Microchannel as a Green Processes, Compared to Conventional Methods for Extraction of Quercitannin

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Summary: In the present study, a comparison was made among the efficiencies of four common extraction methods used for extraction of Quercitannin content of oak leaves. These extraction methods are Maceration, Soxhlet, and microfluidic extraction without and with ultrasonic wave irradiation. Several solvents including methanol, ethanol, hexane, and water were used during the experiments. Amount of Quercitannin obtained through a microchannel in the ultrasonic bath was higher than those of Soxhlet, Maceration, and plain ultrasonic bath extractions. This study is also aimed to study the extraction factors including frequency, temperature, and power ultrasonic in a microchannel with ultrasonic wave irradiation. Moreover, the optimal possible hybrid of these factors over response surface methodology was obtained. The optimum condition was the ultrasonic treatment at frequency = 80 kHz, temperature = 75ºC and power = 40w. Under these conditions, the yield using ultrasonic bath with microchannel was increased 17.57% and 32.68% compared with the plain microchannel and simple ultrasonic bath, respectively. The proposed continuous flow system uses less amount of solvent, producing less amount of waste. Besides, this system needs a smaller space compared with other conventional methods. Therefore, the use of microchannels as a way of the continuous method provides an environmentally friendly and high efficiency method in comparison with conventional methods.

Keywords: HPLC; Microfluidic system; Quercitannin; Common extraction methods.

Introduction

Quercitannin is one of complex, poly-phenol, amorphous, and non-toxic compounds of acrid aroma that is found in the defense system of herbs against parasites. The astringent property of Quercitannin as well as their anti-bacterial and fungicidal activity is the main incentive for its application in medicine [1]. Quercitannin affects cells and tissues of animal and human as such they can produce insoluble complexes through a chemical reaction with albumin/proteins that appear through proteins precipitation in superficial layers [2]. The polyphenol existing in Quercitannin affects its antiseptic characteristics. The Quercitannin plays multiple roles in preventing herbal tissue decaying, provides reserve materials for the seed to germinate, and has a role in transporting carbohydrates over the herb as tannin glycosides. The bioactive compounds extraction from natural resources has attracted scientists because of the growing demand for functional ingredients achieved through natural procedures, as functional foods consumers are greatly interested [3]. Maceration and Soxhlet extraction methods are common conventional extraction approaches applied to extract different plant substances [4]. However, these two methods have several disadvantages, which limited their application [5]. These extraction approaches can be applied solely for compounds with the ability to tolerate the boiling temperature of the applied solvent, but cannot be used for thermolabile compounds since a long time of heating may cause degradation of compound [6]. The combination of two methods of ultrasound-assisted extraction (UAE) and microchannel is a new technique for extraction of chemical elements from plant resources efficiently [7, 8]. Moreover, the plant materials solvation can be facilitated using ultrasound through cell swelling and increasing pores size of the cell wall [9]. Better swelling will increase the mass transfer rate and enhance the performance of extraction and/or decrease the time of extraction. The extraction methods should be revised to enhance the extract yield and protect bioactivity [10]. Therefore, the new extraction methods including UAE with microchannel should be presented and compared with the conventional extraction methods. The combination of UAE and microchannel provides an appropriate extraction method because of its simplicity, low-cost, effectively, selectivity, ecologically friendly and compatibility with different analytical methods. Besides, the fast movement of molecules provided by this combined method increases the solvent penetrability and promotes a

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greater dissolution speed of plant elements in short time [11]. Classical extraction method including Maceration and Soxhlet extraction approaches required a substantial matter of time and a large amount of solvent. Besides, they are exposed to probable degradation of the objective product because of overheating [12]. In this study, the effect of three factors on ultrasound extraction (e.g., temperature, frequency, and power) was investigated. Also, various solvents were used to extract a bioactive compound of the oak leaves in extraction methods of Maceration, Soxhlet, ultrasound, and microchannel. Although in many traditional approaches water is applied as an extractant, different polarities of organic solvents are commonly chosen in modern extraction approaches to exploit different solubilities of plant components. The possible interactions between operation factors are considered in response surface methodology (RSM), which contains a set of statistical and mathematical methods applied to develop, improve, and optimize the procedures [13]. This methodology was applied for optimizing the extraction parameters of Quercitannin extracted from Persian oak using UAE technique.

Experimental

Preparation of Leaves of Persian oak

Leaves of Persian oak (Quercus Brantii Lindl., the Fagaceae family) were collected from Zagros Mountains of Ilam province, Iran. The foreign substances were removed from the leaves through cleaning by hand. After drying at ambient temperature, they were washed with distilled water, wrapped in paper bags and stored in a dark, dry and cool environment for further tests. Before applying them, they were crushed with a blender.

Chemicals

Quercitannin (purity≥ 99% by HPLC), ethyl acetate, methanol, hexane, ethanol, sodium hydroxide and orthophosphoric acid were purchased from Merck Chemical Co. (Germany). All solutions were prepared using deionized water.

High performance liquid chromatography

High performance liquid chromatography (HPLC) was used to determine Quercitannin. Liquid chromatography system (Kenauer Germany), equipped with a UV visible detector, vacuum degasser, four single solvent delivery pumps, a thermostated column compartment, and a 1µL sample loop manual injector was used for HPLC analysis. In this work, 80:20 *% (v/v)* of deionized water HPLC grade and methanol was used as the mobile phase with a flow rate of 1mL/min. The applied stationary phase was a reversed-phase C18 analytical column (250 mm- 4.6 mm I.D., 3µm particle size). The wavelength of detection was 280nm. The detected peak was recognized through comparison of their retention time with the standard. The calibration curve was used to calculate the concentration.

Maceration

This simple broadly applied technique includes 10 g pulverized plant soaked in 100 mL of an appropriate solvent (100mL) in a sealed container. Simple Maceration is done through combining the pulverized plant with the solvent at room temperature and shaking or stirring the obtained mixture occasionally for 72 h. Maceration is performed through immersion of the sample in an organic solvent. Organic solvents will penetrate into the wall of the cell and cell cavity, where they dissolve its active material content. It was kept for 72 h and the filtration of solids was performed by Whatman filter. Maceration method is shown in Fig. 1(i).

Soxhlet

Soxhlet is a technique for both initial and bulk extractions. Through this method, 30g powder of the plant is put in a cellulose thimble in an extraction chamber, which is located on top of a collecting flask under a reflux condenser. A solvent (300 ml) is poured in to the flask and the set-up is heated under reflux. The condensed solvent is flushed into the flask beneath such that a certain concentration of it is gathered in the thimble. The key benefit of Soxhlet extraction method (Fig.1ii) that it is a continuous procedure.

Ultrasonic-assisted

An ultrasonic bath was applied in the current research. In order to extract Quercitannin, 10g of the sample and 100 mL of solvent were poured into a conical flask with the volume of 250 mL. Then, the flask was partially sonicated in the ultrasonic bath. The circulation of water in the ultrasonic bath prevents temperature increasing because of the ultrasonic exposure. Four diverse parameters of the composition of solvent, frequency, temperature, and ultrasonic power were studied. Next, a filter paper was used to filter the extract and the obtained filtrate was measured using HPLC.

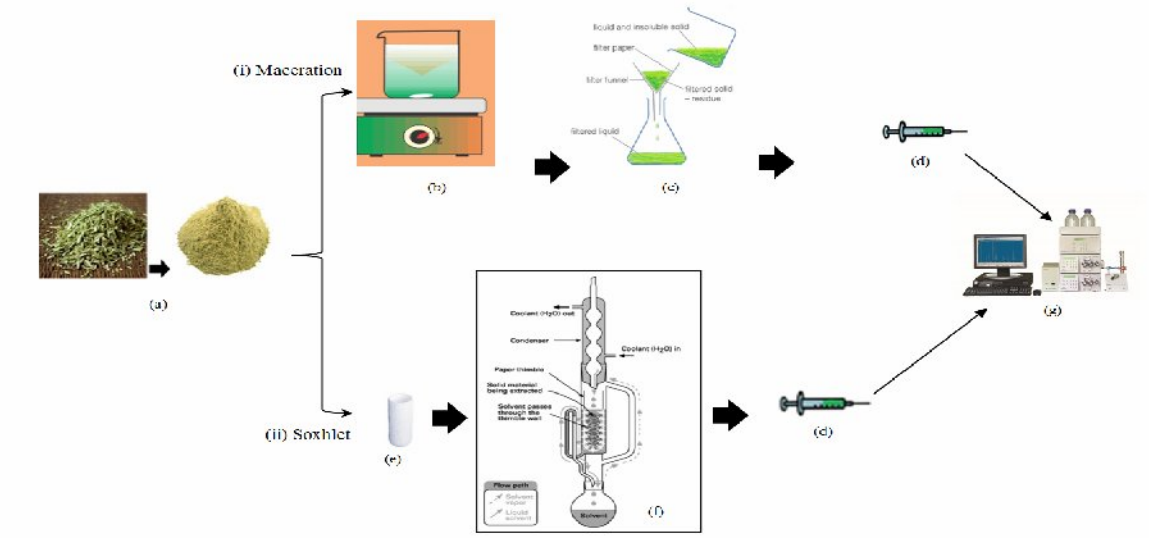

Fig. 1: Conventional extraction methods. (i) Maceration: (a) Leaves of Persian oak (b) Stirrer (c) Filtering the extract (d) Extract, (ii) Soxhlet: (e) thimble (f) Soxhlet extractor (g) HPLC.

Microchannel

Microfluidic extraction technique is the new and the most promising procedure that can be applied as a better choice for extracting Quercitannin from oak leaves at industrial scale owing to its low time of extraction, lower temperature, and an important difference in the extract efficiency. The experimental system included two microsyringe pumps in which 10g of air-dried feed and solvent are pushed out with a constant flow rate. The extraction of pulverized oak leaves was performed through stirring mechanically in 100ml of ethyl acetate for 24h. A glass T-shaped microchannel with diameter and length of 600 µm and 80mm, respectively, was used in this work. The microchannel outlet was linked to a tube where both raffinate and extract were collected. HPLC was used to analyze the obtained extract.

Microchannel with ultrasonic

The microchannel was put in an ultrasonic bath whose condition was adjusted according to the optimum condition obtained by RSM. After separating two phases in the outlet stream, Quercitannin level was measured using HPLC. The outcomes were compared with other methods. Schematic of the microfluidic device in an ultrasonic bath are shown in Fig. 2.

Results and discussion

Different extraction methods

Extraction was defined as a procedure for separation of a material based on different solubility. The extraction principle is to dissolve the polar substances in polar solvents and non-polar substances in non-polar solvents [14]. Though the selection of extraction technique may significantly influence the extracted quality, the applied solvent affords a clear means for affecting the qualitative constituents of the extract. The initial trials were performed for selection of a proper solvent. Fig. 3 demonstrated the impact of solvent constituents on the Quercitannin amount obtained from four diverse extraction approaches. In Maceration, the Quercitannin level of all extracts was according to the following order: methanol (50%)> ethanol (50%)> methanol >ethanol >hexane> methanol (30%)> ethanol (30%)> water. In comparison, in Soxhlet extraction it was in the order of methanol (50%)> ethanol (50%)> methanol (30%) > ethanol (30%)> methanol > ethanol > hexane>water extracts. In the ultrasonic technique, the maximum extract yield was related to the extraction solvent of 50% methanol, while the pure water exhibited the minimum level of rest of solvent systems. On the other hand, in the microfluidic technique, the maximum Quercitannin level was related to the ethanol 30% followed by methanol 30%, water, hexane, and ethanol 50%, respectively. No separation was observed using pure methanol and ethanol. The outcomes revealed that the maximum extraction yield of Quercitannin using the combination of microfluidic and ultrasonic was achieved with applying ethanol 30% as a solvent followed by 30% methanol, water, hexane, methanol (50%), and ethanol (50%), in the order of their appearance. The most common solvents for extraction of polyphenols from natural sources are

alcoholic solvents, which result in more yield for total extract, even though they are not extremely selective in the case of phenols. In this regard, a mix of alcohol and was more effective for extraction of phenolic ingredients compared to the mono-component solvent system. A polar media is usually created by adding water to organic solvents that simplify extracting polyphenols [15]. Fig. 3 demonstrates the comparison of extraction result obtained through Maceration, Soxhlet, and microfluidic systems with and without an ultrasonic bath. The results prove that plain microfluidic system and microchannel with UAE are extraction methods with higher performances. The comparison indicates that greater extraction efficiency at a shorter time is obtained using ultrasonic bath with microfluidic system. In the present work, Design-Expert software was applied to study the effects of frequency, temperature, and power ultrasonic on extraction yield and to determine the optimum parameters to maximize efficiency in microfluidic extraction with ultrasonic bath method.

Statistical analyses

Design-Expert (Stat-Ease, trial version) was used to analyze the data obtained in this work [16]. The one-way analysis of variance with P-values < 0.05 as significant was applied for the statistical analyses. In order to achieve the maximum yield of Quercitannin from oak, the extraction conditions were optimized with central composite design (CCD). Moreover, to create CCD through Design Expert statistical package, three independent variables of ultrasonic frequency (F, kHz), power (P, w), and temperature (T, ℃) were considered. Independent variables in this study that was determined at three levels, +1, 0, and -1 according to Table-1. Finally, 20 tests under different conditions were determined (Table-2). The response and independent variables correlation could be recognized from 3D response surface and 2D contour plots, which are simultaneously showing the interaction of three parameters on the responses and providing the optimal experimental variables location. Analysis of variance (ANOVA) was used to check the statistical significance of the regression equation coefficients. The fitness and the lack of fit of the polynomial model equation to the responses were assessed using R^2 coefficient and F-test, receptively.

Table-1: Experimental design recommended by Design-Expert.

Factors	Units	Low Level (-1)	Level 0	High Level (+ 1)
power(P)	W	40	70	100
ultrasonic frequency(F)	kHz	0	40	80
Temperature(T)	°C	25	50	75

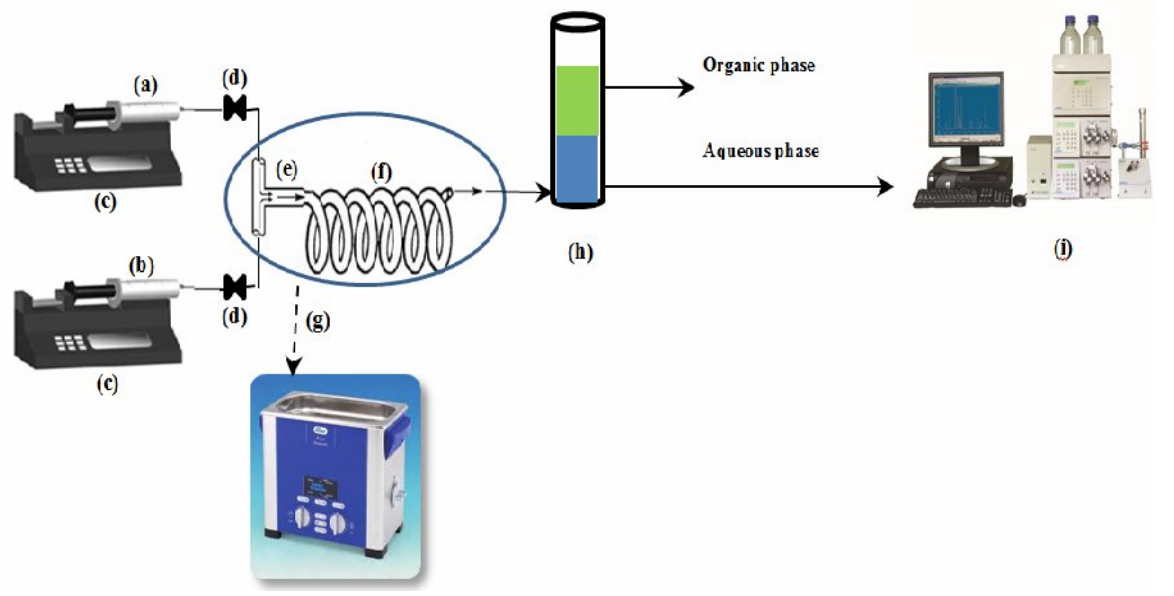

Fig. 2: Modern extraction methods: (a) Organic phase (b) Aqueous phase (c)Microsyringe pumps (d)valve (e)T-shaped Microchannel (f) Coil (g)Ultrasonic bath (h) Extracted sample (i)HPLC.

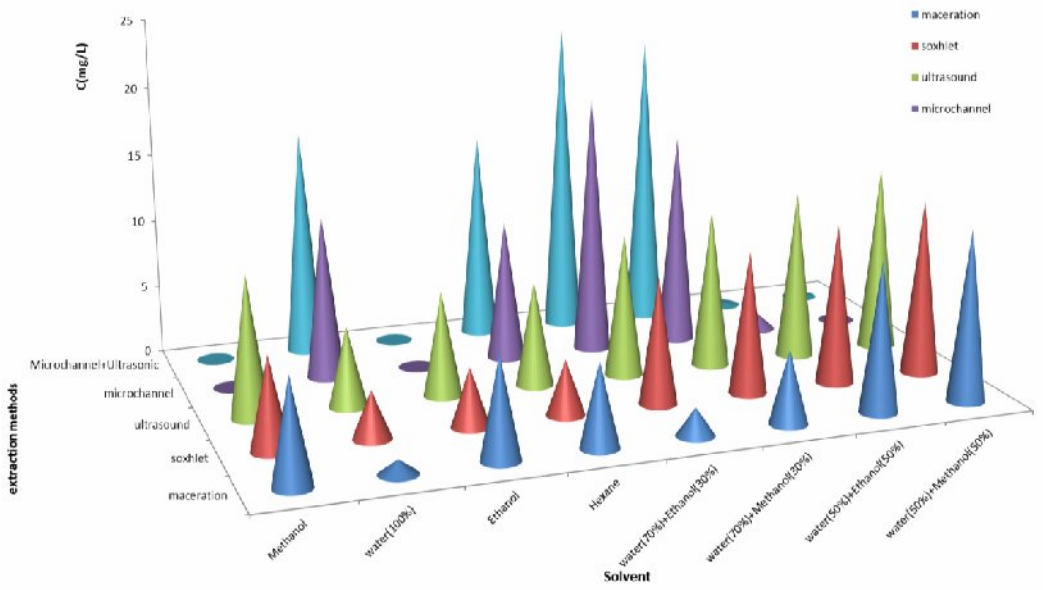

Fig. 3: Effects of different solvents on the extraction Quercitannin for maceration, soxhlet, ultrasound and microchannel.

Table-2: Independent variables and their coded levels used in RSM studies.

Std	Run	Independent factors levels			Yield%
		Frequency(kHz)	Power(W)	Temperature(°C)	
3	1	0	100	25	19.05
12	2	40	100	50	56.4
4	3	80	100	25	59.03
10	4	80	70	50	60.63
5	5	0	40	75	23.5
16	6	40	70	50	46.34
2	7	80	40	25	58.92
18	8	40	70	50	40.95
7	9	0	100	75	25.29
9	10	0	70	50	19.07
20	11	40	70	50	43.59
1	12	0	40	25	19.01
6	13	80	40	75	73.99
8	14	80	100	75	64.55
11	15	40	40	50	50.51
13	16	40	70	25	44.89
14	17	40	70	75	56.51
17	18	40	70	50	58.92
19	19	40	70	50	41.37
15	20	40	70	50	42.48

Table-3: Analysis of variance of the quadratic regression model fitted for yield extraction.

Source	Sum of Squares	df	Mean Square	F -Value	Prob > F
Model	4934.66	9	548.3	17.14	< 0.0001
A-F	4460.54	1	4460.54	139.44	< 0.0001 significant
B-P	0.26	1	0.26	8.103E-003	0.9301
C-T	184.38	1	184.38	5.76	0.0373
AB	15.57	1	15.57	0.49	0.5013
AC	12.15	1	12.15	0.38	0.5514
BC	7.60	1	7.60	0.24	0.6364
A^2	240.30	1	240.30	7.51	0.0208
B^2	49.84	1	49.84	1.56	0.2404
C^2	6.21	1	6.21	0.19	0.6690
Residual	319.89	10	31.99		
Lack of Fit	88.63	5	17.73	0.38	0.8420 not significant
Pure Error	231.26	5	46.25		
Cor Total	5254.55	19			

$R^2 = 0.9391$ $R^2 - Adj. = 0.8843$ Adeq Precision= 14.017

$$yield = 32.20957 + 1.01506 * F - 0.55593 * P - 0.026996 * T - 1.16458 \times 10^{-3} * F * P + 1.235 \times 10^{-3} F * T - 1.30333 \times 10^{-3} P * T - 5.84176 \times 10^{-3} * F^2 + 4.73131 \times 10^{-3} * P^2 + 2.40509 \times 10^{-3} * T^2$$

Model fitting

Moreover, an empirical second-order polynomial model, which is the most common model, was used to optimize procedures. ANOVA, R^2, and lack of fit were applied to evaluate the accuracy of the suggested model. According to ANOVA results presented in Table-3, the F-values of all four responses are very high and P-values (0.0001) of all four responses are very low. Furthermore, great values of R^2 and inconsiderable lack of fit ($P>0.05$) show that the quadratic model implementation was extremely significant for the attained information. Accordingly, it can be stated that the relationship between the extraction conditions and responses can be explained during ultrasonic technique using the suggested model. Eq.1 presents the fitted quadratic model of extraction yield. Moreover, Table-3 demonstrates the significance of all coefficients.

Effect of temperature

The pretreatment of samples was performed using ultrasonic treatment at different temperatures including 25, 50, and 75℃. A gradual increase in Quercitannin yield is observed with enhancing the temperature (Fig. 4). The pressure of vapor is lower at a lower temperature. High acoustic cavitation threshold in ultrasound yields a few cavitation bubbles, which detonate with moderately larger force and result in the improved cell tissues disruption over extraction. The pressure of vapor was higher at higher temperatures, where more bubbles were also formed; however, they collapsed with a smaller amount of intensity because of the small difference between the pressure inside and outside the bubbles [17]. The surface tension, which was reduced by increasing the temperature, may be another cause of formation and collapse of bubbles. The collapse of bubbles may occur easier at higher temperatures and lead to increase mass transfer. Additionally, increase in temperature will allow the solvent to have a higher capacity to solubilize analytes, while surface tension and solvent viscosity decrease with temperature, which will improve sample wetting and matrix penetration, respectively [18]. However, beyond certain temperature, phenolic compound can be denatured [19], temperatures above 75°C cause rapid polyphenol degradation. Ultrasonic-assisted are helpful to intensify mass transfer, cell disruption, more enhanced penetration and capillary effects. Very high temperature in Ultrasonic-assisted increases the solubility, diffusivity and pressure, which help the waves to penetrate the tissue and transport contents in a variety of solvents, both organic and inorganic.

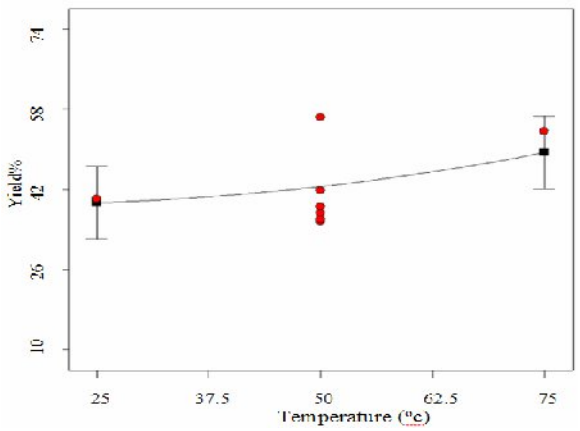

Fig. 4: Effect of Temperature (°c) on extraction yield.

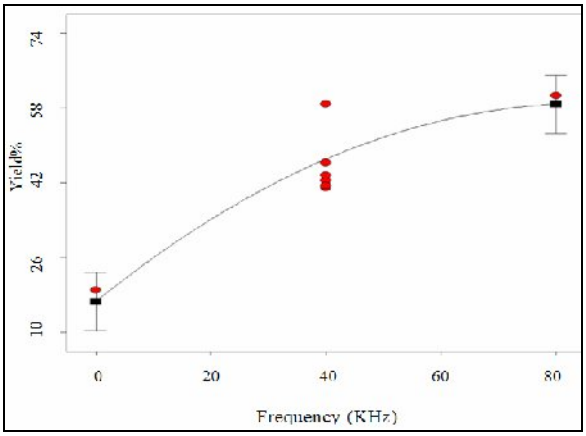

Fig. 5: Effect of ultrasound wave Frequency (KHz) on extraction yield.

Effect of ultrasonic frequency

Various frequencies of ultrasonic were applied for treatment of oak leaves, with results shown in Fig. 5. The results show that passing greater amplitude ultrasonic through a liquid medium results in the formation and collapse of more bubbles [20]. Since the temperature and pressure inside the bubbles were very high and the bubbles collapsed quickly, solvent penetration into tissues of the cell speed up releasing the intracellular product into the solvent through disruption of the cell walls. Furthermore, the violent shock wave and high-speed jet might have resulted in the molecules to mix better improving the mass transfer speed. Ultrasound is transmitted through a medium via pressure waves by inducing vibrational motion of the molecules which alternately compress and stretch the molecular structure of the medium due to a time-varying pressure. The sound waves that propagate into the

liquid media result in the production of an alternating high-pressure (compression) and low-pressure (rarefaction) cycles, whose rates depends on the frequency of vibration of sound wave. The frequency of ultrasound is an important parameter and influences the bubble size. Due to the presence of the hard cell walls which are not so permeable, the large increase in ultrasonic power resulted in a moderate rise in yield.

Fig. 5 is shown that extraction of Quercitannin was gradually increasing with increase in the ultrasonic frequency. As the larger amplitude ultrasonic wave travelled through a liquid medium, more bubbles were created and collapsed [21]. Moreover, the violent shock wave and high-speed jet might have caused the molecules to mix better and enhancing the mass transfer rate.

Effect of ultrasonic power

It can be observed that there are developments in the achieved extracts since ultrasonic output power rises from 70 to 100w. Penetration of solvent into the cell might occur and the components are released from the cells into the solvent. In the meantime, a considerable increase in the mass transfer speed also occurred [22]. Fig. 6 show that the power of sound has no significant effect on the extraction efficiency that this result is in agreement with the ANOVA table.

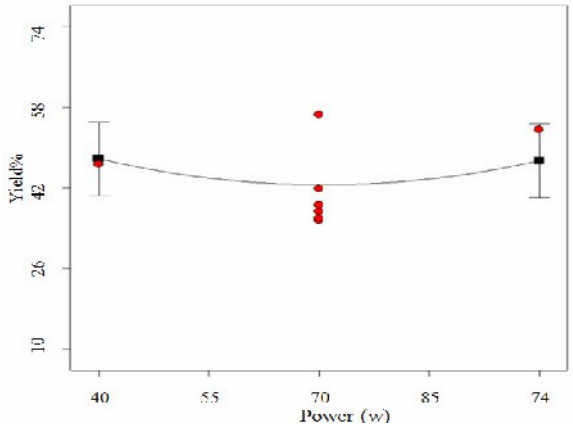

Fig. 6: Effect of ultrasonic Power (w) on extraction yield.

Optimization of the microfluidic extraction process

The results of the analysis of variance Table-3 represents the significance of frequency and temperature effect on the separation efficiency in ultrasonic bath, because the value of $p < 0.05$. Regarding the secondary order effects of the studied factors, the frequency has a significant effect. Investigation of the mutual effects between variables shows that among three factors of frequency, power, and temperature, there is no significant mutual interaction.

The accuracy of model is not specified with a specific graph, but through the variance analysis and the values of R^2 and R^2-Adj. obtained in Table-3. R^2 is a criterion that using it, the accuracy of the model can be measured. In the R^2-Adj. instead of using the sum of the squares, the average sum of squares is used. The advantageous of this is that the degrees of freedom actually representing the number of factors would be involved in the calculations. In Table-3, the signal to noise ratio by Adeq. Precision are shown and favorable values for this ratio, is numbers greater than 4. The obtained number in this study is 14.017 indicating that the signal is sufficiently larger than the noise and this model can be used to design the process.

The F-Value resulted from ANOVA was used to evaluate the suitability of response surface quadratic model on Quercitannin yield . According to ANOVA of the quadratic regression model, the coefficient of determination (R^2) and the adjusted coefficient of determination (R^2 -Adj.) were 0.9391 and 0.8843, respectively, suggesting that the model could describe 93.91% response variable variability. In addition, the lack of fit, which is commonly applied for measuring the model, was insignificant (p-value = 0.8420). Therefore, the model was well fitted with this experimental project. The F-value of the model, which was 17.14, shows its acceptable performance. Values of Probe> F showed that the terms of the model were considerable. In this case F, T, and F^2 were considerable model terms. These outcomes demonstrate the considerable impact of two variables on the Quercitannin yield that their order is as follows: frequency > temperature > power. Figs. 7A and 7C present three-dimensional surface and contour plot for direct reflecting the interaction between different parameters on the response values. The impacts of temperature and power on the Quercitannin yield are shown in Fig. 7A. Because the surface of layer is smooth and changes in temperature and sound power are relatively linear, so no significant mutual effect between these two parameters was observed.

The impacts of frequency and other two variables (i.e., temperature and power) are shown in Fig. 7B and 7C, respectively. Based on Figs. 7A and 7C, power showed a weaker influence. However, the frequency had a considerable effect on the Quercitannin yield. The highest value of response for Quercitannin yield (72.63%) was predicted with

Design-Expert software as the frequency of 80 kHz, power of 40w, and temperature of 75℃. Nevertheless, considering the operability in real production, the modification of optimum procedure would be as follows: frequency of 80 kHz, power of 70w, and temperature of 75℃. Under these conditions, the Quercitannin yield was 78.15% and near to the estimated value, implying suitability of the model for extraction procedure.

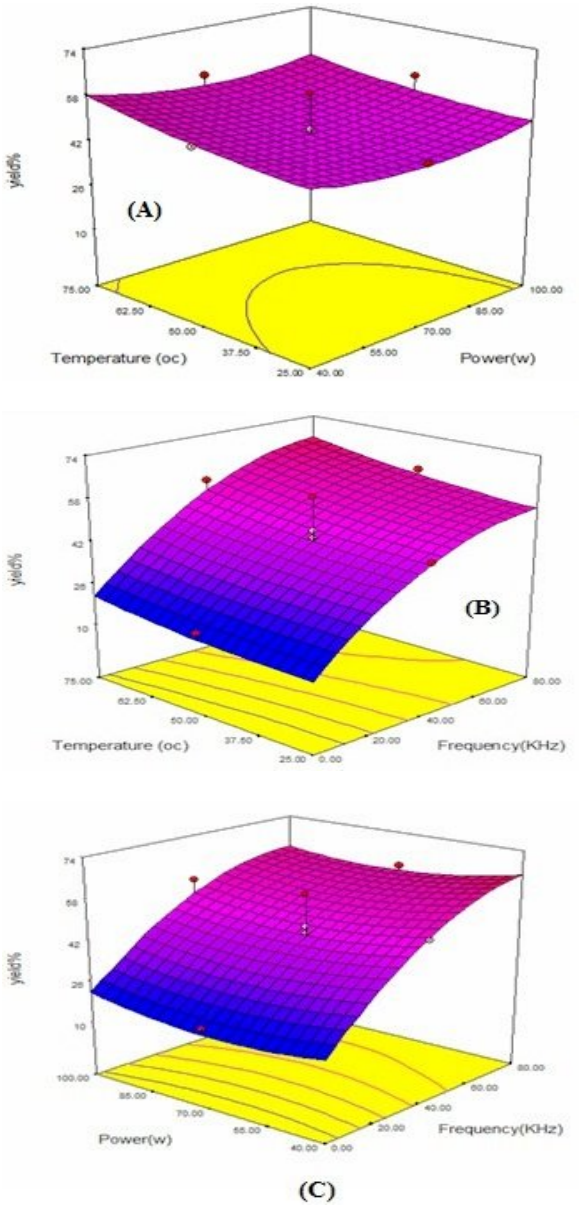

Fig. 7: Response surface plots for the extract yields of oak leaves (A) ultrasonic power to temperature (B) ultrasonic frequency to temperature (C) ultrasonic power to ultrasonic frequency.

Conclusions

Selecting extraction approaches depends on extraction efficiency, complexity, the cost of production, environmental friendliness, and safety. Although Soxhlet and Maceration are user-friendly, they require consuming a massive volume of solvent and involve high temperatures, which may affect the active constituents of the plant, and need a long-time duration of extraction. Thus, this extraction technique is not promising for a commercial viewpoint because of the mentioned disadvantages.

The ultrasonic method has a little laboratory repeatability. In the ultrasonic method, the energy generated by the bubble burst and the cavitation causes a high pressure that provides a significant shock to the specimen. Absorbed sound waves are a factor itself in converting acoustic energy to heat, so temperature control is difficult and it damages heat-sensitive compounds. After extraction by the ultrasonic method, filtration and separation of the torn plant cell and its contents are obligatory. However, in the microfluidic method, there is not such a problem. In microfluidic system, two fluids hit each other in very thin channels and because of the special features of this system, an effective mixing occurs between the two fluids. Boundary layer of mass transfer is lower than normal conditions, so resistance against the mass transfer, size and weight of equipment would reduce. Microfluidic system acts continuously that by applying several parallel systems, mass production can be achieved without errors due to increased production volumes common in non-continuous systems.

Difference of macro and micro systems, is due to type of mass transfer phenomena in two scales. In the macro systems, much of the mass transfer is due to displacement and by creating turbulence in these systems; the rate of mass transfer can be increased. This factor can produce error while increasing system size as with the increase of size, the possibility of creating a uniform mixture would reduce. So, the results of extraction by ultrasonic cannot be extended to industrial scales. The amount of solvent used in non-continuous processes increases. The possibility of effective collision compared to micro-system would be lower.

The use of microchannel alone, given the benefits mentioned, can be a useful way of extracting the effective compounds of medicinal plants. Using this method with other common methods, such as ultrasonic, can improve the efficiency to a certain

extent. Fig. 8 shows the results of comparing the different methods of Quercitannin extraction from oak. Benefit of microfluidic technologies is in analysis is that in the systems show useful capabilities including: The ability to use very small amounts of sample and reagent products, doing separations and detections with high resolution and sensitivity, low cost, short analysis time, and the low effects on the analysis tools, and new capabilities fundamentally provide regarding the flow rate control in time and space, compared to conventional extraction methods such as soxhlet and ultrasonic. The extraction efficiency is higher with this method.

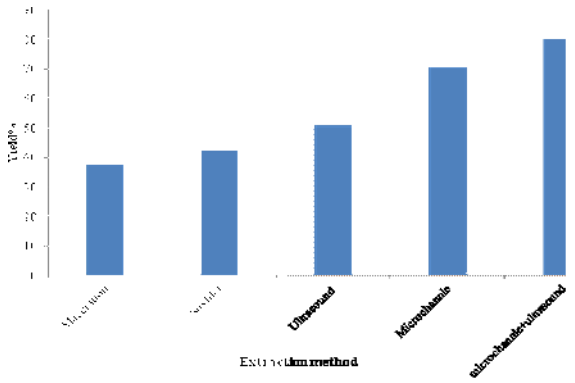

Fig. 8: Compare methods of Quercitannin extraction.

In the present research, the optimum extraction conditions by RSM were achieved at an ultrasound frequency of 80 kHz, solvent power of 100w, and temperature of 50ºC. Under these optimum conditions, Quercitannin concentrations were higher compared to those using conventional extraction methods, such as Soxhlet and Maceration. Microfluidic extraction technique is assistance to avoid the thermal degradation, enhance the bioactive components bioavailability that enhances the activity of antioxidant and overcomes the weakness of the Soxhlet and Maceration approaches. The maximum extraction selectivity can be achieved for Quercitannin extraction using the microfluidic extraction. Microfluidic extraction with the ultrasonic method as an alternative technique has received growing attention for numerous reasons such as (1) a lower extraction time (2), a lower consumption of solvent (3), an improved extraction efficiency, and (4) environmentally friendliness and safety.

Acknowledgments

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