



POSSIBILITIES VOLATILOMICS APPROACH COMBINATION CHEMOMETRICS FOR HALAL AUTHENTICATION IN PHARMACEUTICAL PRODUCTS

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Abstract

Pharmaceutical products require attention for the Muslim community in relation to their halal status. Therefore we need a method that is able to authenticate the halalness of pharmaceutical products, one of which is through the volatilomics and chemometric approaches. This study is a narrative review on the application of volatilomics and chemometrics for halal authentication of pharmaceutical products from 2013 to 2020. The study results show that volatile compounds in a sample are typical compounds that can be used for halal authentication in various products, including pharmaceutical products. Halal pharmaceutical products containing alcohol and its derivatives critical points, gelatin, and collagen will be able to be detected using this method. Volatilomics using GC-MS as an instrument is a selective and sensitive method for authenticating halal pharmaceutical products. The spectral results from MS will be interpreted and visualized using chemometrics to make it easier to understand. PCA, PLS-DA, and cluster analysis are chemometrics methods that reduce and present data more simply. The volatilomics approach combined with chemometrics is a method that can be an alternative for authenticating halal pharmaceutical products.

Keywords: halal pharmaceutical products; authentication; volatilomics; chemometric

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1. Introduction

Currently, halal products continue to develop in various countries, including Indonesia, which is predominantly muslim [1]. One of the halal products that is of concern is pharmaceutical products [2]. Pharmaceutical products include drugs, medicinal ingredients, traditional medicines and cosmetics [3]. In the process of processing pharmaceutical products there are still many that intersect with non-halal products, thus making products that should be halal become non-halal [4]. Non-halal products that intersect with pharmaceutical preparations such as the use of alcohol as a drug solvent [5], the use of methanol as a solvent when extracting traditional medicines [6], and the use of gelatin for cosmetics [7]. Pharmaceutical products that are closely related to alcohol and gelatin make it a challenge to make these products safe for consumers [8]. Therefore it is necessary to have a method capable of authenticating the halalness of pharmaceutical products to protect consumers from non-halal products, one of which is through the volatilomics approach [9].

Volatilomics is the study that continues to grow about all the volatile organic compounds present in the sample [10]. Volatilomics is widely applied for halal analysis targeting volatile organic compounds, such as alcohol, so this method is appropriate when used for halal authentication of pharmaceutical products [11]. Apart from alcohol, gelatin is also a critical ingredient in halal pharmaceutical products, especially for cosmetic products [12]. Gelatin derived from pork is a non-halal compound, so if it is exposed to cosmetics, it will become non-halal. Gelatin is a protein product composed of many organic compounds, including volatile organic compounds [13]. This volatile organic compound can be used as a reference to differentiate the origin of gelatin, so that it can be used to authenticate cosmetic halalness. Volatilomics is able to answer cosmetic halalness, by analyzing volatile organic compounds in gelatin [14]. In the volatilomics analysis, many compounds will be produced from the database so that chemometrics analysis is needed to answer the halal authentication of pharmaceutical products.

Chemometrics is an analytical method for presenting volatilomics data in the analysis of halal authentication of pharmaceutical products which is so much simpler that it is easier to understand [15]. The most popular chemometrics analyzes used for halal authentication of pharmaceutical products are PCA (Principle Component Analysis) and PLS-DA (Partial least squares-discriminant analysis) [16]. PCA is an analysis to reduce data and see the distribution of halal and non-halal volatile compounds in pharmaceutical products [17]. Meanwhile, PLS-DA is to predict which volatile

compounds will determine the halalness of pharmaceutical products. The existence of chemometrics analysis will make it easier to ascertain whether a sample of a pharmaceutical product is halal or non-halal [18].

This review will discuss the volatilomics approach combined with chemometrics for halal authentication of pharmaceutical products. Volatile organic compounds are typical compounds that are able to distinguish between halal and non-halal components. Chemometrics analysis will be able to interpret a lot of volatilomics data to be easier to understand.

2. Methods

This study was a literature review with a narrative review approach. PubMed, Scopus, and Google Scholar databases were searched with the following “volatilomics”, “chemometrics”, “pharmaceutical products”, “alcohol”, “gelatin”, “cosmetic”, and “halal” or “non-halal”. The relevance of the articles obtained with the reviewed topic were then determined. The number of articles that match the keywords was 175 in the range from 2013 to 2023, but 50 articles are used. This is because there are those who do not use volatilomics or chemometrics analysis in the manuscript.

3. Results And Discussion

Halal Pharmaceutical Products

Halal pharmaceutical products are all pharmaceutical products that are free from non-halal compounds, both directly in their ingredients and in the production process [19]. Halal pharmaceutical products include drugs that are free from alcohol and their derivatives [20] and are also free from pork components and their derivatives [21]. Alcohol is a compound that is not allowed in pharmaceutical products [22]. One of the alcohol group compounds that are widely used in pharmaceutical product processes is methanol and ethanol [23]. This compound is often used as a solvent in the extraction of natural products. The extraction results will then be formulated into pharmaceutical products [24]. Pharmaceutical products are made from materials whose extraction process uses methanol or ethanol, making them products that are not halal [25]. Other components besides alcohol that are the center of attention in pharmaceutical products are pigs. One of the currently trending pork components is the origin of gelatin, whether gelatin comes from halal or non-halal materials [26]. The main use of gelatin in medicine is as a capsule shell. Gelatin has very good properties as a material for making capsule shells, but the origin of gelatin must be ascertained [27]. Gelatin derived from non-halal materials, for

example pork gelatin will make pharmaceutical products containing this material non-halal. Currently, besides drugs, pharmaceutical products that continue to be developed are halal cosmetics [28].

Cosmetics are part of pharmaceutical products. Cosmetics are materials or preparations intended for use on the outside of the human body such as the epidermis, hair, nails, lips and external genital organs, or teeth and oral mucous membranes, especially for cleaning, perfuming, changing appearance and/or improving body odor or protecting or keep the body in good condition. Halal cosmetic products may not contain ingredients derived from pigs, carcasses, blood, human body parts, predatory animals, reptiles, insects, and others. Cosmetic ingredients derived from permitted animals must be slaughtered according to Islamic law to be considered halal [29]. The critical points for the use of ingredients in the most popular cosmetics are alcohol, gelatin and collagen [30]. The use of alcohol in cosmetics is to kill bacteria and shrink pores. Gelatin is used for gel formation in cosmetic formulations, while collagen is used to smooth and increase skin elasticity. These three ingredients are ingredients that are often used in cosmetic preparations, even though there are those whose halal status has to be traced. The Indonesian Ulema Council (MUI) states that the limit for the use of alcohol is 0.5%, however exposure to alcohol in pharmaceutical products should be avoided [31].

Gelatin and collagen derived from animal products need to be confirmed of their origin [32]. As with gelatin, collagen derived from non-halal animals will result in the cosmetics used being non-halal [33]. Pharmaceutical products continue to grow, and guarantees are needed to ensure that these products are halal [34]. Therefore, an analytical method is needed to authenticate the halalness of pharmaceutical products. The right analytical method will be able to answer the halalness of pharmaceutical products. One of the analytical methods capable of performing halal authentication on pharmaceutical products is volatilomics [35].

Volatilomics Approach for Halal Authentication in Pharmaceutical Products

Volatilomics is a method that analyzes volatile organic compounds in a sample. Volatilomics is widely used in the fields of biology, food, pharmaceuticals and medicine [36]. Currently volatilomics is an alternative choice in analytical method approaches, especially those using GC-MS (Gas Chromatography-Mass Spectrometry) instruments [37]. This is because volatile compounds have not been able to be detected using other omic-based approaches such as metabolomics, proteomics or lipidomics [38, 39]. Volatilomics is a new reference in the authentication process for various products, one of which is pharmaceutical products [40].

Table 1: Volatilomics approach for halal autentifikasi in critical poin pharmaceutical products

No	Author	Title	Object	Equipment	Results	Ref
1	Perestrelo, et al	DLL μ E/GC-MS as a Powerful Analytical Approach to Establish the Volatilomic Composition of Different Whiskeys	Alcohol	DLL μ E/GC-MS	This method is able to identify compounds in the functional groups of alcohol (3-methylbutan-1-ol, propan-1-ol), esters (ethyl decanoate, ethyl octanoate, ethyl hexanoate)	[43]
2	Fereira L, et al	The influence of ethanol containing cosmetics on ethyl glucuronide concentration in hair	Ethanol	GC/MS	Able to detect alcohol marker	[44]
3	Kumar and Rajakumar	Gas Chromatography-Mass Spectrometry Analysis of Bioactive Component from Ethanol of Avicennia Marina Leaves	Ethanol	GC/MS	Able to detect 3S-butane 1,2,3,4 tetranol in the extract	[45]
4	Li, et al	Identification of characteristic volatiles and metabolomic pathway during pork storage using HS-SPME-GC/MS coupled with multivariate analysis	Alcohol	HS-SPME-GC/MS	Capable of detecting alcohol-derived compounds in pig samples	[46]
5	Sugaya, et al	Headspace GC/MS Analysis of Residual Solvents in	Residual Solvent	GC/MS	Able to detect benzene compounds	[47]

		Dietary Supplements, Cosmetics, and Household Products Using Ethyl Lactate as a Dissolution Medium				
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The volatilomics approach to pharmaceutical product authentication will provide new insights. Compounds from MS spectra data matched with databased will provide information on which compounds are present in the sample. Various alcohol compounds and their derivatives, volatile compounds in gelatin and collagen will be able to be detected in this method, so that this method can be used to authenticate the halalness of pharmaceutical products [41]. The volatilomics approach for halal authentication of pharmaceutical products requires the right instrument so that the analysis target can be achieved. GC-MS is an instrument that has good specifications and sensitivity for volatile compounds [42]. Therefore the use of this instrument is very appropriate to answer the volatilomics approach to

ensure the halalness of pharmaceutical products. Several publications regarding the volatilomics approach for halal authentication of critical ingredients in pharmaceutical products are presented in table 1.

It can be seen that the critical points of ingredients in pharmaceutical products can be analyzed using the volatilomics approach. The volatilomics approach will be able to analyze volatile compounds in pharmaceutical product samples, including cosmetic products. Volatile compounds that have been identified from GC-MS are still a large number of raw data. In order to get the samples we are analyzing, whether they are halal or non-halal, we need further analysis with chemometrics, including PCA, PLS-DA, cluster analysis or OPLS-DA.

Application Chemometrics in Volatilomics

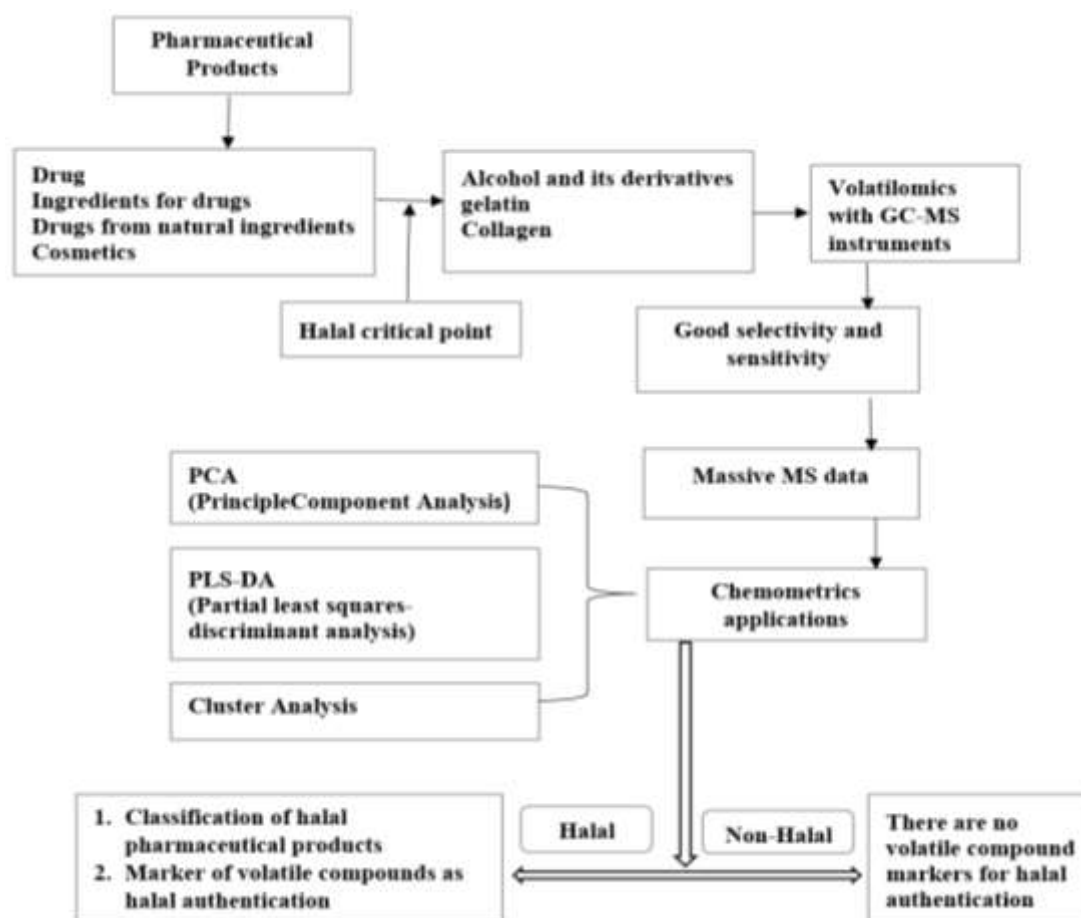


Figure 1: Application of chemometrics in the volatilomics approach for authentication of halal pharmaceutical products

Chemometrics is a combined chemical and statistical data analysis method that can be used to design, process, and visualize volatile data. Large volumes of volatilomics data are easier to translate when presented with this method. Chemometrics used in the authentication of halal pharmaceutical products include PCA, PLS-DA and cluster analysis [48]. PCA is an unsupervised chemometrics method in which with this method only the distribution of halal and non-halal volatile compounds can be seen [49]. The results of the PCA analysis were unable to provide predictions of the halal compounds determining whether the groups formed could be calcified, so further chemometrics analysis was needed, namely supervised chemometrics. The supervised chemometrics analysis will answer whether the MS spectral results from the volatilomics approach for pharmaceutical products can be classified as halal or non-halal, or which volatile compounds can be used to determine halal. PLS-DA is a chemometrics method that is able to predict which volatile compounds will determine halal based on the VIP score [49]. To ensure that our PLS-DA method is correct, it is necessary to look at the value of R², the higher the value of R², the better the PLS-DA analysis. Cluster analysis is a chemometrics method used to classify halal and non-halal volatile compounds. The results of the heatmap analysis will answer whether the pharmaceutical product groups are halal and non-halal based on their similar characteristics [50]. The application of chemometrics in the volatilomics approach for authentication of halal pharmaceutical products is presented in figure 1.

The results of this study are expected to enrich the dissemination of knowledge regarding the application of chemometrics in the health sector, especially pharmaceutical products, as well as for other purposes such as disease detection [51] and so on.

4. Conclusion And Future Perspective

Volatilomics is a strategy for analyzing volatile organic compounds. Volatile compounds in a sample are typical compounds that can be used for halal authentication in various products, including pharmaceutical products. Halal pharmaceutical products containing alcohol and its derivatives critical points, gelatin, and collagen will be able to be detected using this method. Volatilomics using GC-MS as an instrument is a selective and sensitive method for authenticating halal pharmaceutical products. The spectral results from MS will be interpreted and visualized using chemometrics to make it easier to understand. PCA, PLS-DA, and cluster analysis are chemometrics methods that reduce and present data more simply. The volatilomics approach combined with chemometrics

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5. References

- Purwanto, H.; Fauzi, M.; Wijayanti, R.; Al Awwaly, K.U.; Jayanto, I.; Mahyuddin; Purwanto, A.; Fahlevi, M.; Adinugraha, H.H.; Syamsudin, R.A.; et al. Developing Model of Halal Food Purchase Intention among Indonesian Non-Muslim Consumers: An Explanatory Sequential Mixed Methods Research. *Syst. Rev. Pharm.* 2020, 11, 396–407, doi:10.31838/SRP.2020.10.63.
- Kiyat, W. El; Monica, A.; Qomariyah, N.; Manurung, B.S. The Role of Chemical Analysis in the Halal Authentication of Food and Pharmaceutical Products. *J. Food Pharm. Sci.* 2013, 1, 1–6, doi:10.14499/JFPS.
- Bajaj, S.; Sakhuja, N.; Singla, D. Stability Testing of Pharmaceutical Products. *J. Appl. Pharm. Sci.* 2012, 129–138.
- Norazmi, M.N.; Lim, L.S. Halal Pharmaceutical Industry: Opportunities and Challenges. *Trends Pharmacol. Sci.* 2015, 36, 496–497, doi:10.1016/J.TIPS.2015.06.006.
- Park, S.; Kim, J.C.; Lee, H.S.; Jeong, S.W.; Shim, Y.S. Determination of Five Alcohol Compounds in Fermented Korean Foods via Simple Liquid Extraction with Dimethyl-Sulfoxide Followed by Gas Chromatography-Mass Spectrometry for Halal Food Certification. *LWT* 2016, 74, 563–570, doi:10.1016/J.LWT.2016.08.030.
- Saati, E.A.; Aisyah, R.; Wachid, M.; Winarsih, S. Non-Alcoholic Extraction of Rose Pigment as a Halal and Safe Natural Colorant and Bioactive Compound. 2015.
- Rohman, A.; Windarsih, A.; Erwanto, Y.; Zakaria, Z. Review on Analytical Methods for Analysis of Porcine Gelatine in Food and Pharmaceutical Products for Halal Authentication. *Trends Food Sci. Technol.* 2020, 101, 122–132, doi:10.1016/J.TIFS.2020.05.008.
- Nurilmala, M.; Suryamarevita, H.; Husein Hizbullah, H.; Jacoeb, A.M.; Ochiai, Y. Fish Skin as a Biomaterial for Halal Collagen and Gelatin. *Saudi J. Biol. Sci.* 2022, 29, 1100–1110, doi:10.1016/J.SJBS.2021.09.056.
- Andrade, C.; Perestrelo, R.; Câmara, J.S. Valorization of Spent Coffee Grounds as a Natural Source of Bioactive Compounds for Several Industrial Applications—A Volatilomic Approach. *Foods* 2022, 11, 1731, doi:10.3390/FOODS11121731/S1.

- Olander, A.; Lawson, C.A.; Possell, M.; Raina, J.B.; Ueland, M.; Suggett, D.J. Comparative Volatilomics of Coral Endosymbionts from One- and Comprehensive Two-Dimensional Gas Chromatography Approaches. *Mar. Biol.* 2021, 168, 1–13, doi:10.1007/S00227-021-03859-2.
- Cozzolino, R.; Câmara, J.S.; Malorni, L.; Amato, G.; Cannavacciuolo, C.; Masullo, M.; Piacente, S. Comparative Volatilomic Profile of Three Finger Lime (*Citrus Australasica*) Cultivars Based on Chemometrics Analysis of HS-SPME/GC-MS Data. *Molecules* 2022, 27, 7846, doi:10.3390/MOLECULES27227846/S1.
- D, L.; M, N.; G, B.; P, Z.; JM, R. Collagen and Gelatin. *Annu. Rev. Food Sci. Technol.* 2015, 6, doi:10.1146/ANNUREV-FOOD-031414-111800.
- Nurilmala, M.; Suryamarevita, H.; Husein Hizbullah, H.; Jacob, A.M.; Ochiai, Y. Fish Skin as a Biomaterial for Halal Collagen and Gelatin. *Saudi J. Biol. Sci.* 2022, 29, 1100–1110, doi:10.1016/J.SJBS.2021.09.056.
- Baena-Pedroza, A.; Londoño-Giraldo, L.M.; Tabora-Ocampo, G. Volatilome Study of the Feijoa Fruit [*Acca Sellowiana* (O. Berg) Burret.] with Headspace Solid Phase Microextraction and Gas Chromatography Coupled with Mass Spectrometry. *Food Chem.* 2020, 328, 127109, doi:10.1016/J.FOODCHEM.2020.127109.
- Mazivila, S.J.; Olivieri, A.C. Chemometrics Coupled to Vibrational Spectroscopy and Spectroscopic Imaging for the Analysis of Solid-Phase Pharmaceutical Products: A Brief Review on Non-Destructive Analytical Methods. *TrAC Trends Anal. Chem.* 2018, 108, 74–87, doi:10.1016/J.TRAC.2018.08.013.
- Berenguer, C. V.; Pereira, F.; Pereira, J.A.M.; Câmara, J.S. Volatilomics: An Emerging and Promising Avenue for the Detection of Potential Prostate Cancer Biomarkers. *Cancers* 2022, Vol. 14, Page 3982 2022, 14, 3982, doi:10.3390/CANCERS14163982.
- Azira, N.; Amin, I.; Man, C. Differentiation of Bovine and Porcine Gelatins in Processed Products via Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) and Principal Component Analysis (PCA) Techniques. *Int. Food Res. J.* 2012, 19, 1175–1180.
- Grosso, R.A.; Walther, A.R.; Brunbech, E.; Sørensen, A.; Schebye, B.; Olsen, K.E.; Qu, H.; Hedegaard, M.A.B.; Arnsparang, E.C. Detection of Low Numbers of Bacterial Cells in a Pharmaceutical Drug Product Using Raman Spectroscopy and PLS-DA Multivariate Analysis. *Analyst* 2022, 147, 3593–3603, doi:10.1039/D2AN00683A.
- Nordin, F.N.M.; Aziz, A.; Zakaria, Z.; Wan Mohamed Radzi, C.W.J. A Systematic Review on the Skin Whitening Products and Their Ingredients for Safety, Health Risk, and the Halal Status. *J. Cosmet. Dermatol.* 2021, 20, 1050–1060, doi:10.1111/jocd.13691.
- Mansur, A.R.; Oh, J.; Lee, H.S.; Oh, S.Y. Determination of Ethanol in Foods and Beverages by Magnetic Stirring-Assisted Aqueous Extraction Coupled with GC-FID: A Validated Method for Halal Verification. *Food Chem.* 2022, 366, doi:10.1016/J.FOODCHEM.2021.130526.
- Shabani, H.; Mehdizadeh, M.; Mousavi, S.M.; Dezfouli, E.A.; Solgi, T.; Khodaverdi, M.; Rabiei, M.; Rastegar, H.; Alebouyeh, M. Halal Authenticity of Gelatin Using Species-Specific PCR. *Food Chem.* 2015, 184, 203–206, doi:10.1016/J.FOODCHEM.2015.02.140.
- Halim, M.A.A.; Salleh, M.M.M.; Kashim, M.I.A.M.; Ahmad, A.A.; Nordin, N. Halal Pharmaceuticals: Legal, Shari'ah Issues And Fatwa Of Drug, Gelatine And Alcohol. Pauzi, N.; Man, S.; Nawawi, M.S.A.M.; Abu-Hussin, M.F. Ethanol Standard in Halal Dietary Product among Southeast Asian Halal Governing Bodies. *Trends Food Sci. Technol.* 2019, 86, 375–380, doi:10.1016/J.TIFS.2019.02.042.
- Saati, E.A.; Aisyah, R.; Wachid, M.; Winarsih, S. Utilization of Non-Alcoholic Extract of Pigment Derived From Local Rose of Indonesia (Batu City) as Natural Colorant and Bioactive Safe and Halal Products. 2015.
- Ab Halim, M.A.B.; Kashim, M.I.A.B.M.; Salleh, M.M.M.; Nordin, N.B.; Husni, A.B.M. Halal Pharmaceuticals. *Soc. Sci.* 2015, 10, 490–498, doi:10.3923/SSCIENCE.2015.490.498.
- Lassoued, I.; Jridi, M.; Nasri, R.; Dammak, A.; Hajji, M.; Nasri, M.; Barkia, A. Characteristics and Functional Properties of Gelatin from Thornback Ray Skin Obtained by Pepsin-Aided Process in Comparison with Commercial Halal Bovine Gelatin. *Food Hydrocoll.* 2014, 41, 309–318, doi:10.1016/J.FOODHYD.2014.04.029.
- Ahmed, M.A.; Al-Kahtani, H.A.; Jaswir, I.;

- AbuTarboush, H.; Ismail, E.A. Extraction and Characterization of Gelatin from Camel Skin (Potential Halal Gelatin) and Production of Gelatin Nanoparticles. *Saudi J. Biol. Sci.* 2020, 27, 1596–1601, doi:10.1016/J.SJBS.2020.03.022.
- Sugibayashi, K.; Yusuf, E.; Todo, H.; Dahlizar, S.; Sakdiset, P.; Arce, F.J.; See, G.L. Halal Cosmetics: A Review on Ingredients, Production, and Testing Methods. *Cosmet.* 2019, Vol. 6, Page 37 2019, 6, 37, doi:10.3390/COSMETICS6030037.
- Yusuf, E.; Yajid, M.S.A. Related Topic: Halal Cosmetics. *Ski. Permeat. Dispos. Ther. Cosmeceutical Compd.* 2017, 101–107, doi:10.1007/978-4-431-56526-0_8/COVER.
- Duasa, J.; Husin, A.M.; Asmy Mohd Thas Thaker, M.; Rahman, M.P. An Alternative Source of Collagen for Muslim Consumers: Halal and Environmental Concerns. *J. Islam. Mark.* 2022, 13, 2232–2253, doi:10.1108/JIMA-09-2020-0268/FULL/XML.
- ANNISA, F. Batas Penggunaan Kadar Alkohol Pada Kosmetik Dan Obat-Obatan (Analisis Terhadap Fatwa Mui Nomor: 40 Tahun 2018 Perspektif Maqasid Syariah). 2021.
- Hashim, P.; Hashim, M. SCIENCE & TECHNOLOGY A Review of Cosmetic and Personal Care Products: Halal Perspective and Detection of Ingredient. *Pertanika J. Sci. Technol* 2013, 21, 281–292.
- Zabidi, A.R.; Fauzi, F.N.; Abd Razak, F.N.; Rosli, D.; Jamil, M.Z.M.; Wan Ibrahim, W.K.; Yahaya, N. Screening Porcine DNA in Collagen Cream Cosmetic Products. *Food Res.* 2020, 4, 151–156, doi:10.26656/FR.2017.4(S1).S05.
- Aziz, N.A.; Ibrahim, I.; Raof, N.A. The Need for Legal Intervention within the Halal Pharmaceutical Industry. *Procedia - Soc. Behav. Sci.* 2014, 121, 124–132, doi:10.1016/J.SBSPRO.2014.01.1114.
- Neves, D.B. da J.; Caldas, E.D. GC–MS Quantitative Analysis of Black Market Pharmaceutical Products Containing Anabolic Androgenic Steroids Seized by the Brazilian Federal Police. *Forensic Sci. Int.* 2017, 275, 272–281, doi:10.1016/J.FORSCIINT.2017.03.016.
- Capitain, C.C.; Nejati, F.; Zischka, M.; Berzak, M.; Junne, S.; Neubauer, P.; Weller, P. Volatilomics-Based Microbiome Evaluation of Fermented Dairy by Prototypic Headspace-Gas Chromatography–High-Temperature Ion Mobility Spectrometry (HS-GC-HTIMS) and Non-Negative Matrix Factorization (NNMF). *Metabolites* 2022, 12, 299, doi:10.3390/METABO12040299/S1.
- Pavlidis, D.E.; Mallouchos, A.; Ercolini, D.; Panagou, E.Z.; Nychas, G.J.E. A Volatilomics Approach for Off-Line Discrimination of Minced Beef and Pork Meat and Their Admixture Using HS-SPME GC/MS in Tandem with Multivariate Data Analysis. *Meat Sci.* 2019, 151, 43–53, doi:10.1016/J.MEATSCI.2019.01.003.
- Harlina, P.W.; Maritha, V.; Musfiroh, I.; Huda, S.; Sukri, N.; Muchtaridi, M. Possibilities of Liquid Chromatography Mass Spectrometry (LC-MS)-Based Metabolomics and Lipidomics in the Authentication of Meat Products: A Mini Review. *Food Sci. Anim. Resour.* 2022, 42, 744–761, doi:10.5851/KOSFA.2022.E37.
- Brendel, R.; Schwolow, S.; Rohn, S.; Weller, P. Volatilomic Profiling of Citrus Juices by Dual-Detection HS-GC-MS-IMS and Machine Learning - An Alternative Authentication Approach. *J. Agric. Food Chem.* 2021, 69, 1727–1738, doi:10.1021/ACS.JAFC.0C07447/SUPPL_FILE/JF0C07447_SI_002.PDF.
- Ibrahim, N.; Moussa, A.Y. A Comparative Volatilomic Characterization of Florence Fennel from Different Locations: Antiviral Prospects. *Food Funct.* 2021, 12, 1498–1515, doi:10.1039/D0FO02897E.
- Wiśniewska, P.; Śliwińska, M.; Dymerski, T.; Wardencki, W.; Namieśnik, J. Application of Gas Chromatography to Analysis of Spirit-Based Alcoholic Beverages. <http://dx.doi.org/10.1080/10408347.2014.904732> 2015, 45, 201–225, doi:10.1080/10408347.2014.904732.
- Vrhovsek, U.; Lotti, C.; Masuero, D.; Carlin, S.; Weingart, G.; Mattivi, F. Quantitative Metabolic Profiling of Grape, Apple and Raspberry Volatile Compounds (VOCs) Using a GC/MS/MS Method. *J. Chromatogr. B* 2014, 966, 132–139, doi:10.1016/J.JCHROMB.2014.01.009.
- Perestrelo, R.; Caldeira, M.; Rodrigues, F.; Pereira, J.A.M.; Câmara, J.S. DLLμE/GC-MS as a Powerful Analytical Approach to Establish the Volatilomic Composition of Different Whiskeys. *Beverages* 2022, Vol. 8, Page 53 2022, 8, 53, doi:10.3390/BEVERAGES8030053.
- Martins Ferreira, L.; Binz, T.; Yegles, M. The Influence of Ethanol Containing Cosmetics on Ethyl Glucuronide Concentration in Hair. *Forensic Sci. Int.* 2012, 218, 123–125,

- doi:10.1016/J.FORSCIINT.2011.10.015.
- Kumar, D.G. Gas Chromatography-mass Spectrometry Analysis of Bioactive Components from The Ethanol Extract of Avicennia Marina Leaves. 2016, 4.
- Li, H.; Geng, W.; Haruna, S.A.; Zhou, C.; Wang, Y.; Ouyang, Q.; Chen, Q. Identification of Characteristic Volatiles and Metabolomic Pathway during Pork Storage Using HS-SPME-GC/MS Coupled with Multivariate Analysis. *Food Chem.* 2022, 373, 131431, doi:10.1016/J.FOODCHEM.2021.131431.
- Sugaya, N.; Takahashi, M.; Sakurai, K.; Tahara, M.; Kawakami, T. Headspace GC/MS Analysis of Residual Solvents in Dietary Supplements, Cosmetics, and Household Products Using Ethyl Lactate as a Dissolution Medium. *J. AOAC Int.* 2020, 103, 407–412, doi:10.5740/JAOACINT.19-0260.
- Maritha, V.; Harlina, P.W.; Musfiroh, I.; Gazzali, A.M.; Muchtaridi, M. The Application of Chemometrics in Metabolomic and Lipidomic Analysis Data Presentation for Halal Authentication of Meat Products. *Mol.* 2022, Vol. 27, Page 7571 2022, 27, 7571, doi:10.3390/MOLECULES27217571.
- Taware, R.; Taunk, K.; Kumar, T.V.S.; Pereira, J.A.M.; Câmara, J.S.; Nagarajaram, H.A.; Kundu, G.C.; Rapole, S. Extracellular Volatilomic Alterations Induced by Hypoxia in Breast Cancer Cells. *Metabolomics* 2020, 16, 1–12, doi:10.1007/S11306-020-1635-X/METRICS.
- Taware, R.; Taunk, K.; Pereira, J.A.M.; Shirolkar, A.; Soneji, D.; Câmara, J.S.; Nagarajaram, H.A.; Rapole, S. Volatilomic Insight of Head and Neck Cancer via the Effects Observed on Saliva Metabolites OPEN., doi:10.1038/s41598-018-35854-x.
- Mrázová V, Makohusová M, Kovács I, Babinská K. Assessment of Hypertension Risk in Children by Chemometrical Techniques. *European Chemical Bulletin.* 2014, 3(6), 563-567.