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EFFECTIVE EXTRACTION OF NATURAL ANTIOXIDANTS FROM *PIPER BETLE* WITH THE AID OF ULTRASOUND: DRYING AND EXTRACTION KINETICS

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Abstract

Medicinal herbs are rich source of natural antioxidants that can serve as excellent alternative to synthetic counterparts. In present study, the effect of temperature on the preservation and recovery of natural antioxidants from the medicinal herb, *Piper betle* was assessed through drying and extraction kinetics. Experimental data was obtained in the form of total phenolic content (TPC) and DPPH (1,1-diphenyl-2-picrylhydrazyl) antioxidant activity. Oven-drying treatment had significant effect on the final outcome as the results indicated that increasing temperature shortened the drying period but subsided the TPC and antioxidant activity. Negative influence with increasing temperature was also observed during extraction of the antioxidants with the aid of ultrasound due to consequent thermal degradation of the bioactive compounds. In both instances, the best results of highest TPC and antioxidant activity were acquired at 50°C of drying as well as extraction temperatures. Seven drying mathematical models and three extraction models were selected to best describe the drying and solid-liquid extraction processes, respectively. Kinetic modelling was achieved by fitting the drying and extraction curves to the respective models. Based on the statistical analysis of high coefficient of determination and low root mean square error, Midilli & Kucuk model ($R^2 \geq 0.99$ and $RMSE \leq 0.023$) and Logarithmic law model ($R^2 \geq 0.88$ and $RMSE \leq 0.24$) were the best suited models to express the drying and extraction of antioxidants from *Piper betle*, respectively.

Keywords: *Piper betle*, Drying, Extraction, Antioxidants, Modelling.

1. Introduction

In recent years, traditional and complementary medicine (TCM) has been identified as a blooming industry by World health organization (WHO). In fact, widespread interest in TCM is expanding exponentially and will continue to do so provided the soaring health care costs and rapidly rising chronic diseases [1]. The said herbs and their extracts are known to possess numerous medicinal and nutritional properties due to the natural bioactive compounds found in them. Primarily, these secondary metabolites are responsible for the organoleptic properties together with providing protection and defence to the plants [2]. However, research has shown them to highly efficient in the prevention and treatment of diseases. Upsurging chronic health complications including cardiovascular diseases, diabetes and various forms of cancer are result of oxidative stress, a term used to define the potential damage caused by reactive oxygen species (ROS) or free radicals [3]. Studies have shown that the intake of natural bioactive (phenolic) compounds or diets enriched with them reduces the potential risks and prevents cellular as well as physiological damage [3, 4].

Phenolic compounds are not only present in herbs but also in fruits and vegetables in abundance. They are known to be excellent natural antioxidants that have piqued the interests of food and pharmaceutical industries alike [5, 6]. *Piper betle* is such a medicinal herb known to have demonstrated high antioxidant potential *via* multiple radical scavenging activities [7, 8]. Widely cultivated in Asian regions, this indigenous plant has been proven to inhibit and reduce lipid peroxidation together with enhancing the levels of natural antioxidants [9]. Typically, the natural antioxidants from *Piper betle* would be recovered through extraction. However, drying treatment of the herbs are essential prior to their extraction for better preservation of the compounds.

Dehydration through drying treatments is an important process that reduces moisture content which in turn prevents microbial contamination, thus, preserving and prolonging the quality of the harvested herbs. Drying also includes additional advantages of weight and volume reduction making it easier for storage and transportation in bulk [10]. Nevertheless, thermal processing can also impose negative effects on the quality, stability and extractability of the compounds. Despite the drying method implemented, temperature and time are two key process conditions identified to influence the structure of the compounds and their degradation [11]. Hence, it is detrimental to identify suitable drying conditions for optimum results. The objective of current study is to investigate the influence of drying temperature and time on the phenolic content and its corresponding antioxidant activity for temperatures range from 40°C to 80°C with 10°C interval.

Drying is generally proceeded with extraction of the natural compounds for their utilisation. Temperature is such a crucial parameter that is also known to affect the extraction process likewise. Studies have shown that increasing temperature has several advantages with enhanced mass transfer and solubilisation of the phenolic compounds [12, 13]. However, the use of high temperature may also cause degradation of the very same compounds [14, 15]. It is imperative to consider the application of appropriate temperature during the extraction process to avoid degradation of the phenolic compounds in order to retain their beneficial properties. Thus, the second objective of current study is to investigate the influence of extraction temperature on the recovery of antioxidants from *Piper betle* for

optimum results. At the same time, models will be utilised for both drying and extraction to investigate the kinetics of the two processes.

Mathematical modelling is an effective engineering tool vital for the understanding, designing, simulation, optimising and controlling of processes that contribute to the utilisation of time, energy, solvent and raw material [16]. Both drying treatment and solvent extraction are processes include highly complex mass transfer driven by the process parameters. The application of kinetic modelling is a swift and inexpensive method of determining the kinetics of any given process. They can also be very useful in providing invaluable information for industrial applications. Several empirical, semi-empirical and theoretical models have been employed in the past for the drying and extraction of bioactive compounds from different plants and herbs [10, 17]. Current study aims to study the impact of drying and extraction temperatures on the recovery of antioxidants by utilising seven drying and three extraction kinetic models, respectively. Concurrently, this study also aims to determine the model among the many that is best suited for optimum preservation and extraction of antioxidants from *Piper betle.*

2.Materials and Methods

2.1. Chemicals

The reagents, Fast blue BB (FBBB) and DPPH (1,1-diphenyl-2-picrylhydrazyl) were purchased from Sigma-aldrich (Sigma-aldrich GmbH, Steinheim, Germany). The solvents used included 95% ethanol, 99.9% methanol and chloroform (HPLC grade) which were of analytical grade. The remaining chemicals used included Gallic acid standard and sodium hydroxide pellets. All of the chemicals mentioned with the exception of the reagents were purchased from Sigma-aldrich (Sigma, St. Louis, MO, USA).

2.2. Plant materials sample preparation and oven-drying treatment

Fresh *Piper betle* leaves were bought from Chow Kit market, Kuala Lumpur, Malaysia. The leaves were washed to get rid of the dirt particles on the surface. Oven-drying of the plant samples were performed using a convective oven (Model UFE-800, Memmert, Germany). The drying oven comprised of a temperature controller and a suction fan where the temperature and speed of the fan were adjusted accordingly. During the treatment, the speed of the suction fan was adjusted to maximum at all times. The selected drying temperature for current study ranged from 40°C to 80°C with 10°C interval based on prior literature [18]. The ambient air temperature was determined to be between 26°C to 28°C and the relative humidity of air to be between 80 to 88%, respectively. The leaf samples were dehydrated at the respective temperatures until the weight of the samples was constant. The average air velocity of the oven was determined to be 1.17±0.16 m/s *via* an anemometer (GM8903, Benetech, China).

During the oven drying treatment, the samples were placed in plastic weighing boat and placed at the centre of the oven. Weight loss was calculated by measuring the overall weight of the boat and the samples periodically by means of a digital balance (TX423L, Shimazdu Corporation, Japan). Three replications of each measurement were carried out to ensure accuracy of the

results. The moisture content of the leaf samples was determined using a moisture analyser directly.

Upon completion of drying experiments at various temperatures, the samples were ground and sieved to obtain uniform powdered leaf samples that were used for extraction. UAE of the samples were performed according to Ameena et al. [19] in an ultrasonic bath (Elmasonic Model P120H, Singen, Germany) which was succeeded by evaporation to obtain the crude extract. Consequent analysis of extraction yield, TPC and DPPH antioxidant activity were performed to determine the optimum drying temperature of the natural antioxidants in *Piper betle.*

2.3. Ultrasound-assisted extraction procedure

Prior to extraction, the leaf samples were pre-treated at the optimum temperature determined from the oven-drying experiments. To investigate extraction kinetics of temperature, powdered leaf samples (1 g) was taken in schott bottles and 30 mL of 90% ethanol solution was subjected into it. The samples were placed in an ultrasonic bath (P120 H, Elmasonic, Germany) where extraction was carried out at temperatures of 50°C, 60°C and 70°C to investigate the influence of temperature. The range of temperature was based on existing literature for conventional means of extraction [20-22]. Samples were retained every 5 mins for a time frame of 80 mins for all respective levels. The samples were subjected to vacuum rotary evaporator (Hei-VAP Platinum 3, Heidolph, Germany) to obtain crude extract which were stored at 4°C for analysis purpose.

2.4. Analysis

Extraction yield was determined as explained by Ameena et al. [19]. The assay of total phenolic content (TPC) was carried out as explained by Medina [23]. DPPH antioxidant activity was determined as described by Pin et al. [20] with the equation presented in Eq. (1)

$$\text{DPPH inhibition } (\%) = \frac{Abs_{control} - Abs_{sample}}{Abs_{control}} \times 100\% \quad (1)$$

where $Abs_{control}$ and Abs_{sample} denotes the absorbance of blank solution containing DPPH solution only and absorbance of extract sample solution with DPPH respectively. All of the analyses were carried out in triplicates and the results expressed in this paper are mean of the triplicated experimental data.

2.5. Kinetic modelling for temperature

The seven models of interest to investigate the drying kinetics were Lewis's model, Page's model, Henderson and Pabris's model, Logarithmic model, two term model, Chavez-Mendez model and Midilli & Kucuk model. The respective constants and coefficients of the selected models are presented in Table 1.

The three models applied in current research to investigate the extraction kinetics were Power law, Page's model and Logarithmic model. The power law model can be expressed as in Eq. (2) [31]

$$c(t) = Bt^n \quad (2)$$

where C_t (g/L) is the concentration of the phenolic compounds extracted from the raw material at any given time, *B* represents the extraction rate (L/g.min) and n is the power law exponent (<1). Page's model can be expressed as Eq. (3) [32]

$$c(t) = e^{-kt^n} \tag{3}$$

where *k* and *n* are the Page model's constants and *c(t)* (g/L) represents the concentration of the phenolic compounds at any given time. The Logarithmic model can be written as Eq. (4) [33]

$$c(t) = a\log t + b \tag{4}$$

where *a* and *b* are Logarithmic model's constants and *c(t)* (g/L) represents the concentration of the phenolic compounds at any given time. t in all of the above model is the extraction time in min. Arrhenius equation was used to further investigate the influence of temperature which is expressed in Eq. (5)

$$k = k_o \, exp\left(-\frac{E_a}{RT}\right) \tag{5}$$

where k_o (min^{-1}) and E_a (kJ/mol) are the temperature-independent factor and activation energy whereas *T* (K) and *R* (j/mol K) are the extraction temperature and gas constant respectively.

Table 1. Kinetic variables of the different drying models.

Model name	Model	Reference
Lewis	$MR = \exp(-kt)$	[24]
Page	$MR = \exp(-kt^n)$	[25]
Henderson and Pabris	$MR = a\exp(-kt)$	[26]
Logarithmic	$MR = a\exp(-kt) + b$	[27]
Two term	$MR = a\exp(-k_1t) + b\ exp\ (-k_2t)$	[28]
Chavez-Mendez	$MR = [1-(1-L_2)L_1t]^{\left(\frac{1}{(1-L_2)}\right)}$	[29]
Midilli & Kucuk	$MR = a\exp(-kt^n) + bt$	[30]

2.6. Statistical analysis

The kinetic coefficients were determined by fitting the experimental data to the general models using Matlab 2017a (The MathWorks Inc., USA). The predicted coefficients were analysed based on two statistical criteria of coefficient of determination (R^2) and root mean square error (*RMSE*) given in Eqs. (7) and (8), respectively.

$$R^2 = \frac{\sum_{i=1}^{n}(y_i-\hat{y}_i)^2}{\sum_{i=1}^{n}(y_i-\bar{y})^2} \tag{7}$$

$$RMSE = \sqrt{\frac{\sum_{i-1}^{n}(y_i-\hat{y}_i)^2}{n}} \tag{8}$$

where y_i and $\hat{y}_i$ predicted and experimental values of TPC, respectively. *n* denotes the number of experiments carried out.

3. Results and Discussion

3.1. Effect of drying temperature on TPC and DPPH antioxidant activity

Drying treatment of any herb is essential for better preservation and extractability of the phenolic compounds in them. Drying process can result in chemical changes in the plant matrix that can affect the phenolic compounds, their concentration and their properties, mainly due to the factors involved. Therefore, the total phenolic content and their corresponding antioxidant activity were assessed after drying treatment at each temperature and presented in Table 2. The results indicated an initial increase in the phenolic content and antioxidant activity with the increase of temperature from 40°C to 50°C. The energy from the heat treatment broke down the ester bond between the phenolics and the cell wall accentuated its release [34]. Furthermore, heat treatment changed the structure of the dried leaves, causing them to be more open that allowed for enhanced solvent penetration and mass transfer. Thus, the extraction of the phenolic compounds increased from within the plant matrix which also led to better antioxidant activity [11].

Drying at 50°C resulted in the maximum TPC and DPPH antioxidant activity with values of 291.08 mgGAE/gDW and 93.22% inhibition, respectively. However, further increase in the temperature caused the results to subside. According to Azeez et al. [34], oxidation of polyphenols took place as a result of heat treatment that increased the antioxidant activity which contradicted with the current studies results. The loss of phenolic content at high temperatures was likely due to thermal degradation as reported by others. Heras et al. [11] reported the loss of flavonoids at high drying temperatures due to degradation, despite the dying method implemented. Volden et al. [35] reported significant losses in phenolic content, anthocyanins, soluble sugars as well as the antioxidant activity in red cabbage at high thermal treatment. Nwozo et al. [36] also made similar observations of long and high thermal treatments resulted in disruption of the phytochemicals and their corresponding antioxidant activity in multiple tropical vegetables which was consistent with current studies' findings.

Table 2. Total phenolic content and DPPH antioxidant activity after drying treatment at different temperatures.

Temperature (°C)	TPC (mgGAE/gDW)	DPPH antioxidant activity (% inhibition)
40	219.28	60.31 ± 0.17
50	291.08	93.22± 0.21
60	276.78	82.87± 0.17
70	256.88	72.53± 0.23
80	240.88	71.61± 0.19

3.2. Drying kinetics and modelling

The drying curves of *Piper betle* at various temperatures of 40, 50, 60 70 and 80°C are graphically presented in Fig. 1. It was evident from the results that increasing drying temperature drastically reduced the drying time. The longest and shortest drying time of 4 and 1.3 hr were achieved with the temperatures of 40 and 80°C, respectively. The heat energy at 40°C might not be sufficient enough for

vaporisation for which such a prolonged drying period was needed to reach equilibrium. Increasing the temperature caused the energy of the water molecules to increase that allowed for rapid vaporisation, thereby, accelerated the drying rate [10]. Similar observations were also made during the drying of plum [37] and soybean [38].

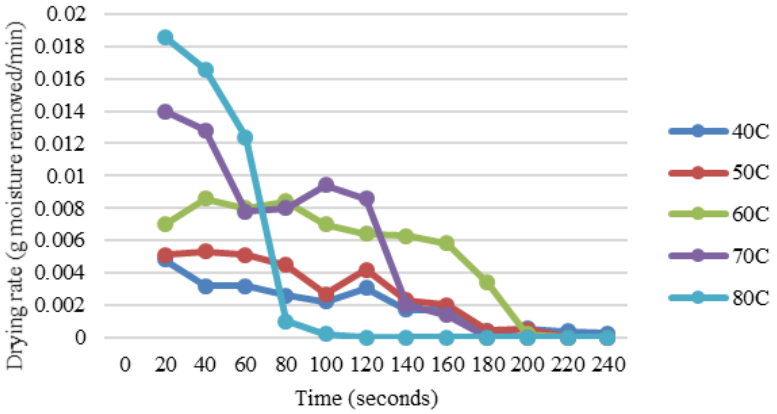


Fig. 1. Drying rate of *Piper betle* at different temperatures.

The variation in the moisture content at different temperatures is presented in Fig. 2. The four stages of drying could be observed over the course of drying period. Initially, there was a warming up period for the heat to provide energy to the water molecules for which no severe changes in the moisture content was observed. This was closely followed by drastic decrease in the moisture content during the drying period until equilibrium was reached. This period, often referred as falling rate period, was where majority of moisture transfer took place through internal diffusion mechanisms was consistent with the findings of Darvishi et al. [44]. Finally, the moisture content reached minimum, indicating complete vaporisation.

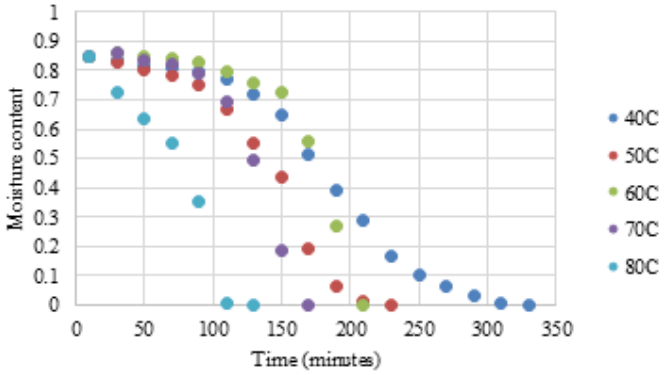


Fig. 2. Variation of moisture content at different temperatures with time.

Five thin-layer models were utilised to describe the drying kinetics of *Piper betle* at the best drying temperature of 50°C. The kinetic variables of all the models are summarised in Table 3. The statistical criteria of R^2 and *RMSE* were used to determine the best model suited for current study. All of the models displayed good fit to the experimental data with high R^2 (>0.98) and low *RMSE* (<0.067). Even though, Midilli & Kucuk had slight edge over the other models with R^2 (0.99) and *RMSE* (0.023), the difference between the best and the worst suited model in terms of R^2 was determined to be merely 1.2%. Thus, indicating that Midilli & Kucuk was marginally better than the rest of the models. Moreover, no significant improvement was observed with the application of complicated models such as Chavez-Mendez or even Midilli & Kucuk. Thus, it could be said that simple models such as Page and Lewis were sufficient to describe the drying kinetics.

Table 3. Parameters of the drying model at drying temperature of 50°C.

Model	Constants and Coefficients	Value
Lewis	k	0.003
	n	1.000
	R^2	0.989
	RMSE	0.00095
Page	k	0.003
	n	1.176
	R^2	0.989
	RMSE	0.030
Henderson and Pabis	k	0.0076
	a	1.023
	R^2	0.982
	RMSE	0.039
Logarithmic	k	0.0076
	a	1.0239
	R^2	0.982
	RMSE	0.0390
Two term	k_1	0.00462
	k_2	0.0134
	a	0.5902
	b	0.4118
	R^2	0.947
	RMSE	0.0665
Chavez-Mendez	L_1	0.00738
	L_2	0.9231
	R^2	0.984
	RMSE	0.0359
Midilli & Kucuk	K	0.00102
	n	1.3659
	a	0.91008
	b	0
	R^2	0.994
	RMSE	0.0231

3.3. Effect of extraction temperature on total phenolic content and DPPH antioxidant activity

In this research, the influence of the parameter temperature on extraction kinetics was investigated. UAE of phenolic compounds in *Piper betle* was carried out following the optimum results of drying treatments. Three different temperatures levels were chosen based on existing literature for different conventional extraction techniques. The results (not shown) revealed that the highest TPC and antioxidant activity were obtained with extraction temperature of 50°C. According to literature, the application of high temperature facilitated the extraction process as the heat energy weakened the bonds between the phenolics and other cellular components [39]. Mass transfer was also enhanced at high temperatures as reported by Tuˇsek et al. [32] in the extraction of polyphenols from Asteraceae plants where the best results were obtained with extraction temperature of 80°C. However, in present study, opposite results were found which could be explained by the sensitive nature of the compounds.

Several authors had reported the thermo-sensitive nature of the phenolic compounds. Xu et al. [4] reported that an extraction temperature of 40°C resulted in optimum extraction of antioxidants from the flowers of *Limonium sinuatum.* Maran et al. [40] also reported of similar findings where the authors found 50°C to be optimum temperature for extraction which supported the results of current study. Furthermore, high temperature could attenuate the induced cavitation from ultrasound and thereby resulted in decreased mass transfer and extraction of antioxidants [41].

3.4. Extraction kinetics and modelling

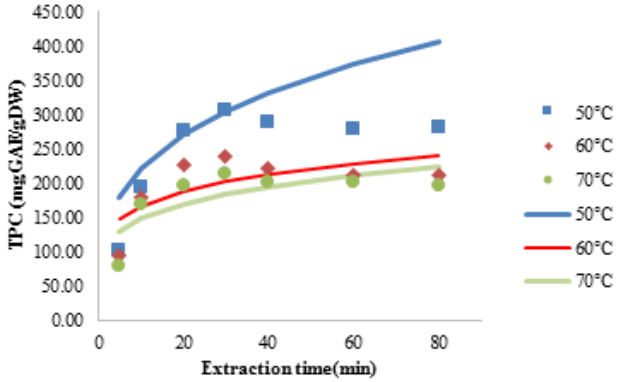
Three kinetic extraction models, Power law, Logarithmic and Page's model were applied to understand the kinetics of the solid-liquid extraction process. The experimental data of TPC were utilised to determine the kinetic parameters for all models which are summarised in Table 4. The experimental and predicted TPC curves for all the models are provided in Figs. 3. In all instances, the highest constants and coefficient were obtained for the extraction temperature of 50˚C. This was expected as 50°C resulted in the maximum TPC and DPPH antioxidant activity. The application of high temperature resulted in the degradation of the phenolic compounds which resulted in the loss of the antioxidant activity [14]. Based on the correlation coefficients from the same table, Logarithmic model provided best fit with the highest R^2 (0.88) and lowest *RMSE* (0.24). It was noteworthy to note that the Logarithmic model was found to be among the best in terms of both drying and extraction kinetics, thus, disclosing its universal value in kinetic modelling.

To further investigate the influence of extraction temperature, Arrhenius law was applied to the same model to determine the two coefficients, E_a (activation energy) and k_o (temperature-independent factor). The activation energy and temperature dependent factor were determined to be 7.25 kJ/mol and 0.26 min^{-1}, respectively. Positive values of E_a denoted the extraction process to be endothermic, meaning energy must be provided for effective extraction to take place. González-Centeno et al. [42] reported that the activation energies ranged from 4.6 to 11.7 kJ/mol for the extraction of phenolics from grape pomace. The authors also reported activation energies for the conventional method of maceration to be in the range of

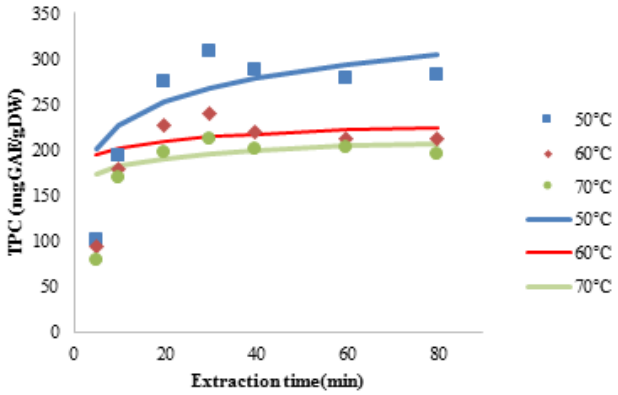
12.5 to 48.3 kJ/mol. It was evident that in current case, the application of ultrasound drastically reduced the amount of energy required for effective extraction to take place. Similar observations were also made by Chemat et al. [43] during the ultrasound-assisted extraction of carvone and limonene from caraway seeds.

Table 4. Kinetic variables of extraction models at different temperatures.

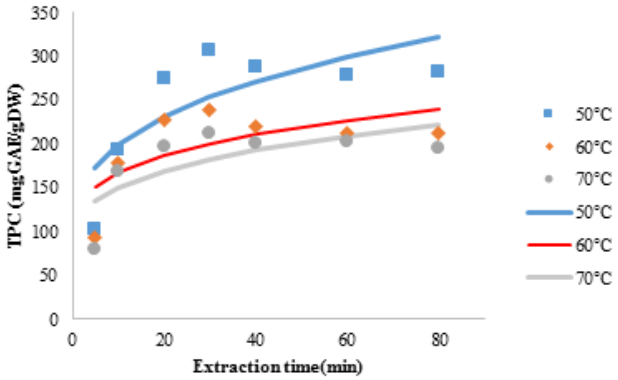
Model	Temperature (°C)	Constants and Coefficients	Value
Power law	50	*B*	3.74
		n	0.29
		R^2	0.66
		RMSE	1.56
	60	*B*	3.68
		n	0.18
		R^2	0.52
		RMSE	1.25
	70	*B*	3.17
		n	0.19
		R^2	0.58
		RMSE	1.09
Logarithmic	50	*a*	2.83
		b	4.75
		R^2	0.88
		RMSE	0.29
	60	*a*	0.84
		b	5.89
		R^2	0.88
		RMSE	0.24
	70	*a*	0.94
		b	5.13
		R^2	0.95
		RMSE	0.30
Page	50	*k*	-1.47
		n	0.11
		R^2	0.78
		RMSE	5.13
	60	*k*	-1.41
		n	0.09
		R^2	0.72
		RMSE	3.17
	70	*k*	-1.27
		n	0.10
		R^2	0.79
		RMSE	2.44



(a) Power law model



(b) Logarithmic model



(c) Page's model.

Fig. 3. Experimental and predicted TPC extraction curves for the three models at different temperatures.

4. Conclusion and Future Works

Present research investigated the drying and extraction kinetics of ultrasound-assisted extraction of natural antioxidants from *Piper betle* for the process parameter of temperature. The influence of drying temperature on TPC and DPPH antioxidant activity was studied for a range of 40°C to 80°C with 10°C interval. The results showed that increasing temperature drastically reduced the drying period. However, due to the sensitive nature of the compounds, high temperature resulted in degradation of the phenolic compounds which led to reduced antioxidant activity. Drying at 50°C was found to give the best results of TPC (291.08 mgGAE/gDW) and antioxidant activity (93.22%).

Experimental data was fitted to seven thin layer models to determine the kinetic coefficients that gave better understanding of the drying process that can be employed in the future applications. All of the seven models displayed good fit to the data with Midilli & Kucuk having the best statistical coefficient of R^2 (0.99) and *RMSE* (0.023).

Together with drying kinetics, extraction kinetics was also evaluated for the parameter of temperature. UAE of natural antioxidants for temperatures ranged from 50 to 70°C was investigated. The findings showed that increasing extraction temperature resulted in the loss of phenolic compounds and its corresponding antioxidant potential. The optimum results were determined at 50°C, which was similar to drying. Three extraction models were fitted to experimental data to describe the solid-liquid extraction process. Logarithmic model displayed the best fit among the three with highest R^2 (0.88) and lowest *RMSE* (0.24). The activation energy and temperature dependent factor for the same law were determined to be 7.25 kJ/mol and 0.26 min^{-1}, respectively.

In future research, the influence of more extraction parameters can be studied as literature has shown, together with temperature, the extraction process is also driven by other parameters. To take a step further, process optimisation could also be done as kinetic modelling can investigate the influence of one parameter as a time. Process optimisation would involve the combined impact of multiple parameters at a time. Successful optimisation of the extraction process could prove to be even more valuable in identifying the best combination of parameters for the recovery of phenolic compounds if they are to be utilised in food and pharmaceutical industries.

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Nomenclatures

Abs_{sample}	Absorbance of plant sample
$Abs_{control}$	Absorbance of DPPH solution
C_t	Concentration of solute at any given time, g/L
E_a	Activation energy, kJ/mol
k_o	Temperature-dependent factor, min^{-1}
R	Gas constant, j/mol K
R^2	Coefficient of determination
W_p	Dried peel powder, g
W_t	Dried pectin mass, g

Abbreviations

DPPH	2,2-diphenyl-1-picrylhydrazyl
Fast	Fast Blue BB
Blue BB	High Performance Liquid Chromatography
HPLC	Root Mean Square Error
RMSE	Total Phenolic Content
TPC	
UAE	Ultrasound-Assisted Extraction
WHO	World Health Organisation

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