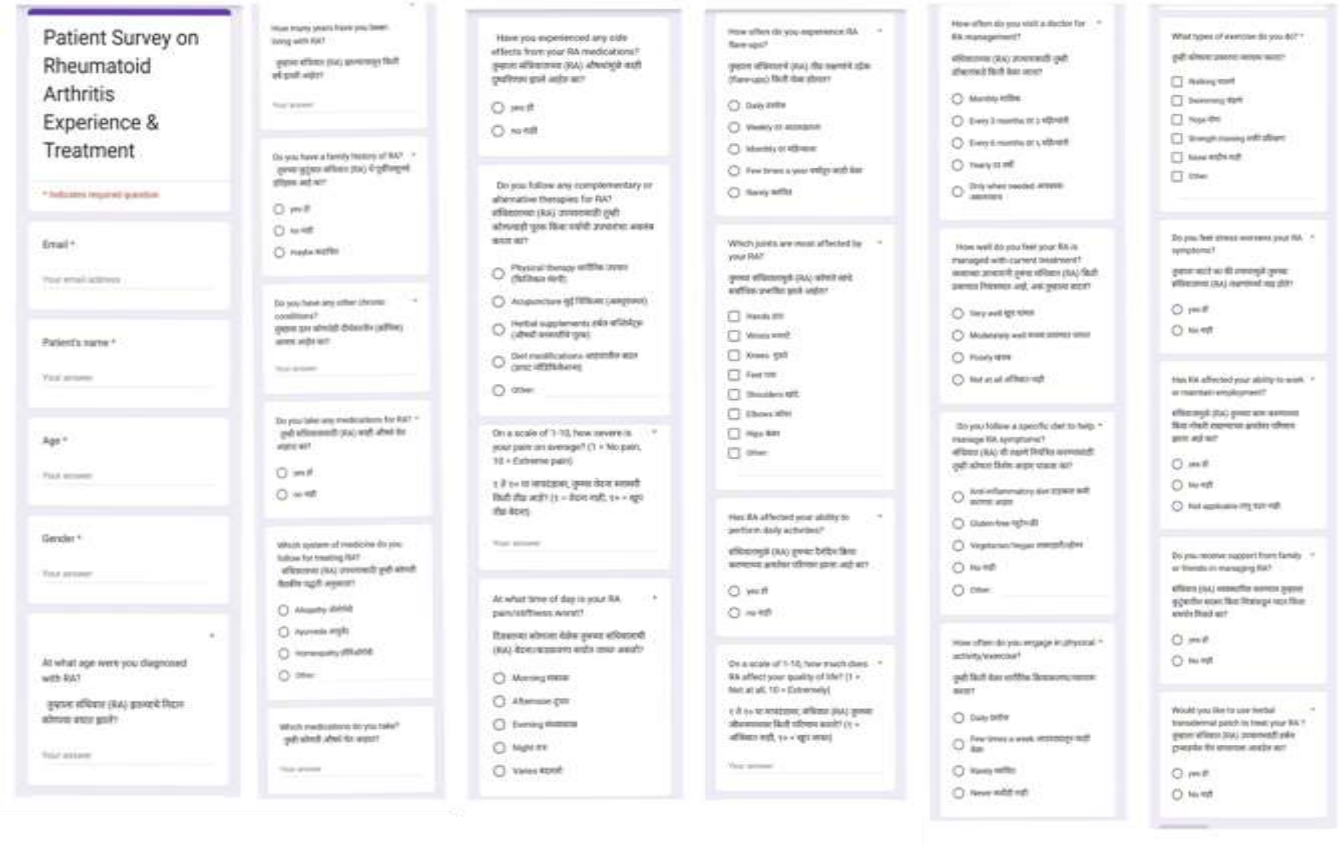

Figure 14: Sample Questionnaire

5. PATIENT SURVEY RESULTS AND DISCUSSION

Table 3: Survey results

Question	Options	Percentage (%) / Number of Responses
Do you have a family history of RA?	Yes / No / Maybe	43.3% Yes, 43.3% No, 13.3% Maybe
Do you take any medications for RA?	Yes / No	86.7% Yes, 13.3% No
Which system of medicine do you follow for treating RA?	Allopathy / Ayurveda / Homeopathy / Others	30% Allopathy, 40% Ayurveda, 23.3% Homeopathy, 6.6% Others
Have you experienced any side effects from your RA medications?	Yes / No	13.3% Yes, 86.7% No
Do you follow any complementary or alternative therapies for RA?	Physical therapy / Acupuncture / Herbal supplements / Diet modifications / Others	33.3% Physical therapy, 23.3% Acupuncture, 16.7% Herbal supplements, 16.7% Diet modifications, 9.9% Others
At what time of day is your RA pain/stiffness worst?	Morning / Afternoon / Evening / Night / Varies	36.7% Morning, 0% Afternoon, 13.3% Evening, 30% Night, 20% Varies
How often do you experience	Daily / Weekly / Monthly /	16.7% Daily, 23.3% Weekly, 13.3%

RA flare-ups?	Few times a year / Rarely	Monthly, 30% Few times a year, 16.7% Rarely
Which joints are most affected by your RA?	Hands / Wrists / Knees / Feet / Shoulders / Elbows / Hips / Others	3.3% Hands, 33.3%Wrists, 60% Knees, 43.3% Feet, 33.3% Shoulders, 13.3% Elbows, 30% Hips, 0% Others
Has RA affected your ability to perform daily activities?	Yes / No	66.7% Yes, 33.3% No
How often do you visit a doctor for RA management?	Monthly / Every 3 months / Every 6 months / Yearly / Only when needed	10% Monthly, 20%Every 3 months, 26.7% Every 6 months, 0% Yearly, 43.3%Only when needed
How well do you feel your RA is managed with current treatment?	Very well / Moderately well / Poorly / Not at all	26.7% Very well, 70% Moderately well, 3.3% Poorly, 0% Not at all
Do you follow a specific diet to help manage RA symptoms?	Anti-inflammatory diet / Gluten-free / Vegetarian or vegan / No / Other	3.3% Anti-inflammatory diet, 0% Gluten-free, 16.7% Vegetarian or vegan, 80% No, 0% Other
How often do you engage in physical activity/exercise?	Daily / Few times a week / Rarely / Never	66.7% Daily, 33.3% Few times a week, 0% Rarely, 0% Never
What types of exercise do you do?	Walking / Swimming / Yoga / Strength training / None / Other	90% Walking, 3.3% Swimming, 60% Yoga, 0% Strength training, 0% None, 0% Other
Do you feel stress worsens your RA symptoms?	Yes / No	73.3% Yes, 26.7% No
Has RA affected your ability to work or maintain employment?	Yes / No / Not applicable	36.7% Yes, 13.3% No, 50% Not applicable
Do you receive support from family or friends in managing RA?	Yes / No	100% Yes, 0% No
Would you like to use herbal transdermal patch to treat your RA?	Yes / No	100% Yes, 0% No

The Rheumatoid Arthritis (RA) survey included participants aged 38 to 65, with a higher number of female respondents. Most were diagnosed in their late 30s to early 50s and had been living with RA for 2 to 35 years. While some reported a family history of RA, others were either unsure or denied it. A majority did not have other chronic conditions, though a few reported diabetes, hypertension, or hyperthyroidism.

Most participants were undergoing treatment for RA, with doctor visits ranging from monthly to only when needed. Many felt their condition was well- or moderately well-managed. Dietary habits varied, with some following vegetarian or vegan diets, while others had no specific dietary routine. Regular physical activity, particularly walking and yoga, was common. Stress was widely recognized as a trigger for worsening symptoms.

The impact of RA on employment varied—some faced limitations, while others reported no significant effect. Notably, all respondents had family or social support. A key finding was unanimous interest in trying a herbal transdermal patch, indicating strong openness to alternative, plant-based treatment options with potentially fewer side effects.

6. CONCLUSION

The developed herbal transdermal patch exhibited desirable physicochemical properties. The combination of eucalyptus oil, camphor, ginger, methyl salicylate, and nicotine contributed synergistically to its anti-inflammatory activity. Survey results reinforced the need for alternative herbal-based treatments. Further in-vitro and in-vivo studies are needed to confirm efficacy.

REFERENCES

1. V.C. Romão, J.E. Fonseca, "Etiology and risk factors for rheumatoid arthritis: A state-of-the-art review", Frontiers in Medicine, 2021, 8, 689698. https://doi.org/10.3389/fmed.2021.689698
2. H.U. Scherer, T. Haupl, G.R. Burmester, "The etiology of rheumatoid arthritis", Journal of Autoimmunity, 2020, 110, 102400. https://doi.org/10.1016/j.jaut.2019.102400
3. R.S. Nithyashree, R. Deveswaran, "A comprehensive review on rheumatoid arthritis", Journal of Pharmaceutical Research International, 2020, 32 (12), 18–32. https://doi.org/10.9734/jpri/2020/v32i1230541
4. M.M.F.A. Baig, C.H. Kwan, H. Wu, S.Y. Chair, "The etiology, pathogenesis, treatment, and development of transdermal drug delivery systems for rheumatoid arthritis", RSC Pharmaceutics, 2024. https://doi.org/10.1039/d4pm00085d
5. B.N. Lindler, K.E. Long, N.A. Taylor, W. Lei, "Use of herbal medications for treatment of osteoarthritis and rheumatoid arthritis", Medicines, 2020, 7 (7), 67. https://doi.org/10.3390/medicines7110067
6. B. Khare, T.P. Shukla, "A review on polyherbal formulation used in the treatment of rheumatoid arthritis", Journal of Advanced Scientific Research, 2022, 13 (1), 31–42. https://doi.org/10.55218/JASR.202213103
7. S. Mishra, P. Verma, S.K. Gupta, S. Pandey, S. Ojha, "Nanocarrier and herbal based transdermal patch: An advantage over other drug delivery systems", Annals Ayurvedic Medicine, 2022, 11 (2), 145–156. https://doi.org/10.5455/AAM.11486
8. M. Mahajan, V. Vaidya, P. Farande, S. Bhagde, R. Jadhav, "Review on essential oils and ways to use them for the treatment of arthritis", Biosciences Biotechnology Research Asia, 2023, 20 (4), 1181–1194. https://doi.org/10.13005/bbra/3167
9. B. Arooj, S. Asghar, M. Saleem, S.H. Khalid, M. Asif, T. Chohan, I.U. Khan, H.M. Zubair, H.S. Yaseen, "Anti-inflammatory mechanisms of eucalyptol-rich Eucalyptus globulus essential oil alone and in combination with flurbiprofen", Inflammopharmacology, 2023, 31, 1849–1862. https://doi.org/10.1007/s10787-023-01237-6
10. W. Zhang, X. Pan, J. Fu, W. Cheng, H. Lin, W. Zhang, Z. Huang, "Phytochemicals derived from Nicotiana tabacum L. plant contribute to pharmaceutical development", Frontiers in Pharmacology, 2024, 15, 1372456. https://doi.org/10.3389/fphar.2024.1372456
11. C. Laszlo, K. Kaminski, H. Guan, M. Fatarova, J. Wei, A. Bergounioux, W.K. Schlage, S. Schorderet-Weber, P.A. Guy, N.V. Ivanov, K. Lamottke, J. Hoeng, "Fractionation and extraction

optimization of potentially valuable compounds and their profiling in six varieties of two Nicotiana species", Molecules, 2022, 27, 8105. https://doi.org/10.3390/molecules27228105

12. B.O. Udoye, S.I. Okeke, "Phytochemical properties, pharmacological activities, and ethnomedicinal uses of Nicotiana tabacum L.: A comprehensive review", International Journal of Applied Science Research, 2021, 1.
13. P. Michel, M.A. Olszewska, "Phytochemistry and biological profile of Gaultheria procumbens L. and wintergreen essential oil: From traditional application to molecular mechanisms and therapeutic targets", International Journal of Molecular Sciences, 2024, 25, 565. https://doi.org/10.3390/ijms25010565
14. N. Versteeg, V. Wellauer, S. Wittenwiler, D. Aerenhouts, P. Clarys, R. Clijsen, "Short-term cutaneous vasodilatory and thermosensory effects of topical methyl salicylate", Frontiers in Physiology, 2024, 15, 1347196. https://doi.org/10.3389/fphys.2024.1347196
15. T. Jurca, L. Jozsa, R. Suciu, A. Pallag, E. Marian, I. Bacskay, M. Muresan, R.L. Stan, M. Cevei, F. Cioara, L. Vicas, P. Feher, "Formulation of topical dosage forms containing synthetic and natural anti-inflammatory agents for the treatment of rheumatoid arthritis", Molecules, 2021, 26 (24), Article 24. https://doi.org/10.3390/molecules26010024
16. R. Kiyama, "Nutritional implications of ginger: Chemistry, biological activities, and signaling pathways", Journal of Nutritional Biochemistry, 2020, 86, 108486. https://doi.org/10.1016/j.jnutbio.2020.108486
17. M.J.A. Fazmiya, A. Sultana, K. Rahman, M.B.B. Heyat, F. Sumbul, F. Akhtar, S. Khan, S.C.Y. Appiah, "Current insights on bioactive molecules, antioxidant, anti-inflammatory, and other pharmacological activities of Cinnamomum camphora Linn", Oxidative Medicine and Cellular Longevity, 2022, Article ID 9354555, 23 pages. https://doi.org/10.1155/2022/9354555
18. R.B. Malabadi, K.P. Kolkar, N.T. Meti, R.K. Chalannavar, "An age-old botanical weapon for herbal therapy: Cinnamomum camphora", International Journal of Innovation Scientific Research and Review, 2021, 3 (7), 1518–1523.
19. D. Trivedi, A. Goyal, "Formulation and evaluation of transdermal patches containing dexketoprofen trometamol", International Journal of Pharmaceutical Chemistry and Analysis, 2020, 7 (2), 87–97. https://doi.org/10.18231/j.ijpca.2020.014
20. P. Kriplani, A. Sharma, Aman, P. Pun, B. Chopra, A. Dhingra, G. Deswal, "Formulation and evaluation of transdermal patch of diclofenac sodium", Global Journal of Pharmacy and Pharmaceutical Sciences, 2018, 4 (4), 555647. https://doi.org/10.19080/GJPPS.2018.04.555647
21. M.R. Shivalingam, A. Balasubramanian, K. Ramalingam, "Formulation and evaluation of transdermal patches of pantoprazole sodium", International Journal of Applied Pharmaceutics, 2021, 13 (5), 287–291. https://doi.org/10.22159/ijap.2021v13i5.42175