Original Article

TIPS Trends in Pharmaceutical Sciences 2023: 9(4): 261-270.

Design of a cinnamon essential oil cream-based formulation as an analgesic for headache topical management

Fateme Gholami[1,2,3];PharmD$_{student}$, Zahra Sobhani[4];PhD, Mohammad M. Zarshenas[1,2];PhD

[1]Medicinal Plants Processing Research Center, Shiraz University of Medical Sciences, Shiraz, Iran
[2]Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Student Research Committee, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran
[4]Department of Quality Control, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

Abstract

Headache is one of the most common types of pain that approximately every individual experiences at some point in their life. Due to unknown pathophysiology, identification of the exact origin and causes of headache are challenging. Headache is a chronic condition that disturbs a person's life. Various intervention such as including medication, massage therapy, aromatherapy, and herbal treatments are used to alleviate headaches. Medication is administered orally, intranasally, via injection, or topically through skin absorption. Traditional Persian medicine (TPM) introduces various herbal remedies to manage headaches. Cinnamon (*Cinnamomum verum* J.Presl), belongs to Lauraceae family, mentioned for the alleviation of headaches in TPM. Accordingly, current study was carried out to design and prepare a new topical herbal dosage form from Cinnamon essential oil. Following essential oil extraction, volatile constituents were analyzed via a Gas chromatography/Mass spectroscopy (GC/MS). Cinnamaldehyde was found as the major compound. Subsequently, appropriate amounts of the oil were subjected to cream formulations to check the pharmaceutical parameters. The final preparation underwent evaluations, including macroscopic and microscopic tests for odor, color, appearance, phase separation, as well as pH, rheology, centrifugation, microbial limits, and texture analysis. Finally, based on the quantification via GC, cinnamaldehyde was determined as 3982.68±116.04 µg in a 50 mg tube of 2.5% of the cinnamon bark essential oil. This investigation can be introduced to be examined as an herbal topical medication in the management of headache and cephalic pain.

Keywords: Headache, Cinnamon, Formulation, Cinnamaldehyde, Essential oil

Please cite this article as: Gholami F, Sobhani Z, Zarshnas M.M*. Design of a cinnamon essential oil cream-based formulation as an analgesic for headache topical management. Trends in Pharmaceutical Sciences. 2023;9(4):261-270. doi: 10.30476/TIPS.2024.100592.1219

1. Introduction

Headache has been documented throughout the history of mankind, with evidence of treatments dating back to 9000 years ago, as seen in the trepanation of Neolithic skulls (1). The pathophysiology of headache remains unknown, leading to challenges in identifying the precise cause of exacerbation of pain in some cases (2). Although common headaches like migraines and cluster headaches can often be managed, they may significantly impact a person's daily life (3). Headache disorders ranked sixth among the leading causes of years lived with disability (YLDs) globally (4, 5). According to the international classification of headache disorders (ICHD), two main types as primary and secondary are introduced. Primary headaches, such as migraines, cluster headaches,

Corresponding Author: Mohammad M. Zarshenas, Department of Phytopharmaceuticals (Traditional Pharmacy), School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran. Email: zarm@sums.ac.ir

Received: 22/10/2023; Accepted: 01/12/2023

and tension type, are very common. Conversely, secondary types are associated with trauma and brain-related conditions. In certain types of headaches, pharmacotherapy may not be necessary, but in most cases, it can lead to drug overuse (6). Drug-induced headache, also known as Medication-overuse headache (MOH), is linked to over us of various types of drugs (7). Due to the side effects and limited effectiveness of drugs, people often seek non-pharmacological treatments, such as plant-based remedies (8).

The rout of drug administration can significantly impact both side effect and efficacy. Oral administration may cause gastrointestinal side effects, posing challenges for patients with gastrointestinal issues. Nasal and subcutaneous routes face difficulties due to their low bioavailability. An alternative approach for headache treatments is topical application, which can be applied to the forehead or temples. This rout avoids gastrointestinal issues and is easily applicable, making it more acceptable to patient. Moreover, it can be formulated as controlled or sustained-release drug (9). Examination of traditional Persian medicine (TPM) by referencing various original significant treatises, including The Liber Continents by Rhazes (9th and 10th centuries), The Canon of Medicine by Avicenna (10th and 11th centuries), and The Storehouse of Medicaments (Makhzan ol Advieh) by ʻAqīlī ʻAlavī Shīrāzī (18th century) revealed that Cinnamomum verum J.Presl from the Lauraceae family, known as "Darchin" in Persian language can be used as a treatment for a type of headache, which is called "cold" in TPM (10). Certain TPM headaches are associated with weather situations, fasting, alcohol consumption, and more (11). Cold headaches can be triggered by exposure to cold weather or consumption foods with a cold "mezaj", or temperament, a TPM term. TPM suggest using cinnamon topically on the forehead or temples to alleviate headaches (12, 13). Additionally, it is reported that cinnamon oil can be used for headache relief through oral therapy (12).

In this study, based on both pharmaceutical and medical manuscripts of TPM and modern pharmaceutical techniques, cinnamon essential oil with an adjusted dose was subjected and utilized to a topical cream to subsequently be introduced as an intervention for headache and cephalic pain.

2. Material & Methods

2.1. Manuscripts review and Plants authentication

To design a cream formulation based on TPM, we conducted a thorough review of the traditional pharmaceutical encyclopedia (*makhzan aladviye*) using precise keywords: "*soda*" and "sardard". Subsequently, investigation was performed for relevant papers in PubMed, Google Scholar, and SID databases. Taken as a whole, the cinnamon bark was selected due to the wide-ranging classification in TPM for the management of headaches. The purchased sample of cinnamon bark was authenticated and assigned a specific voucher number (PM1208) at the Pharmacy Herbarium of Department of Phytopharmaceuticals, School of Pharmacy, Shiraz University of Medical Sciences.

2.2. Essential oil preparation

Based on the procedure of oil extraction of Cinnamon, rose water was considered instead of distilled water for distillation and essential oil extraction via a Clevenger-type apparatus (10). The essential oil obtained was a mixture of water and essential oil, necessitating the addition of a small amount of sodium sulphate powder to facilitate the separation of oil and water phases. The dried essential oil was then collected in amber glass tube for further analysis.

2.3. Gas chromatography/ Mass spectroscopy

We conducted GC/MS analysis on the yielded essential oil samples using Agilent technologies model 7890A gas chromatograph attached (column; HP-5MS, 25mm, 30 mm) connected to a US Agilent technology mass spectrometer (MS). Helium was selected as the carrier gas with a flow rate of 1 ml/min with a split ratio of 1:100. The injector temperature was 250°C, while column temperature was linearly programmed from 60 to 220°C (rate of 5°C/min) and then held for 10 min at 220°C. The applied voltage was 70 EV and its interface temperature was set at 280 °C. The mass range was set at 30-600 m/z. To prepare the GC fingerprint and determine the frequency of components, first with multiple injections into GC, the best injection method in which the peaks of the compounds were separated was selected and then sample was injected into the device and the final profile of the compounds was analyzed (14).

The compounds were identified using the nl7 library, Adams' textbook and Kovats retention index calculations, compared with previous studies. The Kovats index and mass spectra obtained from the device were the criteria for the diagnosis and identification of compounds.

2.4. Cream preparation and pharmaceutical evaluations

As a foundation, a basic cold cream was designed and adjusted the ingredients as an optimal formulation. phosphate buffer was employed for pH regulation to achieve compatibility with human skin. After routine topical formulation assays (15), various pharmaceutical evaluations including pH, stability (16), rheology (17), centrifugation (15), texture analysis (18) and microbial limits (15) were performed to reach to the final step.

2.5. Determination of specific marker amount in the final cream (cinnamaldehyde)

To quantitatively determine the cinnamaldehyde in the final cream, essential oil was extracted from final cream formulation using the hydrodistillation method with Clevenger-type apparatus. The extracted essential oil was then prepared for injection into GC/FID apparatus after the dehydration process with sodium sulphate (14).

2.6. Content determination via Gas chromatography/flame ionization detector (GC/FID)

Agilent technology US 7890A GC/FID was utilized for content determination and standardization of the product based on the major volatile component. The carrier gas was nitrogen with a flow rate of 1 ml/min. Since the device had an FID detector, it needed two hydrogen and oxygen gases that gave it the best flame at the ratio of 1 to 10. We use split mode (1/50) and 1 µl of the sample was injected into the device. The temperature of the injection chamber was 270°C and the used column was HP-5 (30m, 320 mm). The stationary phase was phenyl methyl siloxane with a diameter of 0.25 µm. The column temperature was set at 60 °C. The sample was kept at this temperature for 2 minutes, then increasing the temperature to 6 °C every minute until it reached 250 °C, and held at this temperature for 10 minutes. The temperature of the detector was also set at 300 °C. We employed cinnamaldehyde with 99% purity (Analytical Standard grade, Sigma Aldrich). Different concentrations (116/5, 325, 750, 1500, 3000, and 6000 µg/ml) were prepared by sequential dilution using dichloromethane. To check the reproducibility, 3 injections were performed for each standard and the standard curve was plotted by mean of three injections for each standard. For the essential oil of the final formulation, the mean of three injections was considered as the sample concentration. Method validation involved injections a concentration of 9000 µg/ml for 3 different days, 3 times daily to calculate Intra- and inter-day differences and Relative Standard Deviation (RSD). The Limit of Detection and the Limit of Quantification (LOQ) were also determined for each marker (14). The essential oil of the final formulation was injected into GC/FID three times to determine the markers.

3. Results

3.1.Results of pharmacognosy evaluations

3.1.1. Various analysis such as GC/MS and GC/FID were determined.

3.1.1.1. Essential oil yield

The amount Essential oil extracted from 250 g of cinnamon bark powder using a Clevenger apparatus for 3 hours, was 3.5 ml, resulting in a yield of 1.4% V/W (volume per weight). Furthermore, the amount of Essential oil extracted from 50 g final cream formulation (with 2.5% essential oil) using a Clevenger apparatus for 3 hours, was 0.75 ml, leading to yield of 60%.

3.2. GC/MS analysis of the essential oil sample

The chromatogram obtained from GC/MS spectroscopy revealed the chemical constituents present in the essential oil samples, which are detailed in table1.

3.3. Result of pharmaceutical tests

Quality and quantity control tests such as change in physical characteristics, centrifuge, pH, rheology, texture analysis and microbial limit were determined.

3.4. Quality attributes assessment

The change in odor, color, spreadability and feelability on the skin, centrifuge, and also thermal stability have been examined during 1 and 6 months after the final product manufactur-

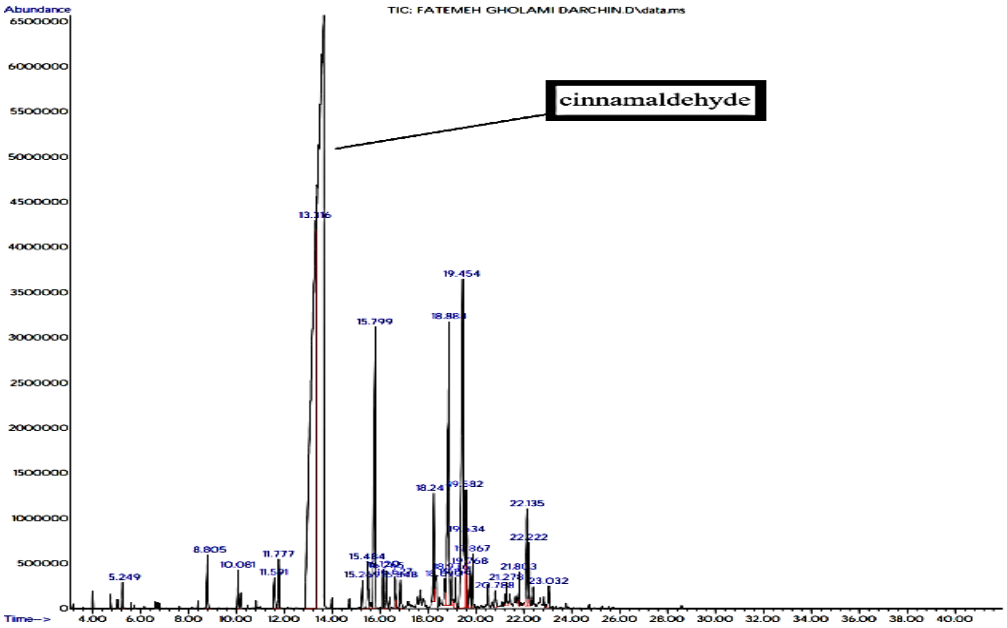

Figure 1. Chromatogram results of essential oil.

ing date. The result indicated the stability of final product.

3.5. pH measurement

The pH of the final formulation remained approximately 6 in different thermal conditions. and after 1 and 6 months from the manufacturing date, demonstrating compatibility with the skin's pH value.

Table 1. Chemical constituents of essential oil (Cinnamaldehyde as the major component).

Number	Component	Retention Time	Area %	KI	MS-KI	Ref.
1	Benzaldehyde	5.249	0.45	960.949	960.8	(19)
2	Phenylethyl Alcohol	8.805	1.25	1116.040	116.0	(20)
3	3-Phenylpropanal	10.081	0.85	1165.004	1163.0	(21)
4	3-Phenylacrylaldehyde	11.591	1.03	1222.703	1222.0	(22)
5	Citronellol	11.777	1.15	1229.765	1229.0	(23)
6	Cinnamaldehyde	13.316	**42.58**	1288.193	1283.0	(24)
7	3-Allyl-6-methoxyphenol	15.269	0.61	1363.866	1362.0	(25)
8	Cycloisosativene	15.484	1.2	1372.229	1371.0	(22)
9	α-Copaene	15.799	8.1	1384.481	1384. 0	(22)
10	1,4-Methano-1H-indene	16.12	1.52	1396.966	1396.3	(26)
11	Isosativene	16.627	0.62	1417.439	1417.6	(22)
12	trans-Caryophyllene	16.848	0.8	1426.423	1426.0	(27)
13	α-Muurolene	18.247	12.92	1483.293	1483.0	(28)
14	δ-cadinene	19.454	12.91	1533.815	1533.0	(29)
15	trans-Cadina-1,4-diene	19.634	1.1	1541.461	1540. 0	(30)
16	β-Bisabolene	19.768	1.07	1547.154	1547.0	(31)
17	α-Calacorene	19.867	0.98	1551.359	1550. 0	(32)
18	α-Cadinol	22.135	2.55	1650.291	1650. 0	(33)
19	Levomenol	23.032	0.47	1690.461	1690. 0	(34)
Identification		92.16				

Table 2. Texture analysis data of final formulation at different thermal situation over time changes

samples	Hardness (g)	Deformation at hardness (%)	Load at target (g)	Peak stress (dyn/cm2)	Hardness work (mj)
First day	87±19/4	11/2±0/22	87±19/4	16837/6±3420/1	1/86±0/2
Stored at 25ºC for 1 month	72/3±13/8	11/16±0/19	72/3±13/8	13999/1±2731/0	1/63±0/2
Stored at 25ºC for 6 months	95±14/9	11/06±0/22	95±14/9	18385/9±2966/7	1/9±0/3
Stored at 4ºC for1 month	70±1/6	11/23±0/11	70±1/6	13547/5±290/1	1/7±0/0
Stored at 4ºC for 6 months	60±6/5	11/33±0/04	60±6/5	11612/1±1112/2	1/33±0/1
Stored at -20ºC for 1 month	124/6±31/2	11/36±0/04	124/6±31/2	24127/4±6141/9	2/13±0/4
Stored at -20ºC for 6 months	96.3±22/8	11/2±0/20	96.3±22/8	22127/5±8021/6	1/9±0/4
Stored at 40ºC for 1 month	67±15/5	11/33±0/05	67±15/59	12966/9±3105/2	1/33±0/2
Stored at 40ºC for 6 months	99±21/9	11/2±0/50	99±21/92	19160±4185/6	1/86±0/4

3.6. Rheology test

The rheogram of final formulation was plotted by Brookfield R/S-CPS+ cone & plate rheometer, indicating that the final formulation is a non-Newtonian, plastic system with thixotropic characteristic. The average viscosity is 2/507 pa. moreover, the thixotropy index is 33689/954 pa/s.

3.7. Texture analysis

Texture analyses was conducted using Brookfield CT3 texture analyzer with Texture Profile Analysis (TPA) state. Texture analyses of final formulation was determined in different thermal conditions after 1 and 6 months of its manufacturing date. Each sample has been tested 3 times and result is presented as mean ± standard deviation in table2.

Hardness results aligned with the load at target. Thus, the samples stored at -20ºC, have the highest level of hardness, that shows the firmness of sample (35).

Strain at peak load number was consistent across all samples (approximately 0/11). Accordingly, the higher peak stress numbers show the higher viscosity of samples. Therefore, the samples stored in -20ºC, have higher viscosity in comparison with other samples.

Hardness work number provided insight into spreadability of the cream during penetration on skin. Consequently, the samples stored in -20ºC, have lowest spreadability on skin (35).

Deformation at hardness number demonstrated the deformation of formulation when the probe touches the sample's surface. Considering that, the result indicated consistent deformation of all samples, reflecting stability and minimal deformation across different thermal situation over time.

3.8. Microbial limit tests

The microbial tests on the final formulation yielded satisfactory results, with no fungus growth on Yeast extract glucose chloramphenicol agar (YGC agar) and a low total bacteria count on Triple soy agar (TSA agar). This signifies the microbial safety and quality of the formulated cream,

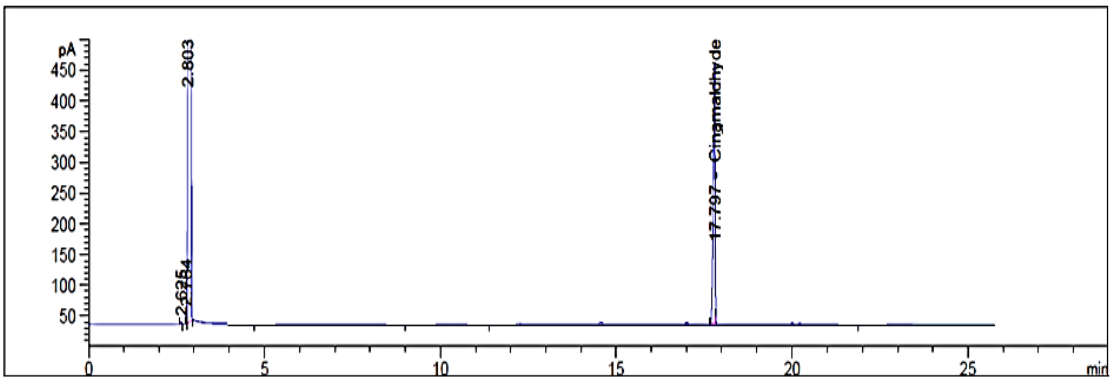

Figure 2. Standard cinnamaldehyde peak in GC/FID chromatogram.

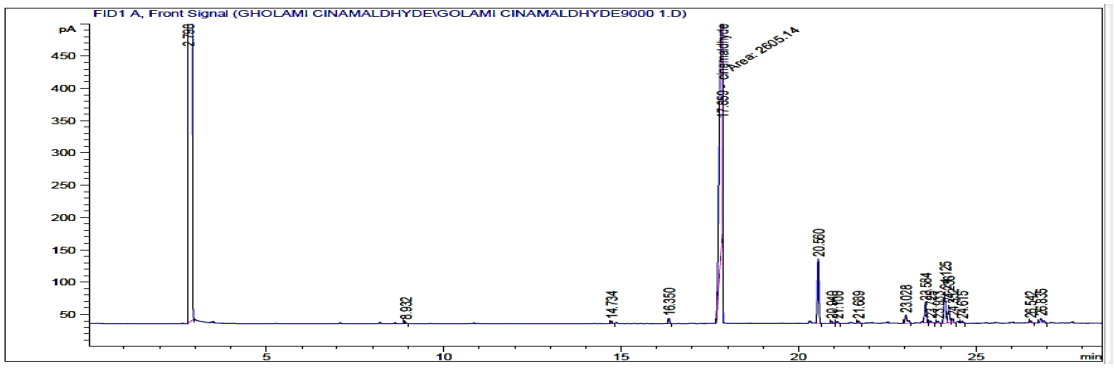

Figure 3. GC/FID chromatogram of essential oil extracted from final formulation

supporting its suitability for use.

3.9. GC/FID-based quantification of cinnamaldehyde in the final product

Following the analysis of GC/MS data, it was determined that the main volatile compound in the essential oil was cinnamaldehyde. The temperature program used for the essential oil and the standard cinnamaldehyde assessments by GC/FID closely resembled that of the GC/MS analysis. To determine the cinnamaldehyde content, stock and subsequent serial dilutions were prepared using cinnamaldehyde standard at concentration of 116.5, 325, 750, 1500, 3000 and 6000 µg/ml. Calibration curve was plotted using the standards, and linearity parameter was observed. Figures 2 and 3 illustrated a Comparison of the cinnamaldehyde presence in the final formulation samples with the standard sample. All pertinent data related to the determination of the marker is presented in table 3, and the respective calibration curve is depicted in Figure 4.

4. Discussion and Conclusion

The objective of this study was to develop a plant-based formulation derived from traditional Persian medicine (TPM) manuscripts known for their headache healing properties. Cinnamon bark was chosen because of its great headache healing effect, which is mentioned in TPM manuscripts. Thus, the essential oil was extracted to add to a formulation. Analytical outcomes included the fingerprint of constituents and the essential oil, GC/MS data, content determination of the final

Table 3. Cinnamaldehyde content in the pure essence of the final formulation.

No.	Area (%)	Product (µg/ml)	Mean± SD (µg/ml)	RSD (%)	LOD (µg/ml)	LOQ (µg/ml)
1	2605.14	5148.59	5310.24 ±154.72	2.91	0.039	0.119
2	2692.93	5456.96				
3	2758.45	5325.17				

RSD: Relative Standard Deviation; SD: Standard Deviation; LOD: Limit of Detection; LOQ: Limit of Quantification.

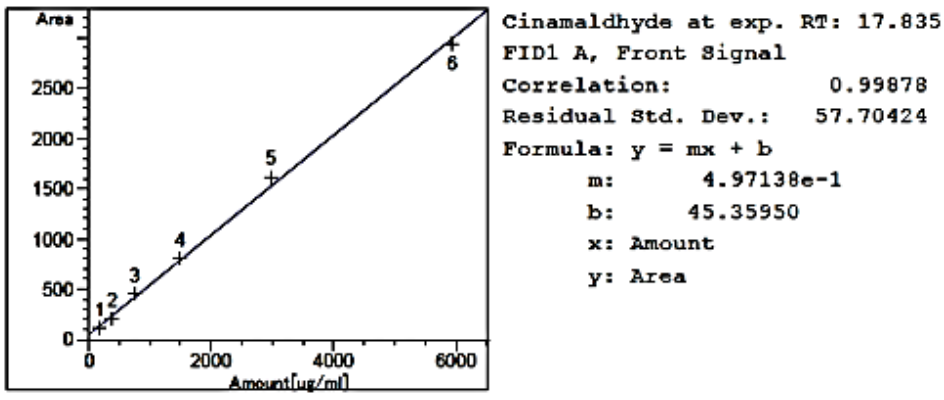

Figure 4. Standard cinnamaldehyde calibration curve.

formulation via GC/FID, and spectrophotometry. The analysis revealed that cinnamaldehyde was the predominant component in the essential oil, constituting approximately 42.58% of the total components. Based on other studies on cinnamon essential oil by GC/MS trans-Cinnamaldehyde, is principal component of cinnamon flavor, and is a potent antimicrobial compound present in essential oils (36). cinnamaldehyde have attracted lots of interest for its bioactivities, especially its anti-inflammatory property. Cinnamaldehyde has the potential, as therapeutic agents (37). Cinnamaldehyde has remarkable analgesic and anti-inflammatory effects (38, 39). Also, Due to a research about evaluation of the analgesic effects of hydroalcoholic extract of *Cinnamomum* in rats by using plantar test the analgesic effect of *Cinnamomum* extract, was confirmed (40). Considering these, cinnamon essential oil can be used to gain a formulation with potent bioactivity and favorable druggability. Through meticulous formulation design, control, and standardization, a novel cream formulation was successfully developed. The study involved testing 19 different pharmaceutical formulations using various excipients for cream preparation. The optimal formulation, contains 2.5% *cinnamon* bark essence, 10% beeswax and 58.5% liquid paraffin as oil phase. Also, 2% borax and 26.89% phosphate buffer as water phase, which has been added to oil phase after both phases warmed up to 70ºc. consequently, 0/1% methyl paraben and 0.01% propyl paraben were added as a preservative agent.

Accordingly, pharmaceutical tests were crucial to stablish the stability and effectiveness of the final formulation. Visual qualities were evaluated over 1 month and 6 month, followed by assessments of pH, texture analysis, rheology and microbial limits, all of which confirmed the acceptability and pharmaceutical quality of the final formulation.

Given the nature of the materials and herb used in the final formulation, it was essential to prepare a specific fingerprints for identification purposes. Chromatographic fingerprinting, a comprehensive identification method, was employed to study the phytochemical information of the herbal medicine. Analyzing major constituents and active ingredients through chromatograms and analytical methods facilitated accurate identification and determination. The study successfully developed a cream formulation based on traditional pharmaceutical manuscripts of Persian medicine known for their headache healing effects.

The total amount of cinnamaldehyde in 1 milliliter of the essential oil was calculated amount of 5310.54 ± 24.72 micrograms, and the final product contained a calculated amount of 3982.68±116.04 micrograms of cinnamaldehyde in a 50g weight, accounting for 2.5% of the essential oil. These findings further support the development of a novel formulation derived from traditional Persian medicine for headache relief.

Acknowledgment

Authors of this manuscript wish to express their appreciation to Shiraz University of Medical Sciences (Project No: 26747).

Conflict of Interest

The authors declare no conflict of interest.

References

1. Assina R, Sarris CE, Mammis A. The history of craniotomy for headache treatment. *Neurosurg Focus.* 2014 Apr;36(4):E9. doi: 10.3171/2014.1.FOCUS13549. PMID: 24684340.

2. Gee JR, Ishaq Y, Vijayan N. Postcraniotomy headache. *Headache*. 2003 Mar;43(3):276-8. doi: 10.1046/j.1526-4610.2003.03053.x. PMID: 12603648.

3. Jensen R, Stovner LJ. Epidemiology and comorbidity of headache. *Lancet Neurol.* 2008 Apr;7(4):354-61. doi: 10.1016/S1474-4422(08)70062-0. PMID: 18339350.

4. Uthman OA. Global, regional, and national disability-adjusted life years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2015: a systematic analysis for the Global Burden of Diseases, Injuries, and Risk Factors (GBD) 2015 Study. *Lancet*. 2016;388(10053):1603-58.

5. Lipton R, Schwedt T, Friedman B. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388(10053):1545-602.

6. Jensen R, Rasmussen BK. Bur-

den of headache. *Expert Rev Pharmacoecon Outcomes Res.* 2004 Jun;4(3):353-9. doi: 10.1586/14737167.4.3.353. PMID: 19807317.
7. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. *Cephalalgia*. 2004;24 Suppl 1:9-160. doi: 10.1111/j.1468-2982.2003.00824.x. PMID: 14979299.
8. Akramo Sadat A, Fatemeh N, Fatemeh E, Laila S, Hoorie Mohammadi K, Mohammad Hossein A. Persian medicine non-pharmacological therapies for headache: phlebotomy and wet cupping. *J Tradit Chin Med.* 2018 Jun;38(3):457-464. PMID: 32185981.
9. Pierce MW. Transdermal delivery of sumatriptan for the treatment of acute migraine. *Neurotherapeutics.* 2010 Apr;7(2):159-63. doi: 10.1016/j.nurt.2010.03.005. PMID: 20430314; PMCID: PMC5084096.
10. Zarshenas MM, Petramfar P, Firoozabadi A, Moein MR, Mohagheghzadeh A. Types of headache and those remedies in traditional persian medicine. *Pharmacogn Rev.* 2013 Jan;7(13):17-26. doi: 10.4103/0973-7847.112835. PMID: 23922452; PMCID: PMC3731875.
11. Domínguez-Rodríguez V, González-Hernández A. Remedies for headaches in a closet for ladies and gentlewomen (1608). *Headache*. 2011 Apr;51(4):632-6. doi: 10.1111/j.1526-4610.2010.01719.x. PMID: 20561064.
12. Moshki P, Moshki H. Treatment with Medicinal Plants. Tehran: Farhang va Ghalam; 1399.
13. Hajimonfarednejad M, Ostovar M, Raee MJ, Hashempur MH, Mayer JG, Heydari M. Cinnamon: A systematic review of adverse events. *Clin Nutr.* 2019 Apr;38(2):594-602. doi: 10.1016/j.clnu.2018.03.013. Epub 2018 Apr 5. PMID: 29661513.
14. Samani SM, Moein M, Petramfar P, Zarshenas MM. Development and Assessment of a Gas Chromatographic Based Method for the Quantification of Thymol from Cream Based Formulation. *Curr Drug Discov Technol.* 2016;13(2):77-83. doi: 10.2174/1570163813666160519111145. PMID: 27193568.
15. Buhse L, Kolinski R, Westenberger B, Wokovich A, Spencer J, Chen CW, Turujman S, Gautam-Basak M, Kang GJ, Kibbe A, Heintzelman B. Topical drug classification. *Int J Pharm*. 2005 May 13;295(1-2):101-12.
16. Oxford Biosciences. Cosmetic Regulation in a Competitive Environment (Chapter 11; Stability Testing of Cosmetic Products). 2023; [1 Screen]. Available from: https://oxfordbiosciences.com/stability-testing/ . Accessed July 16, 2023.
17. Barry BW. Rheology of pharmaceutical and cosmetic semisolids. *Adv Pharm Sci.* 1974;4:1-72. PMID: 4618033.
18. Tai A, Bianchini R, Jachowicz J. Texture analysis of cosmetic/pharmaceutical raw materials and formulations. *Int J Cosmet Sci.* 2014 Aug;36(4):291-304. doi: 10.1111/ics.12125. Epub 2014 Jun 30. PMID: 24575934.
19. Van Durme J, Dewulf J, Sysmans W, Leys C, Van Langenhove H. Abatement and degradation pathways of toluene in indoor air by positive corona discharge. *Chemosphere*. 2007 Aug;68(10):1821-9. doi: 10.1016/j.chemosphere.2007.03.053. Epub 2007 May 8. PMID: 17490711.
20. Alissandrakis E, Tarantilis PA, Harizanis PC, Polissiou M. Comparison of the volatile composition in thyme honeys from several origins in Greece. *J Agric Food Chem.* 2007 Oct 3;55(20):8152-7. doi: 10.1021/jf071442y. Epub 2007 Sep 8. PMID: 17824662.
21. Cheng SS, Liu JY, Lin CY, Hsui YR, Lu MC, Wu WJ, Chang ST. Terminating red imported fire ants using Cinnamomum osmophloeum leaf essential oil. *Bioresour Technol.* 2008 Mar;99(4):889-93. doi: 10.1016/j.biortech.2007.01.039. Epub 2007 Mar 21. PMID: 17369041.
22. Adams RP. Identification of essential oil components by gas chromatography/quadrupole mass spectroscopy. Allured publishing corporation; 2001.
23. Laribi B, Kouki K, Mougou A, Marzouk B. Fatty acid and essential oil composition of three Tunisian caraway (Carum carvi L.) seed ecotypes. *J Sci Food Agric.* 2010 Feb;90(3):391-6. doi: 10.1002/jsfa.3827. PMID: 20355058.
24. Jordán MJ, Margaría CA, Shaw PE, Goodner KL. Volatile components and aroma active compounds in aqueous essence and fresh pink guava fruit puree (Psidium guajava L.) by GC-MS and multidimensional GC/GC-O. *J Agric Food Chem.* 2003 Feb 26;51(5):1421-6. doi: 10.1021/jf020765l. PMID: 12590492.

25. Phutdhawong W, Kawaree R, Sanjaiya S, Sengpracha W, Buddhasukh D. Microwave-assisted isolation of essential oil of Cinnamomum iners Reinw. ex Bl.: comparison with conventional hydrodistillation. *Molecules*. 2007 Apr 30;12(4):868-77. doi: 10.3390/12040868. PMID: 17851439; PMCID: PMC6149509.
26. Zeng YX, Zhao CX, Liang YZ, Yang H, Fang HZ, Yi LZ, Zeng ZD. Comparative analysis of volatile components from Clematis species growing in China. *Anal Chim Acta*. 2007 Jul 9;595(1-2):328-39. doi: 10.1016/j.aca.2006.12.022. Epub 2006 Dec 19. PMID: 17606017.
27. Lawal OA, Oyedeji AO. Chemical composition of the essential oils of Cyperus rotundus L. from South Africa. *Molecules.* 2009 Aug 6;14(8):2909-17. doi: 10.3390/molecules14082909. PMID: 19701133; PMCID: PMC6254851.
28. Zhao C, Zeng Y, Wan M, Li R, Liang Y, Li C, Zeng Z, Chau FT. Comparative analysis of essential oils from eight herbal medicines with pungent flavor and cool nature by GC-MS and chemometric resolution methods. *J Sep Sci.* 2009 Feb;32(4):660-70. doi: 10.1002/jssc.200800484. PMID: 19212980.
29. Sabulal B, Dan M, Kurup R, Chandrika SP, George V. Phenylbutanoid-rich rhizome oil of Zingiber neesanum from Western Ghats, southern India. *Flavour Fragrance J*. 2007 Nov;22(6):521-4.
30. Radulović NS, Đorđević ND, Palić RM. Volatiles of Pleurospermum austriacum (L.) Hoffm.(Apiaceae). *J Serbian Chem Society.* 2010;75(12):1653-60.
31. Tepe B, Akpulat HA, Sokmen M, Daferera D, Yumrutas O, Aydin E, Polissiou M, Sokmen A. Screening of the antioxidative and antimicrobial properties of the essential oils of Pimpinella anisetum and Pimpinella flabellifolia from Turkey. *Food Chem*. 2006 Aug 1;97(4):719-24.
32. Tzakou O, Harvala C, Galati EM, Sanogo R. Essential oil composition of Nepeta argolica Bory et Chaub. subsp. argolica. *Flavour Fragrance J*. 2000 Mar;15(2):115-8.
33. Hazzit M, Baaliouamer A, Faleiro ML, Miguel MG. Composition of the essential oils of Thymus and Origanum species from Algeria and their antioxidant and antimicrobial activities. *J Agric Food Chem.* 2006 Aug 23;54(17):6314-21. doi: 10.1021/jf0606104. PMID: 16910725.
34. Feizbaksh A, Tehrani MS, Rustaiyan A, Masoudi S. Composition of the essential oil of Stachys lavandulifolia Vahl. from Iran. *J Essential Oil Res*. 2003 Mar 1;15(2):72-3.
35. McGregor B, Chiang E,Freeman C. Using Texture Analysis to Benchmark Cosmetic Quality. 2018;[1 Screen]. Available from: https://www.cosmeticsandtoiletries.com/testing/sensory/article/21837283/using-texture-analysis-to-benchmark-cosmetic-quality. Accessed December 19, 2023.
36. Friedman M, Kozukue N, Harden LA. Cinnamaldehyde content in foods determined by gas chromatography-mass spectrometry. *J Agric Food Chem.* 2000 Nov;48(11):5702-9. doi: 10.1021/jf000585g. PMID: 11087542.
37. Chen BJ, Fu CS, Li GH, Wang XN, Lou HX, Ren DM, Shen T. Cinnamaldehyde Analogues as Potential Therapeutic Agents. *Mini Rev Med Chem*. 2017;17(1):33-43. doi: 10.2174/1389557516666160121120744. PMID: 26791737.
38. Ma KJ, Zhu ZZ, Yu CH, Zhang H, Liu J, Qin LP. Analgesic, anti-inflammatory, and antipyretic activities of the ethanol extract from Desmodium caudatum. *Pharm Biol.* 2011 Apr;49(4):403-7. doi: 10.3109/13880209.2010.520322. PMID: 21428865.
39. Churihar R, Solanki P, Vyas S, Hemant Tanwani H, Shubham Atal SJ. Analgesic activity of cinnamaldehyde per se and it's interaction with diclofenac sodium and pentazocine in swiss albino mice. Int. J. Phamacog. 2016;3:97-102.
40. Izadpanah E, Nikandam F, Moloudi MR, Hassanzadeh K. Evaluation of the analgesic effect of hydroalcoholic extract of Cinnamomum in rats. *Sci J Kurdistan Univ Med Sci*. 2016 Oct 10;21(4):41-8.