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Machine learning for a rapid discrimination of ginseng cultivation age using ¹H-NMR spectra

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Wonho Lee[1†], Dahye Yoon[1,2†], Seohee Ma[1], Dae Young Lee[2], Jae Won Lee[2], Ick-Hyun Jo[2], Taekwang Kim[3] and Suhkmann Kim[1*]

Abstract

The scientific and systematic classification of cultivation age is important for preventing age falsification and ensuring the quality of ginseng. Therefore, we applied deep learning to classify the cultivation age of ginseng. Deep learning, which is based on an artificial neural network, is one of the new class of models for machine learning, and is state-of-the-art. It is a powerful tool and has been used to solve complex problems in many fields. In the present study, powdered samples of 4-, 5-, and 6-year-old ginseng were measured using high-resolution magic angle spinning nuclear magnetic resonance (HR-MAS NMR) spectroscopy. NMR data were analyzed with deep learning and partial least-squares discriminant analysis (PLS-DA) to improve accuracy. The accuracy of the PLS-DA was 87.1% and the accuracy of the deep learning model was 93.9%. NMR spectroscopy with deep learning can be a useful tool for discrimination of ginseng cultivation age.

Keywords: Deep learning, Ginseng, NMR, Non-targeted analysis, PLS-DA

Introduction

Ginseng, which is a perennial crop, has been used for a natural medicinal ingredient for thousands of years in East Asia. Ginseng cultivated for 4–6 years is used as a medicine [1]. However, 6-year-old ginseng is known to be the most effective and is therefore the most expensive among them [2]. It is important to establish an efficient and accurate model for classifying and predicting ginseng cultivation age.

Previous studies conducted metabolic profiling and multivariate statistical analyses of origin, species, variety, age, and processing method of ginseng using nuclear magnetic resonance (NMR) spectroscopy, and all of these studies analyzed the extract of ginseng [3–8]. However,
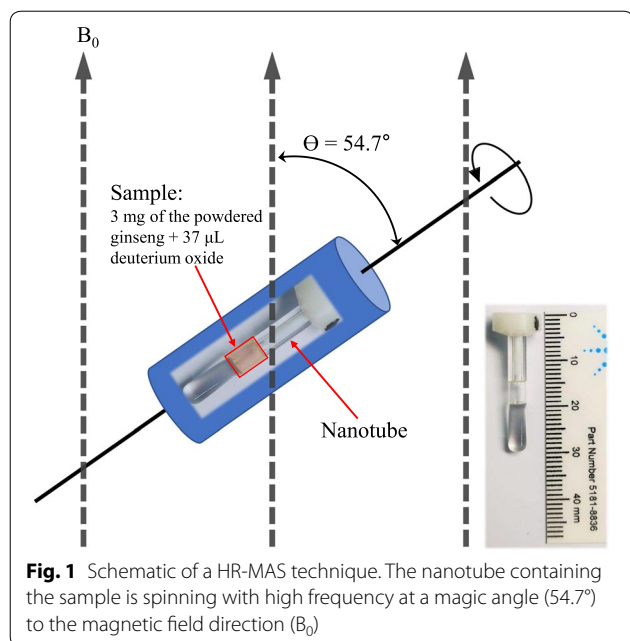
in this study, which analyzed with a lot of samples, the ginseng powder was directly used without extraction because solvents or procedures for extraction can affect the data. Several previous studies performed various tools such as combination of NMR spectrometer, ultra-high-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-QTOF/MS), and gas chromatography quadrupole time-of-fight mass spectrometry (GC-TOF/MS) [9], and Fourier-transform infrared (FT-IR) spectroscopy [10] for age discrimination of ginseng. HR-MAS technique combines the advantage of solid and solution-state NMR. Fast spinning the sample at the magic angle (54.7°) with respect to the static magnetic field (B0) reduces line-broadening interaction caused by dipolar coupling and chemical shift anisotropy (Fig. 1). Thus, high resolution can be achieved [11, 12]. This technique offers spectra with a similar resolution to that of solution without sample extraction process [13]. The advantage of HR-MAS compared to solution-state NMR is that samples are measured in a state close

*Correspondence: suhkmann@pusan.ac.kr
†Wonho Lee and Dahye Yoon contributed equally to this work
¹ Department of Chemistry, Center for Proteome Biophysics and Chemistry Institute for Functional Materials, Pusan National University, Busan 46241, Republic of Korea
Full list of author information is available at the end of the article

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Fig. 1 Schematic of a HR-MAS technique. The nanotube containing the sample is spinning with high frequency at a magic angle (54.7°) to the magnetic field direction (B_0)

to the intact conditions. Furthermore, HR-MAS does not require an extraction process, which therefore reduces the experiment time [14].

In this study, in order to discriminate the age of various ginseng harvested over many years, ^{1}H HR-MAS NMR spectroscopy data was analyzed by partial least-squares discriminant analysis (PLS-DA) which is subfield of machine learning. PLS-DA is widely used in metabolic analyses [15–18]. We also applied deep learning analysis to improve accuracy for discrimination of ginseng age. Deep learning architectures such as deep neural networks (DNN) is one of the new class of models for machine learning [19], and is state-of-the-art. It is a powerful tool and has been used to solve complex problems in many fields. Many important advances in machine learning have been made recently following improvements in computing power and the amount of data available [20]. Moreover, open source machine learning libraries and frameworks have made deep learning more accessible to non-experts. This study is meaningful because it is the first study to apply HR-MAS NMR data to machine learning.

Materials and methods
Plant materials
Panax ginseng roots were cultivated in the experimental field at Kyung Hee University and at the Department of Herbal Crop Re-search located in Gangwon Province, according to the protocol described in the 'ginseng GAP standard cultivation guide' developed by the Rural Development Administration, Republic of Korea (Rural

Development Administration, 2009). Four-, five-, and six-year-old ginseng roots were harvested in October 2014, October 2015, and October 2016, respectively. The voucher specimens (NIHHS141010 and NIHHS161001) were deposited at the herbarium of the Department of Herbal Crop Research, NIHHS, RDA, Eumseong, Republic of Korea.

Sample preparation
We analyzed a total 385 ginseng samples, which contained 162 of 4-year-old samples, 108 of 5-year-old samples, and 115 of 6-year-old samples. Each sample was dried at 40 °C in a forced-air convection-drying oven for 48 h after washing, and then weighed. The main roots were used for the experiments after removing the lateral and fine roots. The roots were ground (< 0.5 mm) and thoroughly mixed using a Hanil Scientific Inc. mixer (Seoul, Korea), and the subsamples were homogenized further using a Retsch MM 400 mixer mill (Retsch GmbH, Haan, Germany) for the analyses.

NMR experiments
For measuring high-resolution magic angle spinning (HR-MAS) nuclear magnetic resonance (NMR) spectroscopy, each ginseng sample (3 mg) was transferred to a 4-mm HR-MAS NMR sample tube (Agilent Technologies, Santa Clara, CA, USA). Heavy water (D_2O; 37 μL) containing 2 mM of 3-(trimethylsilyl) propionic-2,2,3,3-d_4 acid sodium salt (TSP-d_4) was added to each sample tube.

All NMR spectra were measured using a 600.167 MHz Agilent spectrometer equipped with a 4-mm gHX NanoProbe (Agilent Technologies). The spinning rate was 2050 Hz for HR-MAS. We collected 128 transients using the Carr–Purcell–Meiboom–Gill (CPMG) pulse sequence with PRESAT for the suppression of water and high-molecular-mass compounds [21]. The one-dimensional (1D) spectra were obtained using a 1.704 s acquisition time, a 1 s relaxation delay. The TSP-d_4 peak at 0.00 ppm was used as a reference to calibrate the chemical shift [22]. And correlation spectroscopy (COSY), which is one of the homonuclear two-dimensional (2D) experiment, was recorded and processed with 128 of scans and 256 of t1 increments.

Metabolic profiling
All spectra were phased, and baseline corrected manually. Metabolites in spectra were assigned using Chenomx NMR Suite 7.1 professional with the Chenomx 600 MHz library database (Chenomx Inc., Canada). Concentrations of metabolites were calculated based on the concentration of TSP-d_4 at 2 mM. And overlapped signal

areas were analyzed by a 2D correlation spectroscopy (COSY) NMR spectra [23].
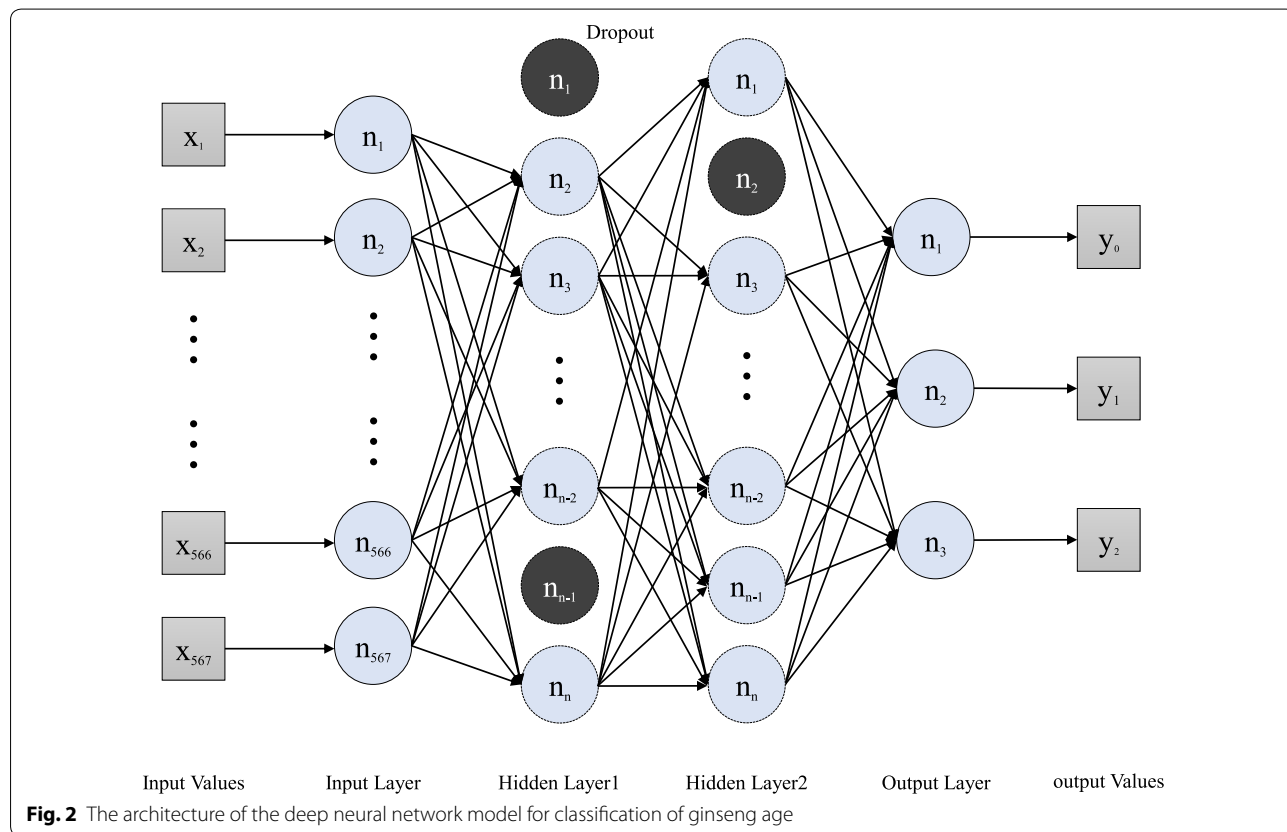
Data pre-processing

Each NMR spectrum was binned from 0.83 to 6.8 ppm, and the water peak area and spinning sideband area (1.15–1.185, 1.948–1.995, and 4.68–4.88 ppm) were excluded using Chenomx NMR suite 7.1 professional. The binning size was 0.01 ppm. To minimize the difference in concentration between the samples, the binning data were normalized to the total area. In this procedure, the NMR spectrum was divided into 480 variables. The pre-processed dataset was used to train and validate the classification model for cultivation age classification of ginseng. The dataset (385 samples) was randomly divided into a training dataset (70%) and test dataset (30%).
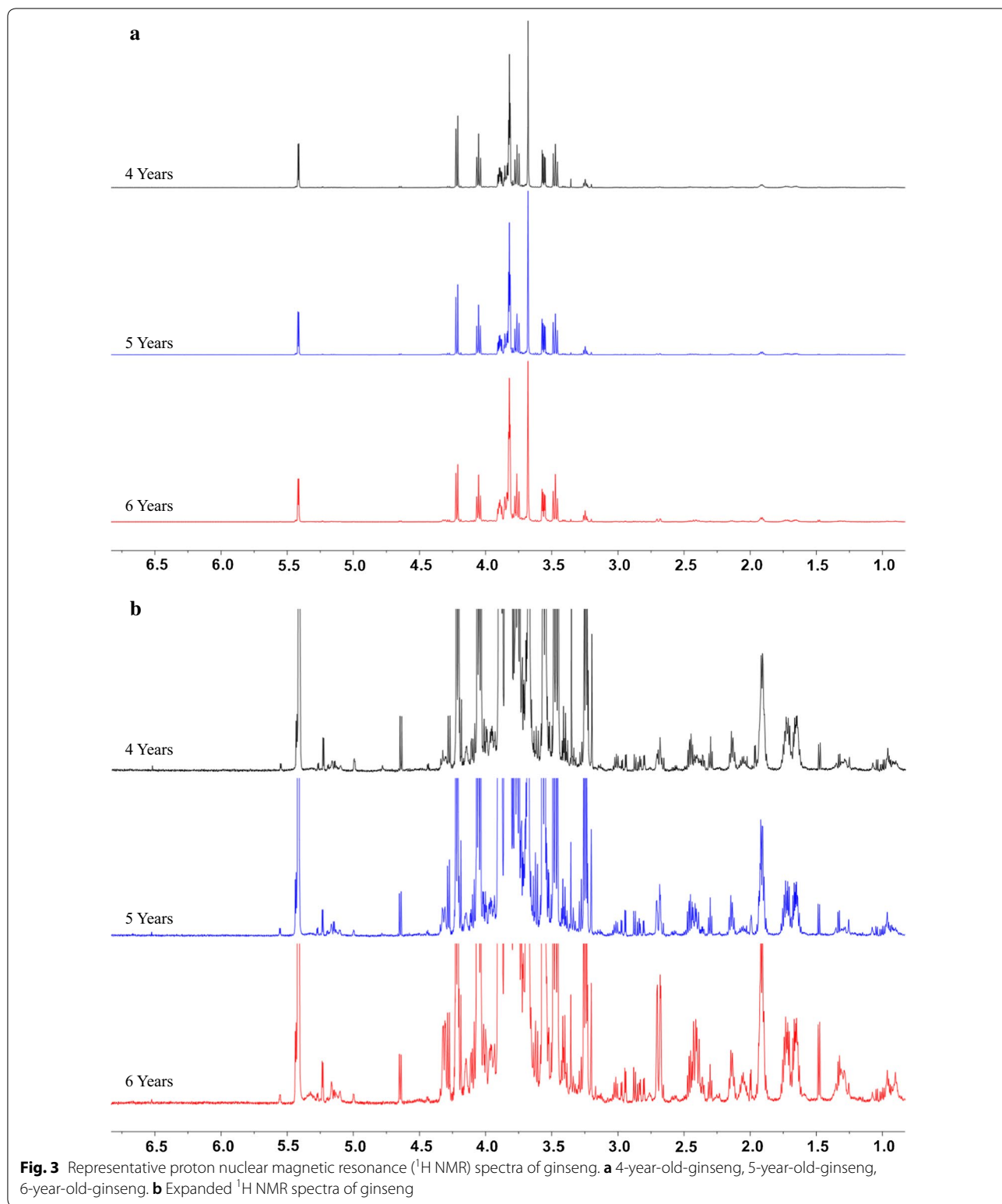
PLS-DA

Partial least-squares discriminant analysis (PLS-DA) is one of the multivariate data analysis methods and is currently a popular classification method for metabolic analysis. The procedure was conducted using the scikit-learn 0.19.2 [24] along with custom python codes. And, PLS-DA model was optimized by finding the suitable number of components that minimizes the validation loss.

Deep learning

Deep learning processes were carried out using Keras package 2.2.2 in Python language 3.6. Figure 2 illustrates the construction of a deep neural network (DNN) model. Deep learning comprises a multi-layered neural network with multiple hidden layers in between the input and output layers. Each neuron takes in a weighted input on the connection and provides an activation value as output through an activation function. In this non-linear processing, raw data can be automatically transformed into learned features and representative data [25–28]. The DNN comprises four layers: an input layer, two hidden layers, and an output layer. Rectified Linear Units (ReLU) was used as an activation function in each layer [29] except for the output layer, in which Softmax was used instead of ReLU. This function is often used in multiclass classification methods in the output layer [30]. Dropout (the dropout ratio = 0.1) and batch normalization [31] were used in the present model. Dropout is effective for avoiding overfitting, and batch normalization enables higher learning rates and regularization. We used 'categorical_crossentropy' optimizer, 'Adam' loss function, and 'accuracy' metric function to compile the model. Other hyper-parameters were set to default. When training the deep learning models, we used 'Modelcheckpoint'

Fig. 2 The architecture of the deep neural network model for classification of ginseng age

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Fig. 3 Representative proton nuclear magnetic resonance (^{1}H NMR) spectra of ginseng. **a** 4-year-old-ginseng, 5-year-old-ginseng, 6-year-old-ginseng. **b** Expanded ^{1}H NMR spectra of ginseng

to ensure that only the best model was saved if the validation loss improves over the best values. The stored best prediction model was then applied to make predictions on the test dataset.
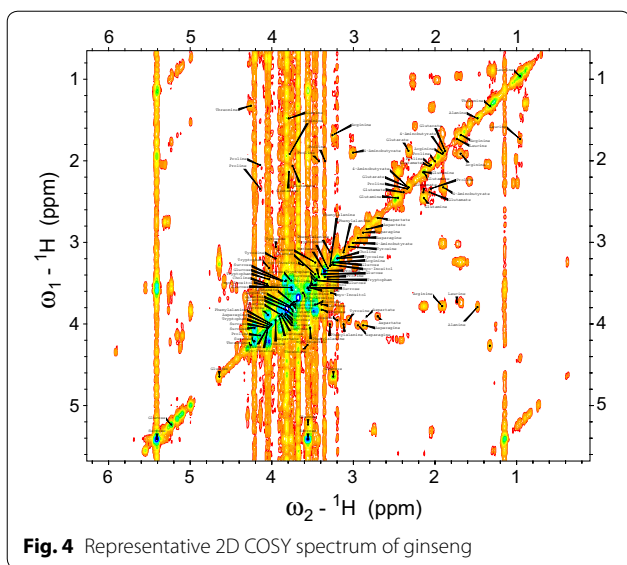
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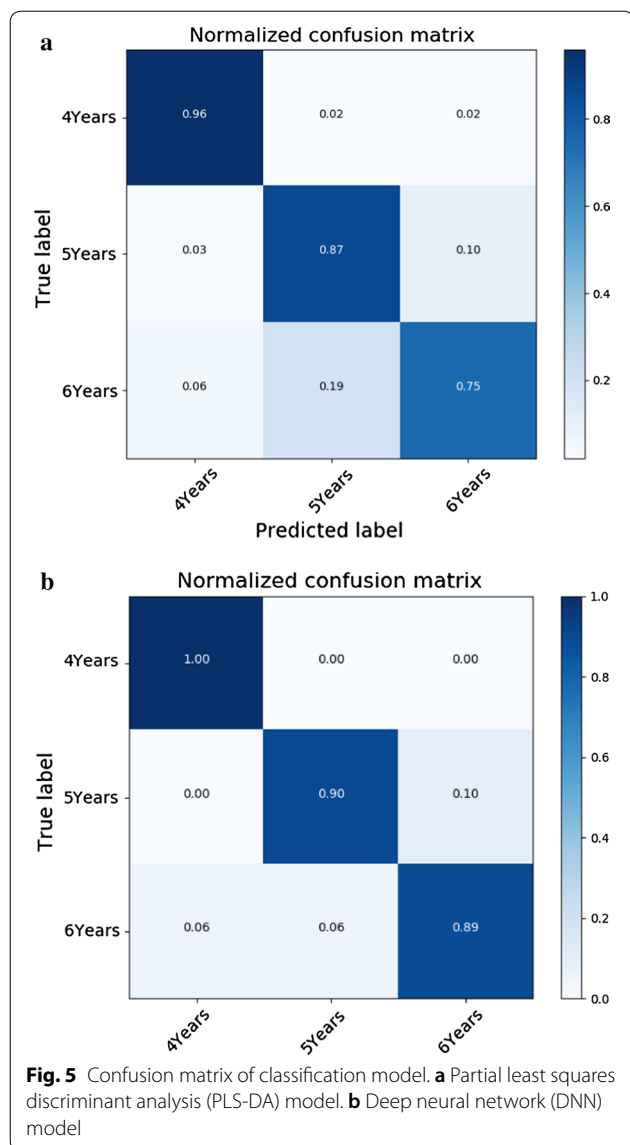**Fig. 4** Representative 2D COSY spectrum of ginseng

Table 2 Classification report of classification model (a) Partial least squares discriminant analysis (PLS-DA) model (b) Deep neural network (DNN) model

Label	Precision (%)	Recall (%)	F1-score (%)
(a) PLS-DA			
4 years	94.1	96.0	95.0
5 years	76.5	86.7	81.2
6 years	87.1	75.0	80.6
Weighted avg	87.4	87.1	87.0
(b) Deep learning			
4 years	96.2	100	98.1
5 years	93.1	90.0	91.5
6 years	91.4	88.8	90.1
Weighted avg	93.9	93.9	93.9

Table 1 Metabolites identified in the powdered ginseng from NMR data: assigned chemical shifts (multiplicities), relative concentrations

Metabolite name	Chemical shifts δ ^{1}H (ppm), multiplicity	Relative concentrations (%)		
		4 years	5 years	6 years
4-Aminobutyrate	2.29 (t), 1.89 (m), 3.00 (t)	0.7483	0.5596	0.6598
Alanine	1.46 (d), 3.78 (q)	0.4255	0.4903	0.9251
Arginine	1.66 (m), 1.91 (m), 3.27 (t), 3.77 (t)	7.8227	7.4908	9.5260
Asparagine	2.94 (dd), 2.84 (dd)	0.6440	0.8331	1.3128
Aspartate	2.67 (dd), 2.81 (dd)	1.0417	1.1327	1.2112
Choline	3.18 (s) 3.50 (dd), 4.05 (t)	0.4441	0.2738	0.2984
Ethanolamine	3.13 (t), 3.83 (t)	0.1699	0.1313	0.1381
Fumarate	6.51 (s)	0.0826	0.0545	0.0670
Glucose	3.65–3.92 (m), 5.22 (d), 4.63 (d)	3.6931	4.1924	2.8540
Glutamate	2.04 (m), 2.13 (m), 2.33 (m), 3.36 (m)	0.9006	0.7732	0.9592
Glutamine	2.11 (m), 2.14 (m), 2.42 (m), 2.46 (m) 3.76 (t)	3.8839	2.4603	2.6230
Isoleucine	0.92 (t), 1.00 (d), 1.24 (m) 1.45 (m)	0.2511	0.1446	0.1848
Leucine	0.94 (d), 0.95 (d) 1.71 (m), 3.73 (m)	0.5503	0.3288	0.3505
Malate	2.41 (dd), 2.69 (dd), 4.33 (dd)	0.8298	2.1772	2.7428
myo-Inositol	3.27 (t), 3.53 (dd), 3.62 (t), 4.05 (t)	0.0496	0.0190	0.0203
Phosphocholine	3.21 (s)	0.2421	0.1788	0.1930
Phenylalanine	7.33 (d), 7.37 (m), 7.43 (m)	0.3864	0.2516	0.2930
Proline	2.00 (m), 2.34(m), 3.32 (m), 3.41(m), 4.12 (dd)	74.8584	76.3855	72.9590
Glycerophosphocholine	3.21 (s)	0.2714	0.2534	0.3033
Sucrose	5.40 (d), 4.20 (d), 4.03 (t), 3.88 (m), 3.82 (m), 3.75 (t), 3.67 (s), 3.65 (s), 3.54 (dd), 3.46 (t)	0.2434	0.2339	0.2893
Threonine	1.32 (d), 3.57 (d), 4.25 (m)	0.3300	0.1979	0.2336
Tyrosine	6.89(d), 7.18 (d)	1.8735	1.2515	1.6550
Valine	0.98 (d), 1.03 (d), 2.26 (m)	0.2577	0.1861	0.2007

S singlet, *d* doublet, *t* triplet, *m* multiplet, *dd* doublet of doublet

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Fig. 5 Confusion matrix of classification model. **a** Partial least squares discriminant analysis (PLS-DA) model. **b** Deep neural network (DNN) model
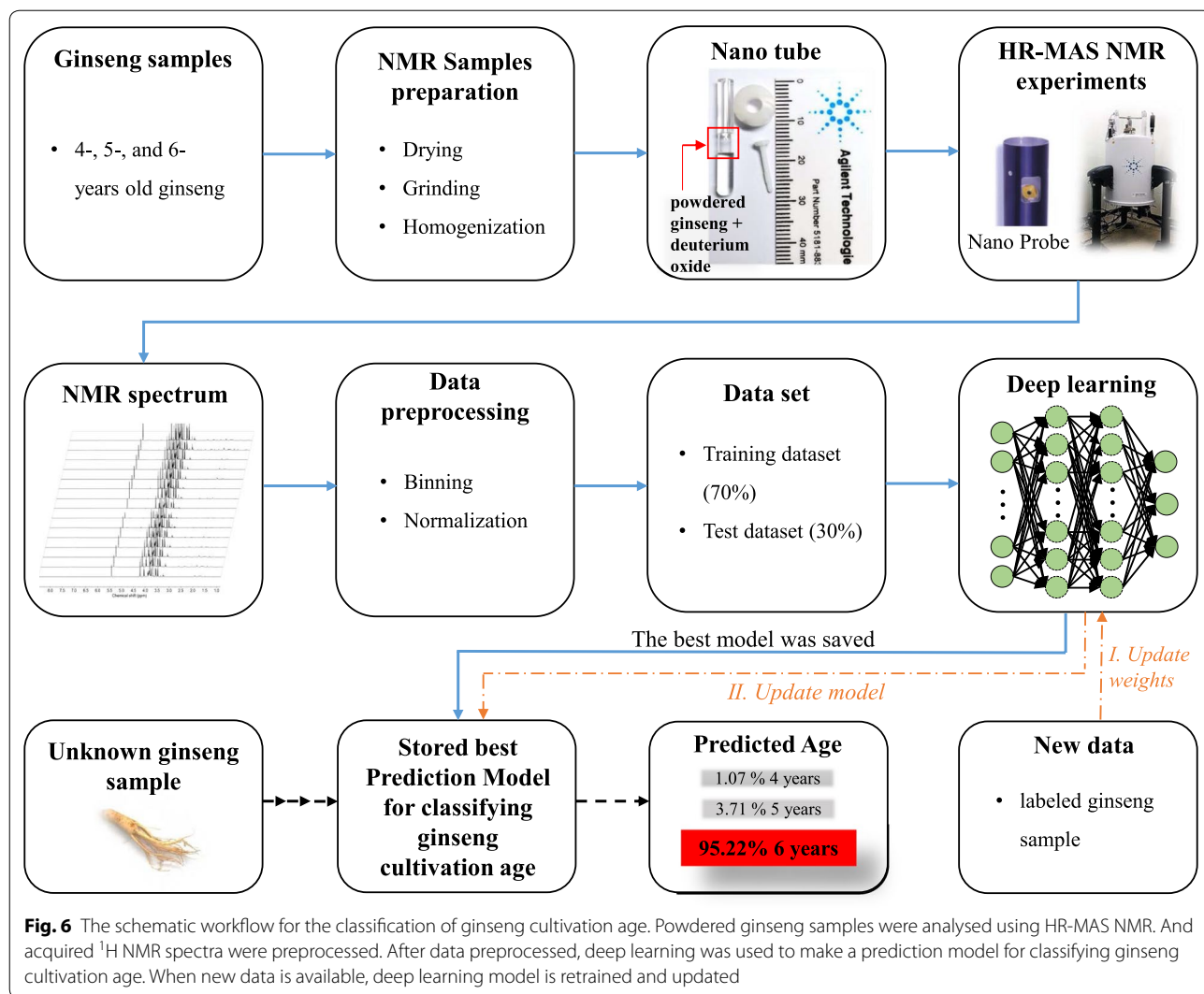
Results and discussion

Total 385 ginseng samples were measured by ^{1}H high-resolution magic angle spinning (HR-MAS) nuclear magnetic resonance (NMR) spectroscopy. By using HR-MAS NMR spectroscopy, the easy sample preparation without extraction process and the short analysis time are possible. Therefore, minimal sampling process allows to minimize the handling variations in sample preparation process. Representative ^{1}H-NMR spectra are shown in Fig. 3. They reflect individual metabolites of ginseng measured by HR-MAS NMR spectroscopy. And metabolites in the spectra were assigned and quantified using Chenomx NMR Suite 7.1 professional and 2D COSY spectra which provide the information of spin–spin coupling between protons (Fig. 4)

[23]. Metabolites in each spectrum were identified and quantified by targeted analysis (Table 1). However, this approach is time-consuming and costly for a routine use in the quality control of ginseng. Therefore, we focused on a non-targeted analysis such as PLS-DA and deep learning to compare the patterns of the entire spectra. Since this approach compares the calculated values by digitizing the spectra, subjective interpretation can be excluded and a large amount of data can be handled simultaneously.

Classification report (Table 2) and confusion matrix (Fig. 5) were carried out using scikit-learn 0.19.2 [24] to show performance of classification models. The accuracy of the PLS-DA model when used to distinguish between 4-, 5-, and 6-year-old ginseng was 87.1%. Table 2a shows the classification report of the PLS-DA model. The classification report included the precision, recall, and F1 score for each class of the test dataset. The precision is the fraction of true positives among the total predicted positive observations. The recall is the fraction of true positives within all observations of relevant instances. The F1 score is a harmonic average of the precision and recall; the optimum F1 score is 100%. In the PLS-DA model, the values of precision, recall, and F1 score for the 4-year-old ginseng sample were better than for the 5- and 6-year-old ginseng samples. The weighted average values for all classes were 87.4% precision, 87.1% recall, and 87.0% F1 score. Figure 5a shows the confusion matrix of the PLS-DA model. The confusion matrix provides an evaluation of the quality of the output of a classification model for the ginseng test dataset. The diagonal elements represent the number of values for which the predicted class is equal to the true class, whereas off-diagonal elements are those that are mislabeled by the classification model. The higher the diagonal values, the more accurate the predictions are. The accuracy of the DNN model was 93.9%. In DNN model (Table 2b), the values of precision, recall, and F1 score for the 4-year-old ginseng sample were better than for the 5- and 6-year-old ginseng samples. The average values for all classes were 93.9% precision, 93.9% recall, and 93.9% F1 score. Figure 5b shows the confusion matrix for the DNN model. Compared to the PLS-DA model, all classification report values were higher in the DNN model. Therefore, the DNN model achieved a higher classification result than the PLS-DA model. Previous studies conducted multivariate statistical analyses with NMR data for discrimination of ginseng ages, and the ginseng samples were extracted with the solvent consisted of methanol and water [5–7]. As in our study, when comparing the 4 to 6-year old ginseng that are

Fig. 6 The schematic workflow for the classification of ginseng cultivation age. Powdered ginseng samples were analysed using HR-MAS NMR. And acquired ^{1}H NMR spectra were preprocessed. After data preprocessed, deep learning was used to make a prediction model for classifying ginseng cultivation age. When new data is available, deep learning model is retrained and updated

most widely distributed on the market, it was found that the discriminant rate was not high compared to the overall discriminant rate in their papers. This study was able to further increase the discrimination rate, which was low in the PLS-DA model, by using the DNN model, even though the variation between samples with varying regions and harvesting times.

These results demonstrate that HR-MAS NMR spectroscopy with deep learning, which achieved a higher classification result than the PLS-DA, might be useful model for the classification of ginseng cultivation age. The schematic workflow for the classification of ginseng cultivation age using HR-MAS NMR Spectroscopy with deep learning is shown in Fig. 6. In the present study, the number of ginseng datasets were relatively small, which might have caused increased overfitting in the classification models. A limited number of training datasets compared to the number of learnable variables can lead to overfitting. This is a major challenge in training models. Nevertheless, we obtained an encouraging result by applying dropout, batch normalization, and model checkpoint to prevent overfitting. It is possible to improve the classification capability by using more datasets. Moreover, by using HR-MAS NMR, we were able to reduce the sampling variation and achieve reproducibility. Furthermore, samples from two different cultivation areas and three different harvesting years helped to improve the reliability of the results in classifying ginseng cultivation age.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

Author details
[1] Department of Chemistry, Center for Proteome Biophysics and Chemistry Institute for Functional Materials, Pusan National University, Busan 46241, Republic of Korea. [2] Department of Herbal Crop Research, National Institute of Horticultural and Herbal Science, RDA, Eumseong 27709, Republic of Korea. [3] Department of Electrical and Computer Engineering, Pusan National University, Busan 46241, Republic of Korea.

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