

The use of chemometrics in combination with molecular spectroscopy and chromatography methods for determining the levels of gingerol compounds in ginger (*Zingiber officinale*): a review

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Article history:

Received: 1 April 2022

Received in revised form: 5

July 2023

Accepted: 28 July 2023

Available Online: 5 June

2024

Keywords:

Chemometric,

Herbal,

Ginger,

Gingerol,

Zingiber officinale

DOI:

[https://doi.org/10.26656/fr.2017.8\(3\).165](https://doi.org/10.26656/fr.2017.8(3).165)

Abstract

Ginger (*Zingiber officinale* Roscoe), a member of the Zingiberaceae family, is a herb with a global reputation in medicines, food seasonings, beverages and cosmetics. It is rich in antioxidants due to some active components, including gingerol, shogaol and zingerone. These components are reported to have more powerful antioxidants than vitamin E. The phytochemicals and their levels are significantly influenced by environmental factors such as harvesting time, soil condition, and the cultivating place. Therefore, this study highlighted the analytical method to determine the gingerol content in ginger using chemometrics. Several databases including Scopus, PubMed, and Science Direct, were explored to obtain relevant articles using specific keywords related to the reviewed topic. Several chemometrics methods are used for the characterization and profiling of fingerprints, such as Fourier-transform infrared spectroscopy (FTIR), Fourier-transform near infrared spectroscopy (FT-NIR), high-performance liquid chromatography (HPLC), and High-performance thin-layer chromatography (HPTLC), including pattern recognition and multivariate calibration combined with molecular spectroscopy and chromatography. The fingerprint profiling is processed and combined with chemometrics analysis or multivariate data for faster, sensitive and valid results.

1. Introduction

Ginger (*Zingiber officinale* Roscoe) is a member of the Zingiberaceae family that has long been used as a food seasoning in Indonesian cuisine. Furthermore, rhizome is extensively used as a flavor in food, beverage and herbal components in Traditional Medicine (Wu *et al.*, 2018). This plant contains an active anti-diabetic substance that effectively lowers cholesterol levels (Akhani and Vishwakarma, 2001). According to Tsai *et al.* (2005), the compounds that function as antioxidants in ginger are phenolic substances. Additionally, Negri (2005) reported that the active components of plant-derived hypoglycemic include terpenoids, alkaloids, coumarin, flavonoids and capsaicin. Suhaj (2006) also reported that the antioxidants contained in ginger are gingerol, shogaol and others.

The phytochemicals in the rhizome of ginger are proteins, carbohydrates, essential oils, fatty oils and

water (Gabbi and Bajwa, 2017). Additionally, the components of the chemical compounds contained in the rhizome include non-volatile oil, evaporated oil and starch. Volatile essential oils provide a distinctive odor to ginger, while oleoresin of gingerol, shogaol and zingiberene, which are non-volatile, give it a bitter and spicy taste (Ravindran and Babu, 2005).

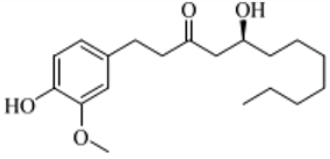
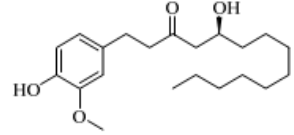
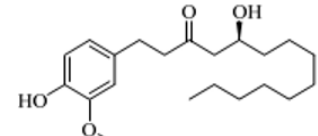
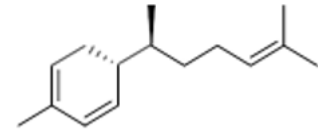
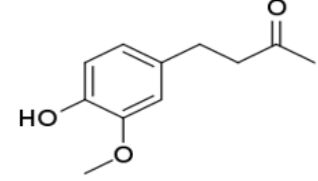
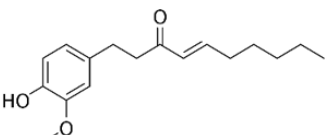
There are 3 varieties of ginger, ginger gajah (*Zingiber officinale* var *fcinarum*), emprit ginger (*Zingiber officinale* var *amarum*), and red ginger (*Zingiber officinale* var *rubrum*). Furthermore, their main components are 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol. Each variant of ginger has its distinctive spicy taste due to the different contents of phenolic compounds. The difference in the number of components of phenolic compounds due to different species, environmental factors, cultivating place, harvesting time, and post-harvesting process influences the characteristics

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of gingers. Figure 1 shows the main chemical volatile compound and constituents of emprit ginger, respectively.

Figure 1. The main chemicals along with chemical structure in zinger.

Chemicals	Chemical Structure
6-Gingerol	
8-Gingerol	
10-Gingerol	
Zingerberene	
Zingerone	
Shagol	

Medicinal plants with complex chemical contents require special methods for quality control through physico-chemical analysis and molecular biology. In addition to depending on a single chemical component, a comprehensive analytical method that can characterize chemical compound fingerprints is required (Ni *et al.*, 2009). The chemical components in medicinal plants can be identified and analyzed using three approaches, including single component, fingerprint, and metabolomic (Esteki *et al.*, 2018), as well as several instrumental techniques such as molecular spectroscopy and chromatographic methods (Mazina *et al.*, 2015). Chemometrics is the science of chemistry that uses mathematics and statistics to process, evaluate and interpret data from chemical analysis (Nurani *et al.*, 2022).

The quality of medicinal ginger improves in direct proportion to the growth in demand. It is important to investigate the gingerol content as the plant's primary constituent. Therefore, this study aims to review the method used to determine the gingerol content in ginger and data analysis through chemometrics. Figures 2 and 3 show the rhizome and whole plant of emprit ginger, respectively.



Figure 2. Rhizome of ginger *emprit* (*Zingiber officinale* var *amarum*).



Figure 3. Whole plant of ginger *emprit* (*Zingiber officinale* var *amarum*).

2. Methodology

Literature related to the subject was collected and analyzed. Databases, including Scopus, PubMed, and Science Direct, were used to identify and download related abstracts, reports, and research papers. The keywords used were ginger (*Zingiber officinale*), *gingerol* and chemometrics. The inclusion criteria for this study are original articles on the subject of ginger (*Zingiber officinale*) with data processing using multivariate analysis (chemometrics) and open-access articles from 2010 to 2020 (10 years). Additionally, the exclusion criteria include articles without full access and research published before 2010. The literature in the database consisted of 42 related articles, with 8, 20, and 14 for Scopus, Science Direct, and PubMed, respectively. Six articles were discarded due to duplication issues. Out of the remaining 36, 24 were discarded for not meeting the required criteria. At the final stage of the screening process, only 12 articles were selected. These articles aim to discuss gingerol compound identification, an analytical method to measure the levels of gingerol compounds.

3. Extraction process

Extraction is separating any chemical content contained in a soluble material with the help of a solvent. Gingerol compounds can be extracted in several ways. The first uses 50 mg of powdered ginger sonicated in 5 mL of methanol for 1 hr at room temperature. Afterwards, the solution is filtered using a 0.45 mm filter membrane and then injected into CLC. The standard solution consists of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol. Finally, the components are mixed and diluted in methanol and analyte for further analysis of the calibration curve (Rafi *et al.*, 2013).

Another extraction process is according to Feng *et al.* (2013). The process involves mixing 50 g of ginger and 100 mL of methanol in an ultrasonic bath (40 kHz) for 30 minutes. After the mixture cools down, another amount of methanol is added. The final solution is then filtered using a 0.22 filter membrane and injected into HPLC for further analysis. Meanwhile, the last extraction is conducted by dissolving the primary stock solution of six standards in methanol to produce zingiberon, 6-shogaol, 6-gingerol, 8-gingerol, 10-gingerol, and diacetoxy-6-gingerdiol. Finally, it is mixed with methanol and stored at 4°C (Ding *et al.*, 2015).

4. Molecular spectroscopy and chromatography

4.1 FTIR Spectroscopic measurement

Before the chemometrics analysis, a standard procedure, such as the FTIR spectrum, is required. The SNV and applied spectra of the first and second derivatives are compared. Its process assesses the standard deviation of the FTIR spectrum data point and calibrates it to determine a unit standard deviation. The SNV abolishes slope variations (Aouidi *et al.*, 2012).

The FTIR spectrum is used to identify and differentiate interrelated medicinal plants. By comparing several plants such as *Curcuma longa*, *Curcuma xanthorrhiza*, and *Zingiber cassumunar*, variations in their peak position and intensity are examined. The three selected plants are differentiated based on the intensity of their OH absorption (Rohaeti *et al.*, 2015).

4.2 FT-NIR spectra measurement

The FT-NIR spectrum requires pre-processing data to achieve a stable and reliable calibration model. This preliminary process is necessary because of the difficulty encountered in determining spectral differences through visual inspection due to the samples' complex and overlapping bands. During this research, spectral pre-processing data is evaluated with SNV, MSC, first-order (FD), second-order (SD), and SG smoothing algorithms (Yan *et al.*, 2021). It is quantified by R², RMSECV,

RMSEC, and RMSEP for model performance. The results are later named SNV + SD for zingerone and 10-gingerol, MSC + SD for 8-gingerol and 6-shogaol, as well as SNV + FD for 6-gingerol. Therefore, a valid PLS model possesses lower RMSEC and RMSEP and higher R values (Li *et al.*, 2010).

The non-destructive FT-NIR was measured by calculating the internal quality parameters of the testing samples. Afterward, the calculation of the quantitative model is compared to the reference value to analyze the chemical content of zingerone, 6-gingerol, 8-gingerol, 10-gingerol and 6-shogaol contained in NS-ginger as well as S-ginger and verify the accuracy, reliability, and validity of the model (Marco, 2014; Zhou *et al.*, 2020).

4.3 HPLC measurement

According to the ICH guidelines, the HPLC method is valid when it shows accuracy, reproducibility, and stability. The accuracy of the HPLC-PDA is examined based on the Relative Standard Deviation (RSD). Furthermore, the reproducibility is examined by independently replicating the sample within one day. The stability is evaluated by analyzing the same sample solution within a four-hour interval for one day. Finally, the RSD value is used as the assessment index (Feng *et al.*, 2013).

HPLC optimization is significant for the separation process in the ginger chromatogram sample. The linear gradient elution is selected to elute the components in the mobile phase, such as water and acetonitrile. Furthermore, the components are resolute and separated by adding phosphate in the mobile phase. The components of the ginger extract sample are carefully separated under the required conditions, as seen below (Feng *et al.*, 2013). Figure 4 shows the standard solution (A) and ginger samples (B).

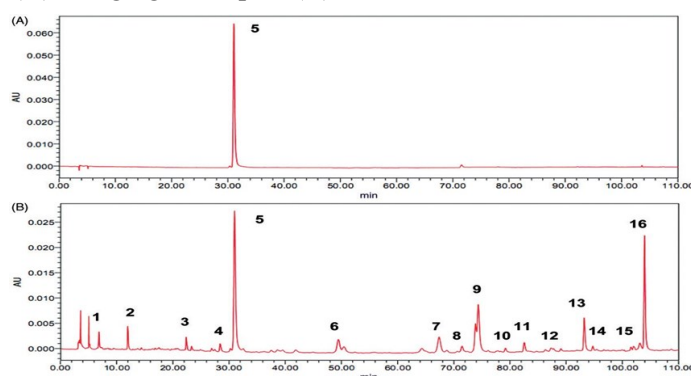


Figure 4. Chromatogram results from the standard solution of gingerol (A) and ginger samples (B) (Feng *et al.*, 2013).

4.4 HPTLC measurement

According to International Conference Guidelines about Harmonization (ICH), HPTLC methods are valid when they show accuracy, precision, specificity,

detection limit (LOD) as well as a limit of quantification (LOQ). Chromatography is performed on a silica gel HPTLC plate. Firstly, 5 μL of the sample solution is mixed with the standard solution on the plate using an applicator. Afterwards, the solution is automatically sprayed with a 100 μL syringe. The plate is carefully measured from the edge to the bottom by 10 mm. A plate with a distance of 80 mm is saturated using a mobile phase of 40 mL with toluene - ethyl acetate ratio of (3: 1 v/v). Finally, the TLC plate is cut out vertically (10 \times 20 cm), after which it is dried and ready for further analysis.

4.5 Chemometrics

Chemometrics is considered a tool to process chemical data in complex, overlapping molecular spectra (Winning *et al.*, 2008). Furthermore, as the science of chemistry, it implements mathematics and statistics for data processing, evaluation, and interpretation during chemical analysis (Nurani *et al.*, 2022). One of its advantages is the capability to analyze multivariate data, which consists of measuring several variables using the same sample (Miller and Miller, 2010). International Chemometrics Society (ICS) also reported that chemometrics is the science that connects chemical measurements through the implementation of mathematical or statistical methods (Gemperline, 2006).

Chemometrics is divided into multivariate classification (or pattern recognition) and regression. Its focus is on multivariate data measurement involving multiple variables of the same sample. Multivariate analysis is divided into two groups, (1) *unsupervised grouping*, such as Principal Component Analysis (PCA) and group/cluster analysis, as well as (2) *supervised grouping* (Rohman, 2014). Chemometric methods in data analysis are broad and essential for decision-making as well as problem-solving processes. Chemical analysis deals with complex mixtures, compounds, and properties, often difficult to analyze. Therefore, chemometrics is suitable for analyzing herbal medicines, which are usually complex in nature (Rohman *et al.*, 2020).

Some software programs with their advantages are used to calculate complex data during chemometric analysis. For example, Unscrambler®, SIMCA®, SIRIUS®, and Pirouette® possess standard multivariate analysis methods such as PCA, cluster analysis, PCR, PLS, and Soft Independent Modeling of Class Analogy (SIMCA) but have low capacity. In addition, programs such as Minitab® and Matlab® help in writing processes, and Grams®32 support the quantitative analysis of data with different pattern recognition techniques (Gemperline, 2006; Miller and Miller, 2010).

LDA linear discriminant analysis requires mathematical models to classify and identify ginger samples based on their origin (Yudthavorasit *et al.*, 2014). Furthermore, it separates the classified samples (Berrueta *et al.*, 2007). PCA helps structure the original data in lower dimensions while LDA allocates the unknown. During this research, 80 original HPLC profiles (RPA) were used without analyzing PCA before LDA (PCA-LDA method). This is because the number of variables is less than the samples. Therefore, PCA is not required, and LDA can be applied immediately for data analysis (Nurani *et al.*, 2022).

Rohaeti *et al.* (2015) used the combination of FTIR spectra and chemometric methods to distinguish three different plant species to obtain a visual inspection of the spectrum. PCA and CVA chemometric techniques are used during this process. The first and second derivatives spectrum are used to eliminate baseline drift and increase the small spectral (Zhou *et al.*, 2020). SNV is used during the initial analysis of FTIR spectra to distinguish between the three different plants. Furthermore, it is selected to calibrate the FTIR spectrum before spectra analysis in PCA and CVA. Figure 5 shows the FTIR Spectrum of three types of ginger plants (A) *Curcuma longa*, (B) *Curcuma xanthorrhiza*, and (C) *Zingiber cassumunar* (Rohaeti *et al.*, 2015). PCA is used to identify the FT-NIR data from NS-ginger and S-ginger samples, then transferred to SIMCA 13.0 software for further analysis. The model shows the predictive ability of $R_2Y = 0.907$ and $Q_2 = 0.888$. The results show that this method effectively identifies NS-ginger and S-ginger

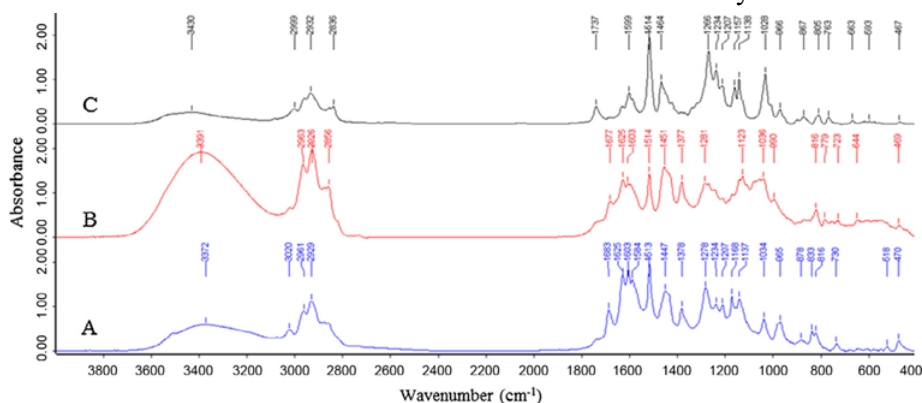


Figure 5. FTIR spectra of (A) *Curcuma longa*, (B) *Curcuma xanthorrhiza*, and (C) *Zingiber cassumunar* (Rohaeti *et al.*, 2015).

samples (Yan et al., 2021).

4.6 Determination of gingerol levels using molecular spectroscopy and chromatography

According to Rafi et al. (2013), Liquid Chromatography (LC) techniques such as High-Performance Liquid Chromatography (HPLC) can identify chemical compounds of gingerol and shogaol when combined with the use of an ultraviolet detector. The standard solutions of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol are mixed and diluted in methanol to obtain seven concentrations. Finally, four analytes could be needed to produce a calibration curve. According to Yan et al. (2021), High-Performance Liquid Chromatography helps produce data on gingerol compounds using multivariate data analysis (MVDA). In addition, PLS and CP-ANN created a calibration model that predicts the concentration of gingerol compounds and biomarkers in NS-ginger and S-ginger samples. The samples in this research are analyzed using HPLC-DAD-MS with a chemometric combination, such as PCA, Hierarchical Cluster Analysis (HCA), and analysis of variance (ANOVA) (Ding et al., 2015). In addition, the fingerprints of ginger samples are examined using a simple, valid, and sensitive HPLC Photodiode Array (PDA) method (Feng et al., 2013).

The HPTLC method is applied digitally to the fingerprint chromatography using imaging software. The result is used for multivariate PCA of pattern recognition. This research applies chemometric HCA as a valid, simple, and fast HPTLC method to examine 6-gingerol, 8-gingerol, 10-gingerol, and 6 shogaol chemical compounds (Ibrahim and Fathy, 2018). Table 1 shows the main chemicals along with the chemical structure present in the zinger.

5. Conclusion

The chemical compounds contained in ginger include gingerol, shogaol and zingerone. The differences in growing locations influence the levels of the three main chemical compounds in ginger. Therefore, several extraction processes are valid for examining the chemical compounds in this plant. Some chemometrics is either pattern recognition (supervised such as discriminant analysis and unsupervised such as PCA) or multivariate calibration such as partial least squares using variables from several instrumental techniques, including spectroscopy and chromatographic methods successfully used for characterization. During the analysis, molecular spectroscopy (FTIR, FT-NIR) and chromatography (HPLC, HPTLC) combined with chemometric techniques are used to produce sensitive and valid results.

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