A review of the effect of UAE optimization parameters on antioxidant activity

H S Elshreef†, M E S Mirghani‡, S Sulaiman§, M S Jami$†

1 Department of Biotechnology Engineering, Faculty of Engineering, International Islamic University Malaysia, P.O BOX 10. 50728, Kuala Lumpur, Malaysia.
2 International Institute for Halal Research and Training, International Islamic University Malaysia, P.O BOX 10. 50728, Kuala Lumpur, Malaysia.

* E-mail: elwathig@iium.edu.my

Abstract. Optimization of Ultrasound-assisted extraction parameters is necessary to determine the optimum level of the parameters, including solvent-to-material ratio, power, extraction time, solvent concentration, temperature, and pH. This review focuses on the UAE parameters' effects on the antioxidant activity, their interactions, and the best method of examining antioxidant activity to respond to the UAE's optimization. It was determined that the optimal extraction time is 15 minutes, and any duration longer than that could result in reduction of antioxidant activity. The temperature effect is important, wherein antioxidant activity decreases significantly when the extraction temperature is higher than 45 °C. Increasing the solvent concentration beyond 50% decreased the antioxidant activity. No increase in antioxidant activity was observed with a solvent/sample ratio greater than 40 ml/g. Increased ultrasound power leads to increased antioxidant compounds, especially in the range of ultrasound power, such as 50 to 150 W. However, higher ultrasound power creates free hydroxyl radicals that destroy the antioxidant compound. With an increase in pH, the radical scavenging activity increases significantly. It should, however, be at a near-neutral level, such as pH 6. Comparative literature has shown that optimizing UAE contributes to enhanced antioxidant activity and enhances resource conservation, such as energy and chemicals.

1. Introduction
Antioxidants are essential substances that slow, regulate, or inhibit oxidation and food quality degradation when present in food. Antioxidants minimize the risk of degenerative diseases induced by oxidative stress in the body [1]. Natural antioxidants from plant materials have recently become important in replacing synthetic ones. They are more appealing than synthetic antioxidants due to safety concerns. Plants contain various compound groups called "phytochemicals," and many compounds have the antioxidant potential [2]. Phenolic compounds, carotenoids, vitamins C and E are the primary antioxidants in plant-based foods. Antioxidant compounds such as carotenoids and flavonoids improve stability and prolong storage life when added to food products [1]. Medical investigations propose that natural antioxidants are essential in decreasing chronic ailments such as cardiomyopathy and cancers [3,4]. Antioxidants protect the cells against homeostatic imbalances and free radical scavenging, thereby enhancing the cellular processes [5]. Antioxidants control free radicals through several mechanisms, namely reducing, scavenging, opposing, or suppressing the free radical molecules [6]. Free radicals are reactive, unstable molecules that damage cells and may be reactive oxygen or reactive nitrogen species. The superoxide anion (O$_2^-$), hydroxyl radical (.OH), and peroxy radicals (H$_2$O$_2$) are examples of oxygen radicals formed in a biological system and are known as Reactive Oxygen Species (ROS). The cell components, such as DNA, lipids, and proteins, can experience oxidative damage by ROS. Reactive Oxygen Species have significant roles in the degenerative system, for example, aging [7], Alzheimer's disease, cardiovascular illnesses, cancer, and other nervous system degeneration [8,9].
The demand for novel extraction techniques to enhance efficiency, reduce processing cycles, and reduce organic solvents usage has been growing in the past few years. Moreover, in conjunction with traditional extraction, ultrasound is a possible strategy for increasing the rate and degree of mass transfer across the sample-solvent interface. Ultra-sound-assisted extraction involves mechanical disruption of the plant cell walls via acoustic cavitation, thereby allowing the solvent to permeate the cells and extract the compounds [10]. Since it can be performed at low temperatures, thermally-volatile substances will not be degraded[11]. It is also commonly used for the removal of phenols from various crops [12]. Acoustic cavitation in UAE induces cell wall damage, decreased particle size, and enhanced interaction with solvents and selected compounds [13]. Maximizing the ultrasound-assisted extraction of antioxidants has many benefits, including the conservation of sample material and solvents.

Furthermore, UAE guarantees the maintenance of the biological properties of the extracts. Understanding how UAE optimization parameters such as time, frequency, power amplitude, extraction temperature, and solvent-to-sample ratio affect antioxidant activity is essential to attaining optimum yield of antioxidant. This study was undertaken since existing literature has not investigated the effects of UAE optimization parameters on antioxidant activity. Therefore, this study aims to provide a useful guide for and future optimizations of ultrasound-assisted extractions. Published journal articles on using optimized UAE to extract antioxidant compounds were analysed using Scopus and Science Direct databases. Ultrasonic-assisted extraction types and their standard parameters Sonication is commonly conducted using ultrasonic baths or ultrasonic probes, operating in batch or continuous flow mode in laboratory-scale extraction systems [14]. Optimization is, therefore, an essential step in the UAE process. The literature has been thoroughly discussed, where a series of study work on the various UAE for natural compounds summarised.

2. Effect of UAE extraction parameter on antioxidant activity
The effect of several factors on the efficient application of the UAE should be considered and described in detail in order to obtain optimal extraction of the antioxidant compound. Factors such as power, temperature, solvent sample ratio, solvent concentration, pH, and extraction time are the most influential parameters on the UAE process [15]. Hence, they play a significant role in getting efficient extraction [16].

2.1. The effect of ultrasonication power
Ultrasound power as a parameter in the optimization has a low significant effect on antioxidant activity [17] due to substantial decreases in total polyphenols and total anthocyanins observed with high ultrasound power [18]. Ultrasonic power with ionic liquid extraction showed a highly significant effect on antioxidant activity [19]. Moreover, it showed a significant effect with the highest antioxidant activity with a power of 50 W. Hence, Increased ultrasound power is attributable to increased antioxidant compound production in specific ultrasound power ranges, such as 50 to 150 W. However, exceeding this range may damage antioxidant compounds due to free radicals in a very high ultrasonic power range. [20].

2.2. The effect of ultrasonic time
The ultrasonic time showed an insignificant effect on antioxidant activity. A longer extraction time improves extraction yields but can lead to unwanted effects in the compounds extracted [14]. The optimal UAE extraction time for extracting phenolic compounds from lime peel was 4 min [21]. However, the optimal extraction time is 15 minutes, and any duration longer than that could result in the depletion of antioxidant activity [22].

2.3. The effect of temperature
Higher temperatures also decrease the surface tension and make the extracts less viscous, improving the extraction yield. The temperature effect was significant for optimization, wherein temperatures greater than 45 °C decreased the antioxidant activity. Antioxidant compounds are easily hydrolyzed and
oxidized at higher temperatures, primarily when extracted over extended periods [23,24]. Hence, the temperature effect is essential, wherein antioxidant activity decreases significantly when the UAE's temperature is higher than 45 °C.

2.4. The effect of solvent concentration
An increase in solvent concentration resulted in a highly significant improvement in antioxidant activity [25]. The more the concentration of the solvent increases, the more the antioxidant extraction increases [26]. Nonetheless, no substantial increase was observed above the 50 percent solvent concentration.

2.5. The effect of Solvent-to-solid ratio
The solvent-to-sample ratio had a highly significant effect on antioxidant activity with a ratio of 40 ml/g. In comparison, the rate of the solvent-to-sample ratio of more than 40 ml/g has remained almost unchanged on antioxidant activity. The considerable effect of solvent to solid ratio can be attributed to the decrease in the mixture's density [16]. Therefore, the solid ratio's solvent effect was significant due to a decrease in the mixture's density, although a solvent to sample ratio of more than 40 ml/g observed no increase in antioxidant activity.

2.6. The effect of pH
In the studies included in this review, the extraction pH conditions significantly impacted DPPH and FRAP antioxidant activities. A low pH resulted in a high level of antioxidant activity measured by the FRAP method. Near-neutral pH ranges resulted in a high level of antioxidant activity measured by DPPH assay [25]. The radical scavenging activity was found to have a significant, directly-proportional relationship. An increase in radical scavenging potential may benefit from a deprotonation balance predicted to occur in an aqueous solution with increased pH [27]. The radical scavenging activity increases dramatically with an increase in pH. However, it should be at a near-neutral level, such as pH 6, since extreme pH values will affect the balance of deprotonation, which will reduce the antioxidant activity.

3. Optimization of antioxidant activity by using ultrasonic-assisted extraction
In the design of optimization experiments, the response surface methodology (RSM) has become an indispensable tool for optimizing the process parameters. The Response Surface Methodology (RSM) is an essential optimization process to determine and predict the optimal levels' design process and analyze the interaction's experimental variables. However, RSM optimization of ultrasound-assisted extraction processes is more efficient than conventional extraction, such as one factor at a time (OFAT) [28]. The use of RSM can reduce the number of experimental runs and quantify the relations between multiple factors [29]. In a study, for optimization of three factors (solvent concentration, time, and ultrasonic power) and at three levels to obtain a high yield of DPPH radical scavenging activity, a Box-Behnken design (BBD) with a total number of 16 experimental runs was employed [21]. In another study, the cube-style central composite design (SCCD) provided five levels for each extraction portion to generate 30 extraction treatments [17]. One of the studies reported that RSM was carried out by a five-level, three-variable CCRD (Central Composite Rotatable Design) [22]. In another study, RSM was also used to obtain the optimal extraction parameters for antioxidant activity based on a four-factor, five-level central composite design (CCD) [29]. For the design of experiments, model building, and data analysis, box-Behnken design (BBD) was applied. Compared to other models, such as the central composite design, lesser experimental runs were obtained in the BBD model [31]. Therefore, the box-Behnken design was the optimization design that was most used.

Many factors govern the choice of a suitable optimization method. For instance, ultrasound probes or cleaning baths available commercially operate at low ultrasound frequencies (20-40 kHz). The exact optimum frequency is possibly unique to the system, and hence it is necessary to design optimization tests that are unique to various extraction processes and configurations.
Many methods of assaying antioxidant activity have been pursued as an optimization response based on inhibitory action, namely: assay Ferric Reducing Antioxidant Strength Assay (FRAP), 2,2’-diphenyl-1-picrylhydrazine (DPPH), Trolox equivalent antioxidant capacity (TEAC) and 2,2’-azino-bis (3 ethylbenzothiazoline-6-sulphonic acids) (ABTS). A summary illustrating the optimum parameters for optimizing antioxidant activity through ultrasound-assisted extraction is shown in Table 1.

The antioxidant assays, when used as responses, are somehow different from each other. The solid/liquid ratio, for example, was significant when the DPPH and TEAC were also increased. On the other hand, in DPPH and TEAC, the extraction time was not significant. Besides, the power showed a slight increase in TEAC [21]. So far, no study has tried several assays of antioxidant activity as a response. As different assays are applied as responses for the optimization, it is not easy to assess and compare the findings across studies. In future studies, researchers should try to incorporate several antioxidant assays.

**Table 1.** Summary of the optimum parameters for optimization of antioxidant activity through ultrasound-assisted extraction.

| Raw material | U.A.E device type | U.A.E parameters (conditions) | Optimum parameters | Antioxidant methods | Result (interaction between the parameters) |
|--------------|-------------------|-----------------------------|-------------------|---------------------|----------------------------------------|
| Flowers of Limonium sinuatum | ultrasonic bath | Ethanol concentration % (v/v) (20, 40, 60), solvent to solid ratio (20, 40, 60 ml/g), ultrasound time (5, 10, 15) min, and temperature (30, 50, 80 °C) | Ethanol concentration (60%), solvent to solid ratio (56.9 ml/g), ultrasound time (9.8) min, and temperature (40°C) | ABTS | Solvent-to-solid ratio and ethanol concentration had a highly significant effect, while the ultrasonic time was not significant for antioxidant activity |
| Oil from papaya seed | ultrasonic bath | time (x1, 5–30 min), temperature (x2, 25–50°C), ultrasound power (x3, 235–700 W) and solvent to sample ratio (x4, 6:1–10:1, v/w) | temperature (62.5°C); 38.5 min; ultrasound power (700 W); solvent to sample ratio (7:1 v/w). | DPPH | temperature and solvent to sample ratio had a highly significant effect on the antioxidant activity. The solvent to sample ratio was not substantial. Ultrasound power with extraction time and temperature showed a considerable shallow impact. |
| Rhizomes of Curcuma longa | ionic liquid-based ultrasonic-assisted extraction, ultrasonic bath | concentration of L.L.s (X1, 0.1–0.5 mol/L), extraction time (X2, 10–90 min) and ultrasound power (X3, 100–250 W) | ultrasonic power, 250 W; liquid-raw ratio, 30 mL/g; extraction time, 90 min; [Omim]Br concentration, 4.2 mol/L. | ABTS and TRAP | The ionic liquid aqueous solution’s concentration had a high effect on antioxidant activity, close to LL.’s concentration coefficient and the ultrasound power effect. The extraction time and ultrasound power showed a highly significant effect on the antioxidant. |
| Cassia auriculata leaves | ultrasonic generator | extraction time (5,10,15 min), pH (5.6,7), solvent concentration (40,50,60%) and ultrasound power (30,40,50 W) | Extraction time 5 min, pH 6.2, solvent concentration 60%, power 50 W. | DPPH and FRAP | Maximum FRAP observed at the medium time, low pH, high solvent concentration, and ultrasound power of 50 W. Low time and pH levels were not significant. In contrast, solvent concentration and power were significant and observed to enhance |
Rhizomes of *Rheum moorcrofti* anum were extracted using an ultrasonic bath with a vessel diameter of 10–40 cm, a sample-to-solvent ratio of 10–30 mL/g, and an extraction time of 10–20 min. A sample to solvent ratio of 1:28.42 g/mL was used, and 40% acetone concentration with 0.2N HCl concentration was employed, with an extraction time of 10 min. The antioxidant activity at a high level was observed. The vessel diameter had a significant influence on the antioxidant activity. The increasing sample-to-solvent ratio had a common effect on antioxidant activity. Increasing extraction temperature above 45 °C resulted in a quadratic decrease in ABTS activity. DPPH: increasing both vessel diameter and sample-to-solvent ratio resulted in a significant positive effect on DPPH activity.

| Parameter                          | Value   |
|------------------------------------|---------|
| Rhizomes of *Rheum moorcrofti* anum |         |
| ultrasonic bath                    |         |
| vessel diameter (10–40 cm)         |         |
| sample-to-solvent ratio (10–30 mL/g) |         |
| extraction time (10–20 min)        |         |
| sample to solvent ratio (1:28.42 g/mL) |         |
| solvent ratio (40%)                |         |
| extraction time (10 min)           |         |
| antioxidant activity               |         |
| ABTS                               |         |

Germinated chickpea was extracted using an ultrasonic probe with a solid/liquid ratio of 10–20 mL/g, an extraction time of 10–40 min, and power (% amplitude) of 10–60. A solid/liquid ratio of 36.16% and a power of 20.17% were used. DPPH and TEAC were observed. Ultrasound power and time were not significant on the DPPH radical scavenging activity. Ultrasound power and extraction time were not significant for the TEAC of the samples.

| Parameter                          | Value   |
|------------------------------------|---------|
| Germinated chickpea                |         |
| ultrasonic probe                   |         |
| Solid/liquid ratio (g/mL)           | X1 10 20 30 |
| Extraction time (min)               | X2 10 25 40 |
| Power (% amplitude) (X3)            | 20 60 100 |
| DPPH and TEAC                      |         |

Alfalfa aerial part was extracted using an ultrasonic bath with a ratio of liquid to solid (30, 40, 50, 60, 70 mL/g). An extraction temperature of 40, 50, 60, 70°C; an extraction time of 20, 40, 60, 80, 100 min; an ethanol concentration of 20, 30, 40, 50, 60% were used. DPPH and ABTS were observed. ABTS and DPPH had a significant effect on antioxidant activities. ABTS concentration (%) and (Ethanol concentration (%), v/v) were significant on ABTS radical scavenging capacity, while only two interactions of (Ratio of liquid to solid (mL/g), Extraction time (min)) and (Extraction temperature (°C), Extraction time (min)) were significant on DPPH radical scavenging capacity.

| Parameter                          | Value   |
|------------------------------------|---------|
| Alfalfa aerial part                |         |
| ultrasonic bath                   |         |
| Ratio of liquid to solid (30, 40, 50, 60, 70 mL/g) |         |
| Extraction temperature (40, 50, 60, 70°C) |         |
| Extraction time (20, 40, 60, 80, 100 min) |         |
| Ethanol concentration (20, 30, 40, 50, 60%, v/v) |         |
| DPPH and ABTS                      |         |

Lime peel waste was extracted using an ultrasound probe with an ethanol concentration of 50, 75, 100% v/v. Amplitude of 20, 30, 40% (v/v), and a time of 2, 3, 4 min were used. DPPH and ABTS were observed. Ethanol concentration has a significant effect on antioxidant activities. At 50-60 percent ethanol concentration, DPPH, and ABTS were optimal.

| Parameter                          | Value   |
|------------------------------------|---------|
| Lime peel waste                    |         |
| ultrasound probe                   |         |
| Ethanol concentration (50, 75, 100% v/v) |         |
| Amplitude (20, 30, 40%), Time (2, 3, 4 min) |         |
| DPPH and ABTS                      |         |

[21] Ethanol concentration has a significant effect on antioxidant activities. At 50-60 percent ethanol concentration, DPPH, and ABTS were optimal.

[28] The highest DPPH was obtained from 45.59 minutes, 54.56 °C, 60.3 milliliters/gram, and 46.67 percent ethanol in the solvent to sample ratio. While the ABTS was obtained from the following parameters: ethanol concentration 60 percent, The liquid to solid ratio of 47.29 mL/g, temperature 63.73 °C, 51.62 min for the time.

[30] Three interactions of (Ratio of liquid to solid (mL/g), Extraction time (min)), (Ratio of liquid to solid (mL/g), Ethanol concentration (%), v/v) and (Extraction time (min), Ethanol concentration (%), v/v) were significant on ABTS radical-scavenging capacity, while only two interactions of : (Ratio of liquid to solid (mL/g), Extraction time (min)) and (Extraction temperature (°C), Extraction time (min)) were significant on DPPH radical-scavenging capacity.

[32] Ethanol concentration has a significant effect on antioxidant activities. At 50-60 percent ethanol concentration, DPPH, and ABTS were optimal.
In conclusion, optimization studies related to the ultrasound-assisted extraction parameters have been discussed in this review. It was shown that optimization is necessary as the findings report a substantial increase in antioxidant activity upon optimizing the extraction parameters. It is well-established that the optimal values of the parameters help to save energy by using less ultrasound power and in conducting the procedure in a shorter time. In addition to that, excess elevated temperatures can also be avoided, which can also save resources. Optimization also avoids the waste of solvent in a high solvent-solid ratio. Furthermore, it helps decide the best antioxidant activity method acceptable or shows a heightened response with optimum parameters. The most popular antioxidant method used to respond to UAE optimization is DPPH, ABTS, FRAP, TRAP, and TEAC due to their simplicity. Generally, UAE optimization mainly influenced solvent concentration, solvent to solid ratio, temperature, extraction time, ultrasonic power, and pH values. The optimum extraction time is 15 minutes, and the depletion of antioxidant activity may result from any period longer than that. The effect of temperature is essential, where antioxidant activity decreases dramatically when the UAE's temperature is higher than 45 °C. Rising solvent concentrations usually leads to an increase in antioxidants' activity. Nevertheless, no noticeable rise above the 50 percent solvent concentration was observed. Free hydroxyl radicals that destroy the antioxidant compound are generated by greater ultrasound strength. The solid to liquid ratio's solvent effect was substantial because of a decrease in the mixture's density. However, there was no increase in antioxidant activity observed by a solvent to sample ratio of more than 40 ml/g. With an increase in pH, the radical scavenging behavior increases significantly. However, it should be at a near-neutral level, such as pH 6, because extreme pH values can influence the deprotonation balance, which will reduce the antioxidant activity. Hence, applying the response surface methodology (RSM) will boost the extraction of antioxidant compounds and ensure that the optimal outcome is obtained in terms of antioxidant activity. The analysis of UAE optimization techniques is essential. A review of existing literature may lead to a significant improvement in future studies to test more parameters with the RSM design.

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