

Near-infrared Spectroscopy as a Process Analytical Technology Tool for Monitoring the Parching Process of Traditional Chinese Medicine Based on Two Kinds of Chemical Indicators

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ABSTRACT

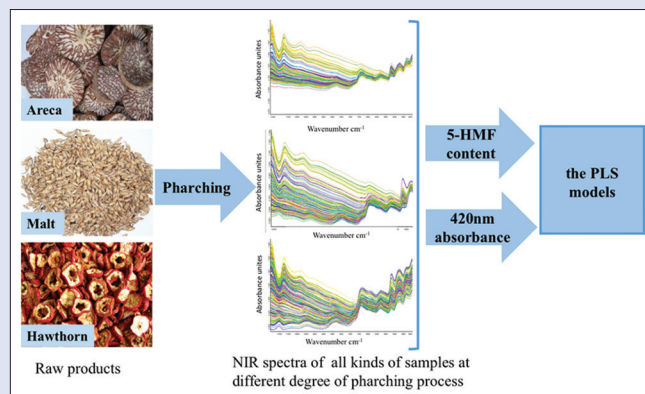
Background: The active ingredients and thus pharmacological efficacy of traditional Chinese medicine (TCM) at different degrees of parching process vary greatly. **Objective:** Near-infrared spectroscopy (NIR) was used to develop a new method for rapid online analysis of TCM parching process, using two kinds of chemical indicators (5-(hydroxymethyl) furfural [5-HMF] content and 420 nm absorbance) as reference values which were obviously observed and changed in most TCM parching process. **Materials and Methods:** Three representative TCMs, Areca (*Areca catechu* L.), Malt (*Hordeum Vulgare* L.), and Hawthorn (*Crataegus pinnatifida* Bge.), were used in this study. With partial least squares regression, calibration models of NIR were generated based on two kinds of reference values, i.e. 5-HMF contents measured by high-performance liquid chromatography (HPLC) and 420 nm absorbance measured by ultraviolet-visible spectroscopy (UV/Vis), respectively. **Results:** In the optimized models for 5-HMF, the root mean square errors of prediction (RMSEP) for Areca, Malt, and Hawthorn was 0.0192, 0.0301, and 0.2600 and correlation coefficients (R_{cal}) were 99.86%, 99.88%, and 99.88%, respectively. Moreover, in the optimized models using 420 nm absorbance as reference values, the RMSEP for Areca, Malt, and Hawthorn was 0.0229, 0.0096, and 0.0409 and R_{cal} were 99.69%, 99.81%, and 99.62%, respectively. **Conclusions:** NIR models with 5-HMF content and 420 nm absorbance as reference values can rapidly and effectively identify three kinds of TCM in different parching processes. This method has great promise to replace current subjective color judgment and time-consuming HPLC or UV/Vis methods and is suitable for rapid online analysis and quality control in TCM industrial manufacturing process.

Key words: 420 nm absorbance, 5-(hydroxymethyl) furfural content, near-infrared spectroscopy, partial least squares, process analytical technology tool, traditional Chinese medicine

SUMMARY

- Near-infrared spectroscopy (NIR) was used to develop a new method for online analysis of traditional Chinese medicine (TCM) parching process
- Calibration and validation models of Areca, Malt, and Hawthorn were generated by partial least squares regression using 5-(hydroxymethyl) furfural contents and 420 nm absorbance as reference values, respectively, which were main indicator components during parching process of most TCM
- The established NIR models of three TCMs had low root mean square errors of prediction and high correlation coefficients

- The NIR method has great promise for use in TCM industrial manufacturing processes for rapid online analysis and quality control.



Abbreviations used: NIR: Near-infrared Spectroscopy; TCM: Traditional Chinese medicine; Areca: *Areca catechu* L.; Hawthorn: *Crataegus pinnatifida* Bge.; Malt: *Hordeum vulgare* L.; 5-HMF: 5-(hydroxymethyl) furfural; PLS: Partial least squares; D: Dimension faction; SLS: Straight line subtraction; MSC: Multiplicative scatter correction; VN: Vector normalization; RMSEC: Root mean square errors of cross-validation; RMSEP: Root mean square errors of validation; R_{cal} : Correlation coefficients; RPD: Residual predictive deviation; PAT: Process analytical technology; FDA: Food and Drug Administration; ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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INTRODUCTION

Parching, a process changes active ingredients and pharmacological efficacy greatly, plays an important therapeutic role in traditional Chinese medicine (TCM).^[1-3] These changes are complex and difficult to measure. The current method to identify the degree of parching process is based on the color judgment, which is not only subjective but also unable to reflect the real variations accurately.^[3] According to the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Q8, the product performance can be gained by the application of process

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analytical technology (PAT).^[4] Moreover, the US Food and Drug Administration (FDA) also advocated the use of PAT to improve the pharmaceutical manufacturing and quality assurance.^[5] Thus, the online analysis and quality control should be studied to identify the critical sources of variability, to manage the process variability, and to improve the quality of industrial products effectively.^[6-11]

Conventional high-performance liquid chromatography (HPLC) or ultraviolet-visible spectroscopy (UV/Vis) methods are not ideal for online analysis to control TCM parching process because they require tedious sample preparation and time-consuming sample analysis. Near-infrared spectroscopy (NIR) is a fast, precise, noninvasive, and nondestructive technique that requires little or no sample preparation. Recently, NIR has been routinely preferred and gradually becomes one of the most efficient online analytical tools for qualitative and quantitative analysis of herb materials, separation monitoring, and extraction process.^[8-18] Therefore, to control the parching process and guarantee the stable quality of parched TCM, NIR spectroscopy in line with the FDA's PAT initiative and guidance was applied in online analysis of TCM parching process.^[5]

Areca, Malt, and Hawthorn have diverse pharmacological efficacy in different degrees of parching process as common TCM. Raw Areca is mainly used to expel parasite, whereas stir-charred Areca is used to disperse food stagnation.^[3,9,19] Raw Malt's efficacy is strengthening the spleen and stomach function, stir-fried Malt is good for digestion and delectation, and stir-charred Malt is helpful in relieving dyspepsia.^[3,20] Raw Hawthorn can eliminate blood stasis and alleviate pain, stir-fried Hawthorn can promote digestion, stir-charred Hawthorn is helpful in anti-diarrhea, and carbonized Hawthorn can stanch bleeding.^[3,21]

Hence, it is meaningful to control the parching process of these TCMs to guarantee product performance of these parched TCMs. During the parching process of most TCM, Maillard reaction (the reaction process includes nucleophilic addition, dehydration, cyclization, Amadori rearrangement, enolization, and Strecker decomposition) and caramelization reaction always occur.^[22] As shown in Figure 1 and 5-(hydroxymethyl) furfural (5-HMF) is an important intermediate product, melanoidins and caramels are the main end products. The reaction degree of browning could be reflected indirectly by measuring the absorbance of nonenzymatic browning reaction products (melanoidins and caramels) at 420 nm.^[22-24] Thus, both 5-HMF content and 420 nm absorbance change obviously in most TCM parching process and can be used as chemical indicators to reflect TCM parching process.

In this study, we took Areca, Malt, and Hawthorn as TCM examples and used NIR to establish two kinds of models of 5-HMF contents and 420 nm absorbance for online analysis and quality control during the TCM parching process, respectively. The validation results showed that the models were robust, accurate, and repeatable for online analysis and quality control. On the above foundation, the product quality can be monitored online by NIR efficiently to get the parched products of best quality.

MATERIALS AND METHODS

Samples and reagents

Areca pieces (Yunnan, China), Hawthorn pieces (Shandong, China), and Malt (Sichuan, China) were all collected from TCM markets (Sichuan, China). Each kind of TCM weighed 18 kg was divided into 18 parts

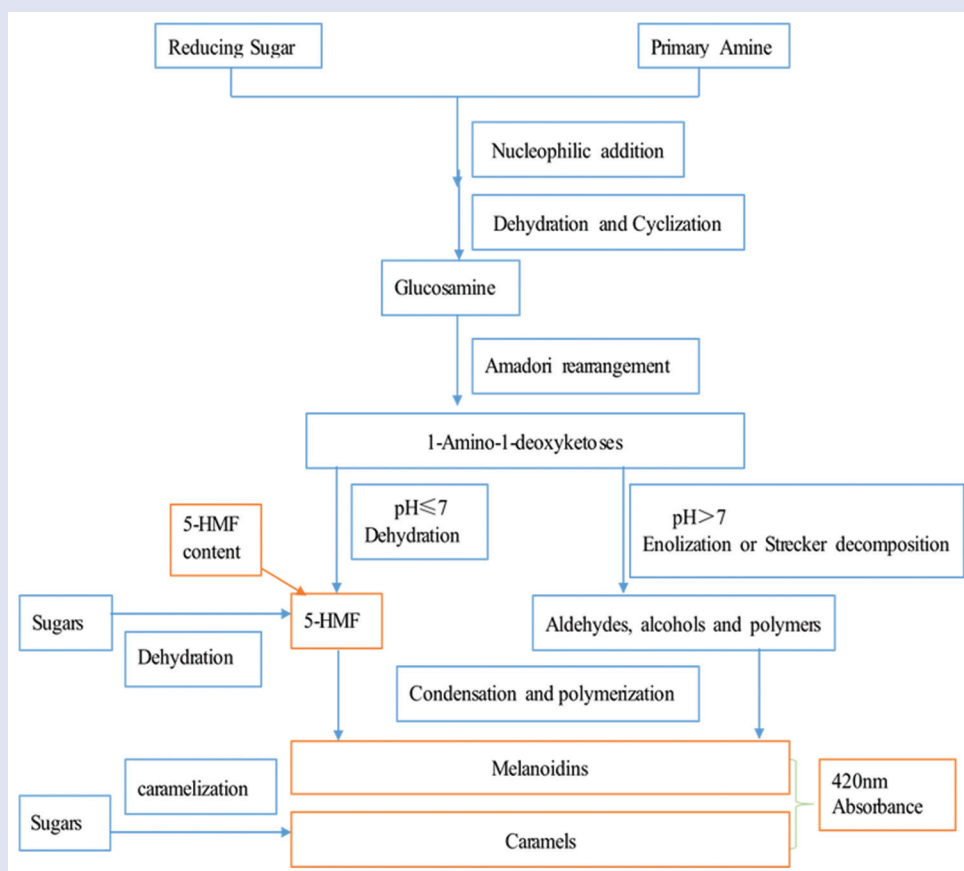


Figure 1: The generation process of (5-(hydroxymethyl)furfural and other components which have high absorbance at 420 nm during parching process

equally. Each part was stir-frying parched; the temperature of the herbal medicine during parching process was controlled by infrared thermometer (GM320, BENETECH). Parched samples were collected at 25°C, 110°C, 130°C, 150°C, 160°C, 170°C, 180°C, 190°C, 200°C, and 210°C, respectively. Hence, 18 batches of parched samples of each herbal medicine were obtained from this process, and each batch contained ten kinds of TCM of different degrees of parching process. To ensure that moisture was not an interfering factor, all samples were dried in a silica gel desiccator for at least 7 h at room temperature until the weight loss was <0.0003 g.

5-HMF was obtained from the Sigma (Sigma-Aldrich Inc., St. Louis, MO, USA). HPLC-grade methanol was obtained from Tianjin Kernel Chemical Reagent Company (Tianjin, PR China). Water was purified by an ultrapure water instrument. All other reagents were of analytical grade.

Near-infrared spectroscopy data collection

The NIR spectra of each parched sample were recorded by QuasIR 3000 spectrometer (Vspec, USA) equipped with a PbS detector, sample cup, and rotary tables. The system was operated by Essential FT-IR spectral acquisition and processing software (Operant LLC Licensed to MTG, USA). The spectra were obtained at a resolution of 8 cm^{-1} over a wavelength range of $12,000\text{--}4000\text{ cm}^{-1}$ with 32 scans per spectrum, and air absorbance was recorded as the reference standard. Each sample measurement was repeated two times. The average NIR spectra were shown in Figure 2.

Reference values collection

All parched samples were first milled into powder and then passed through 60 mesh sieves, respectively. About 1.0 g sample powder was ultrasonic extracted by 25 mL 60% methanol for 45 min and then filtrated by $0.45\text{ }\mu\text{m}$ filters to get the sample solution. A 1100 HPLC system (Agilent Technologies Inc., USA) consisting of UV/VIS detector was used for the quantitative determination of 5-HMF at a wavelength of 280 nm. A Kromasil C18 ($4.6\text{ mm} \times 250\text{ mm}$, $5\text{ }\mu\text{m}$) was employed in 30°C column temperature to separate and analyze $10\text{ }\mu\text{L}$ sample injections. The elution system was composed of methanol–water with 0.5% acetic acid (10:90) at a flow rate of 1.0 mL/min . The 5-HMF content was calculated by daily linear regression equation to ensure the accuracy. Each sample solution was diluted by 10 times with 60% methanol, then tested in 420 nm with UV-6300PC spectrophotometer (MAPADA, Shanghai) to get the absorbance, and the 60% methanol absorbance was recorded as the reference standard.

Data processing by partial least square

The intensity of the measurements at different wavenumbers of NIR spectra can be correlated to the concentrations of the 5-HMF and

420 nm absorbance in the sample through partial least square (PLS) with the OPUS 6.5 software (Bruker Optik, Ettlingen, Germany), respectively.

RESULTS AND DISCUSSION

Sample set selection

To ensure the representativeness of the calibration set and validation set, cluster analysis of NIR spectrum was used first to classify the samples (pretreatment method: vector normalization (VN); Spectral segment: $12,000\text{--}4000\text{ cm}^{-1}$). Each kind of TCM was divided into four categories roughly (raw, stir-fried, stir-charred, and carbonized product, shown in Figure 3). Among the 180 samples, 44 samples were selected randomly from each cluster (11 samples in one cluster) as a validation set to validate the PLS model, and the remaining 136 samples were divided into calibration set to establish the calibration model. Moreover, the calibration set contains full potential variations.

Spectral pretreatment methods

There are ten kinds of important spectral pretreatment methods including constant offset elimination (COE), straight line subtraction (SLS), VN, min/max normalization, multiplicative scatter correction (MSC), first derivative, second derivative, first derivative + SLS, first derivative + VN, and first derivative + MSC. Each pretreatment method was utilized in each NIR spectrum to eliminate noise, baseline shift, enhance the spectral features, and matrix background interference to extract the relevant information before PLS modeling.

Development of calibration models

The spectral pretreatment methods, spectral range, and the dimension factor (D) are critical parameters for the optimum model in PLS. The best parameter was evaluated based on the correlation coefficients of the calibration set ($R_{\text{cal}}\%$), the root mean square errors of cross-validation (RMSECV), and the residual predictive deviation (RPD). The best calibration model was selected by highest $R_{\text{cal}}\%$ and RPD as well as lowest RMSECV.

As shown in Table 1a and 1b, calibration equations were modeled with ten spectral pretreatments and optimized not only by spectral range but also by dimension factor (D).

The evaluation on the predicted result of the validation set

The above-optimized models were used to predict 5-HMF content and 420 nm absorbance of the samples in the validation set individually. The validation set can test the predictive ability of the optimized PLS

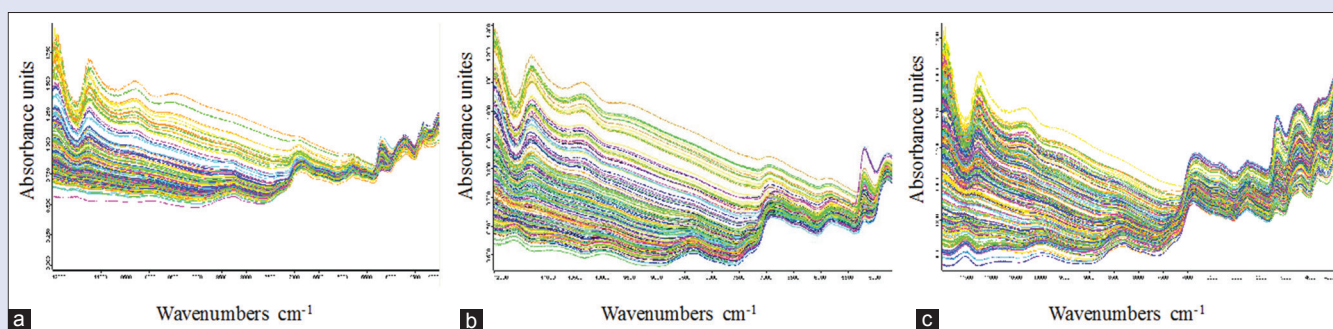


Figure 2: Near-infrared spectroscopy spectra of (a) Areca samples, (b) Malt samples, and (c) Hawthorn samples

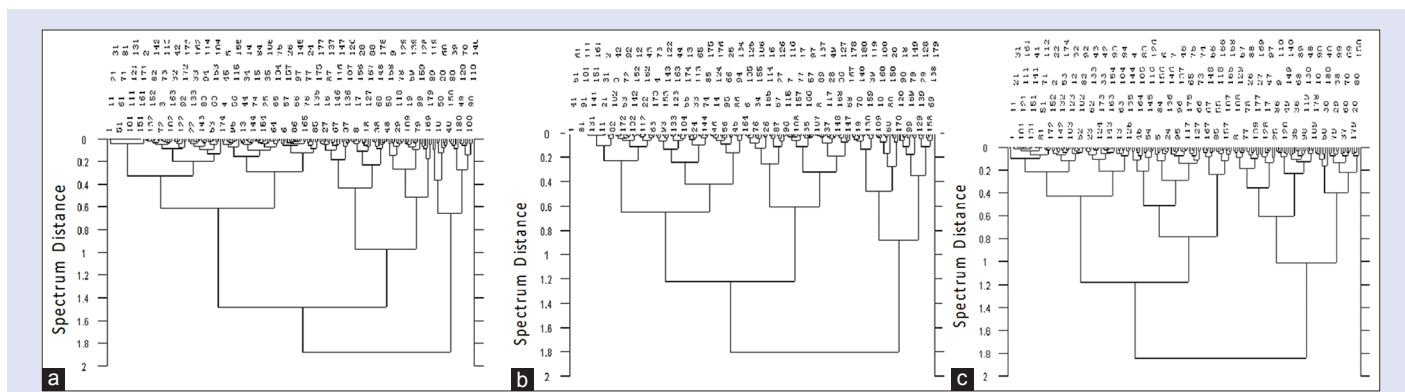


Figure 3: Cluster analysis of (a) Areca samples, (b) Malt samples, and (c) Hawthorn samples near-infrared spectroscopy spectrum

Table 1a: The information of partial least squares models using 5-(hydroxymethyl) furfural content as reference value

TCM	Pretreatment	Spectral range (cm ⁻¹)	D	Calibration set			Validation set	
				R _{cal} ² (%)	RMSECV	RPD	RMSEP	R _{cal} ² (%)
Areca	Constant offset elimination	12000-6098, 5453-4247	8	98.94	0.0329	9.7	0.0192	99.86
	VN	12000-4247	6	98.69	0.0372	8.7	0.0286	99.66
	SLS	12000-5449, 4602-4247	8	98.53	0.0384	8.3	0.0344	99.57
	Min-max normalization	12000-4247	7	98.23	0.0440	7.5	0.0374	99.40
	First derivative + VN	12000-7498, 6101-4247	10	98.73	0.0341	8.9	0.0255	99.75
	MSC	5453-4247	11	96.95	0.0573	5.7	0.0557	98.96
	First derivative	7502-4247	10	98.81	0.0325	9.2	0.0232	99.80
	Second derivative	7502-6098, 5453-4598	8	98.34	0.0407	7.8	0.0369	99.52
	First derivative + SLS	12000-4247	4	97.16	0.0527	5.9	0.0466	99.05
	First derivative + MSC	7502-6098, 5453-4247	7	98.61	0.0339	8.5	0.0284	99.61
Malt	Constant offset elimination	12000-5448, 4424-4249	8	99.70	0.0355	18.2	0.0301	99.88
	VN	12000-4249	6	99.40	0.0511	12.9	0.0460	99.74
	SLS	12000-5448, 4600-4249	7	99.67	0.0371	17.4	0.0326	99.86
	Min-max normalization	12000-5448, 4600-4249	15	99.70	0.036	17.9	0.0324	99.86
	First derivative + VN	7502-4249	8	99.41	0.0499	13.0	0.0454	99.76
	MSC	7502-4249	12	99.26	0.0566	11.6	0.0533	99.67
	First derivative	7502-6097, 5451-4249	9	99.35	0.0523	12.4	0.0507	99.68
	Second derivative	7502-6097, 5451-4596	8	99.03	0.0641	10.2	0.0578	99.60
	First derivative + SLS	7502-4596	10	99.63	0.0395	16.5	0.0364	99.82
	First derivative + MSC	7502-4596	10	99.37	0.0511	12.6	0.0503	99.73
Hawthorn	Constant offset elimination	11997-6098, 5453-4247	10	99.61	0.3550	16.0	0.2600	99.88
	VN	11997-6098, 5453-4247	7	99.17	0.5080	11.0	0.4800	99.58
	SLS	11997-6098, 5453-4247	5	99.17	0.5180	11.0	0.5100	99.34
	Min-max normalization	11997-5449, 4602-4247	9	99.23	0.4910	11.4	0.4310	99.65
	First derivative + VN	11997-4598	8	98.77	0.6260	9.0	0.5610	99.44
	MSC	11997-5449, 4247-4602	7	97.83	0.8120	6.8	0.7270	99.04
	First derivative	11997-4247	7	99.05	0.5520	10.3	0.4160	99.54
	Second derivative	7502-4598	8	97.53	0.8850	6.4	1.2700	96.95
	First derivative + SLS	11997-4247	10	99.04	0.5630	10.2	1.0100	98.34
	First derivative + MSC	11997-4247	8	99.09	0.5470	10.5	0.5370	99.13

calibration model. The optimum models were evaluated by highest R_{cal} (%) and lowest root mean square errors of prediction (RMSEP). The results were shown in Table 1a and 1b.

The optimized near-infrared spectroscopy model

The optimized NIR models with highest R_{cal} (%) and RPD, lowest RMSECV and RMSEP were selected by comparing the parameters of these models. As shown in Table 2a and 2b, calibration equations which used 5-HMF content as reference values were modeled with COE for three kinds of TCM, and calibration equations which used 420 nm absorbance as reference values were modeled with COE for Area and Hawthorn and NV for Malt. The results indicated that the established

models were robust, accurate, and repeatable for online analysis and quality control.

CONCLUSIONS

This research indicated that NIR combined with PLS as well as using 5-HMF content and 420 nm absorbance as reference values, could provide accurate and rapid online analysis of three kinds of TCM (Areca, Malt, and Hawthorn) during parching process. The results showed that the established NIR models had low RMSEP and high correlation coefficients. Compared with the conventional analytical procedures, this method is more comprehensive, more intuitive, and more convenient, and it can be widely applied in TCM

Table 1b: The information of partial least squares models using 420 nm absorbance as reference value

TCM	Pretreatment	Spectral range (cm ⁻¹)	D	Calibration set			Validation set	
				R _{cal} ² (%)	RMSECV	RPD	RMSEP	R _{cal} ² (%)
Areca	Constant offset elimination	12000-6098, 5453-4247	8	98.33	0.0318	7.8	0.0229	99.69
	VN	7502-4598	9	98.23	0.0353	7.5	0.0301	99.52
	SLS	12000-5449	6	97.88	0.0371	6.9	0.0242	99.64
	Min-max normalization	7502-4247	9	97.90	0.0376	6.9	0.0365	99.23
	First derivative + VN	7502-4598	5	97.78	0.0397	6.7	0.0348	99.21
	MSC	7502-4247	8	97.86	0.0370	6.9	0.0353	99.45
	First derivative	12000-4247	4	97.81	0.0365	6.8	0.0344	99.46
	Second derivative	7502-4598	7	97.69	0.0389	6.6	0.0365	99.20
	First derivative + SLS	12000-4247	5	97.45	0.0420	6.3	0.0329	99.33
Malt	First derivative + MSC	7502-4247	6	97.69	0.0401	6.6	0.0373	99.17
	Constant offset elimination	12000-7498, 5451-4249	6	98.60	0.0228	8.4	0.0197	99.27
	VN	12000-4249	13	99.41	0.0144	13.0	0.0096	99.81
	SLS	7502-4249	14	98.81	0.0198	9.2	0.0187	99.30
	Min-max normalization	12000-6097, 5451-4249	6	98.45	0.0211	8.0	0.0209	98.96
	First derivative + VN	7502-5448, 4600-4249	7	98.53	0.0237	8.3	0.0220	99.09
	MSC	12000-4596	4	98.53	0.0216	8.2	0.0211	99.15
	First derivative	7502-6097, 5451-4596	12	98.71	0.0218	8.8	0.0190	99.29
	Second derivative	7502-4249	6	97.39	0.0317	6.2	0.0312	98.11
Hawthorn	First derivative + SLS	7502-6097, 5451-4249	12	99.14	0.0174	10.8	0.0136	99.62
	First derivative + MSC	6100-4249	9	98.14	0.0264	7.3	0.0250	98.26
	Constant offset elimination	11997-4247	11	99.11	0.0481	10.6	0.0409	99.62
	VN	11997-7498, 6101-4247	7	98.21	0.0672	7.5	0.0659	99.02
	SLS	11997-6098, 5453-4247	8	98.94	0.0523	9.7	0.0462	99.52
	Min-max normalization	11997-4247	9	98.28	0.0661	7.6	0.0559	99.23
	First derivative + VN	7502-4247	11	97.82	0.0756	6.8	0.0742	98.86
	MSC	11997-6098, 5453-4247	9	97.02	0.0877	5.8	0.0775	98.63
	First derivative	11997-4247	7	98.58	0.0606	8.4	0.0578	99.34
	Second derivative	7502-4247	6	97.03	0.0876	5.8	0.0777	98.61
	First derivative + SLS	11997-4247	7	98.39	0.0649	7.9	0.0555	99.37
	First derivative + MSC	7502-6098, 5453-4247	11	97.34	0.0831	6.1	0.0816	98.62

Table 2a: Parameters of optimal models using 5-(hydroxymethyl) furfural content as reference values

TCM	Pretreatment	Spectral range (cm ⁻¹)	D	Calibration set			Validation set	
				R _{cal} (%)	RMSECV	RPD	RMSEP	R _{cal} (%)
Areca	Constant offset elimination	12000-6098, 5453-4247	8	98.94	0.0329	9.7	0.0192	99.86
Malt	Constant offset elimination	12000-5448, 4424-4249	8	99.70	0.0355	18.2	0.0301	99.88
Hawthorn	Constant offset elimination	11997-6098, 5453-4247	10	99.61	0.3550	16.0	0.2600	99.88

Table 2b: Parameters of optimal models using 420 nm absorbance as reference values

TCM	Pretreatment	Spectral range (cm ⁻¹)	D	Calibration set			Validation set	
				R _{cal} (%)	RMSECV	RPD	RMSEP	R _{cal} (%)
Areca	Constant offset elimination	12000-6098, 5453-4247	8	98.33	0.0318	7.8	0.0229	99.69
Malt	VN	12000-4249	13	99.41	0.0144	13.0	0.0096	99.81
Hawthorn	Constant offset elimination	11997-4247	11	99.11	0.0481	10.6	0.0409	99.62

parching process because the used reference values (5-HMF content and 420 nm absorbance) in the models are chemical indicators during parching process of most TCM. Therefore, this method is promising for monitoring most kinds of TCM industrial manufacturing processes to achieve rapid online analysis and quality control ensuring stability and desired product quality.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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