Research Article

Optimization of Ultrasonic Assisted Extraction of Bioactive Compounds from Almond Hull

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Abstract | Ultrasonic assisted extraction (UAE) of total phenolic content (TPC) from almond hull was optimized by response surface methodology (RSM). TPC and 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity were used as response variables. Almond hull extract was chemically characterized by Fourier transform infrared spectrometer (FTIR) and gas chromatography mass spectrometer (GCMS). The extraction conditions were optimized by using independent extraction parameters; sample to solvent ratio (1:20-1:40 w/v), solvent concentrations (20-80%, v/v) and time (10-30 min), whereas, TPC and DPPH were used as response variables. At optimized extraction conditions (40 ml/g, 22.5 min and 80% of ethanol), the experimental values for TPC and DPPH inhibition were 110.17 ± 3.44 mg of GAE/g of extract and 87.45 ± 1.28%, respectively. For DPPH inhibition assay, IC_{50} value of almond hull extract was 51.64 µg/ml which was lower than the ascorbic acid (180 µg/ml). Almond hull extract showed antimicrobial effect against *Escherichia coli, Staphylococcus aureus* and *Salmonella typhimurium.* β-sitosterol (44 %), was identified as major phytoconstituent in almond hull extract. Due to antioxidant and antimicrobial potential, almond hull extract can be utilized as a functional food ingredient, and natural preservative.

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Introduction

Almond tree (*Prunus amygdalus*) is popular nut trees worldwide and belongs to family Rosaceae. In 2019, global almond production was 3.53 million tons and United States of America, Australia, Iran and Italy were recognized as major almond producers (FAO, 2020). Almond hull is the main byproduct of almonds and comprised of 35-62% of fresh almond weight (Prgomet *et al.*, 2017). Almond hulls are assumed as a low economic value byproduct and are mainly used in animal feed. However, almond hulls are rich TPC and can be used for the development of functional food products (Kahlaoui *et al.*, 2019). Almond hull contains antioxidants and exhibits free radical-scavenging potential (Wijeratne *et al.*, 2006). The

efficient utilization of agriculture byproducts helps to reduce the environmental hazards associated with organic waste and improved the economic returns (Prgomet *et al*., 2019a). The food commodities have diverse profile of phenolic compounds and extraction of these polyphenols is dependent on extraction method and extraction parameters. Solvent type, temperature, sample to solvent proportion and time of extraction can greatly influence the phenolic extraction from food matrices (Iglesias-Carres *et al*., 2018; Zitka *et al*., 2011). The conventional methods require long extraction time, high temperature and large proportion of solvents, which leads to the degradation of heat sensitive bioactive compounds. Therefore, the concept of modern extraction techniques is gaining interest, such as extraction by ultrasonication and microwave assisted extraction (Guglielmetti *et al*., 2017). These advance extraction techniques offer less solvent consumption, extraction at low temperature, high yield and purity of target compounds. UAE is inexpensive and simple technique which is achieved at lower temperature and short time by creating acoustic cavitation which disrupts plant cell walls and release of internal cellular constituents into the extraction matrix (Piyalungka *et al*., 2019). Due to simple, inexpensive and reproducible technique UAE is effective at industrial scale (Sitthiya *et al*., 2018). The aim of this study was to optimize the UAE of bioactive compounds from almond hull and evaluation of their antioxidant and antimicrobial potential against foodborne pathogens.

Materials and Methods

Sample preparation

Almond fruits were harvested from Hunza valley of Pakistan and hulls were separated manually followed by oven drying for 48 h at 50°C. The samples were ground by mechanical grinder (Philips Co. Ltd., China) and stored at 4°C till further use (Hiranrangsee *et al*., 2016).

Extraction process

TPC from the almond hull were extracted by UAE and conventional extraction methods.

Conventional extraction

The powdered sample (5 g) was added to ethanol (45 ml; 80%, v/v) and placed in a at 25 ℃ and 300 rpm in a shaker. The extraction was carried out for 24 and 48 h, separately. The extracts were filtered and stored at 4 °C (Sadiq *et al*., 2015).

Ultrasonic assisted extraction (UAE)

UAE of almond hull was optimized by RSM using Design-Expert® software (Minneapolis, MN, USA) at a fixed frequency of 20 kHz. UAE was optimized by independent extraction variables, which were sample to solvent ratio (1:20, 1:30 and 1:40 w/v), solvent concentrations (20, 50 and 80%, v/v) and time (10, 20 and 30 min) at fixed temperature of 45°C. TPC and DPPH inhibition were used as response variables (R1 and R2, respectively). The sample was added to beaker containing the extraction solvent and subjected to ultrasonic processor (LSP-500, Industrial Sonomechanics, USA).

TPC and antioxidant activity

TPC was determined using Folin–Ciocalteau regent (Sigma-Aldrich, USA), by following the method described by Sadiq *et al*. (2015). TPC was estimated by using gallic acid standard curve and presented as mg of gallic acid equivalent (GAE) per gram of raw sample.

Antioxidant potential of almond hull extract was estimated by DPPH inhibition assay by following Sadiq *et al*. (2015). The extract (50 µl) was added to 5 ml of DPPH in ethanol (40 ppm). The mixture was kept for half an hour in dark at 25 ℃. After incubation absorbance was measured at 517 nm using UV-Vis spectrophotometer. % DPPH inhibition was calculated using equation 3.

$$DPPH\ (\%\ inhibition) = \frac{(AC - AS)}{AC} \times 100 \quad (3)$$

AC: Absorbance of the control (DPPH without extract); AS: Absorbance of sample.

Optimization of UAE extraction

UAE extraction of almond hull was optimized using response surface methodology and optimized run was selected using 0.994 desirability. The optimized extraction conditions were 1:40 g/ml sample to solvent proportion, 22.5 min time of extraction and 80% ethanol (v/v). The optimized extract was lyophilized (Christ Alpha 1-2 LD plus, Germany) to obtain powdered extract.

Characterization of optimized extract

TPC and antioxidant activity: The stock solution (1 mg/ml) of dried extract was diluted with deionized water to 100 µg/ml and TPC was determined using Folin–Ciocalteau regent. Antioxidant potential of optimized extract was determined by DPPH inhibition and FRAP assay. For %DPPH inhibition, dif-

ferent concentrations (31.25-2000 µg/ml) of extract were prepared and %DPPH inhibition was estimated by using equation 3. IC_{50} values were determined by non-linear regression using GraphPad Prism® version 7. (San Diego, US) (Sadiq *et al.*, 2017). For FRAP assay, almond hull extract (50 µl of 1 mg/ml) was mixed with FRAP reagent (1.5 ml) and incubated at 37°C for 4 min, followed by reading the absorbance at 593 nm. Ferrous sulfate solution (100–1000 µM) was used to develop a standard curve. Ascorbic acid was used as positive control.

Antibacterial activity: Antibacterial activity of almond hull extract was evaluated against *Escherichia coli* (ATCC 8739), *Salmonella typhimurium* (ATCC 14028) and *Staphylococcus aureus* (ATCC 25923). The sterilized cotton swab was used to spread the bacteria (10^8 CFU/ml) on the surface of nutrient agar plates. The extract (100 µl) in different concentrations (1.56-50 mg/ml) was added into the 8 mm wells made on agar plates. After 24 h incubation at 37 °C, the inhibition zone diameter was measured. All experiments were performed in triplicates (Taye *et al.*, 2011). MIC of almond hull extract (1.56-50 mg/ml) was estimated by broth macrodilution method following Kubo *et al.* (2004). After incubation period, the lowest concentration without any visible growth was marked as MIC. MBC was measured by sub-culturing 100 µl of each extract concentrations that had no visible growth on nutrient agar. After 24 h incubation, the minimum concentration without detectable growth on nutrient agar plates was considered as the MBC.

Fourier transform infrared spectroscopy analysis

The optimized extract was characterized by FTIR spectrometer (Agilent technologies, USA). The spectra were recorded (4000-650 cm^{-1}) with a resolution of 4cm^{-1} using absorbance mode.

GCMS analysis

The optimized extract was analyzed by using GC-MS system (GC-7890A/MS-5975C, Agilent Technologies, Santa Clara, CA, USA) with HP-5 MS capillary column. Helium gas was used as carrier (1.0 ml/min) and sample injection was programmed at 200°C. All data were acquired within the range 50–600 a.m.u. The compounds were identified by using NIST 05 spectral library (Gaithersburg, MD, USA).

Statistical analysis

One-way analysis of variance (ANOVA) and Tukey's HSD tests were carried out to find significant ($p < 0.05$) differences among mean observations by using SPSS statistical software package (SPSS, version 23.0).

Table 1: *Optimization of ultrasound assisted extraction of almond hull and effect of extraction parameters on response variables.*

Experiments	Independent variables			Response variables	
	Sample to solvent ratio (g/ml)	Time (min)	Ethanol (%)	DPPH inhibition (%)	TPC (mg GAE/g of raw sample)
1	1:20	20	20	68.18 ± 2.1	5.82 ± 0.11
2	1:40	20	20	72.56 ± 2.48	11.13 ± 0.5
3	1:30	20	50	70.07 ± 0.51	8.39 ± 0.2
4	1:40	20	80	86.27±3.41	11.31 ± 0.19
5	1:30	30	80	82.10 ± 1.66	7.94 ± 0.12
6	1:30	30	20	73.27 ± 1.48	7.10 ± 0.35
7	1:20	20	80	81.26 ± 2.31	4.92 ± 0.5
8	1:30	10	80	73.20 ± 0.92	8.02 ± 0.193
9	1:40	30	50	83.66 ± 2.77	9.75 ± 0.4
10	1:30	20	50	76.01 ± 1.68	7.50 ± 0.36
11	1:30	20	50	76.15 ± 0.51	7.44 ± 0.31
12	1:40	10	50	75.72 ± 0.51	9.76 ± 0.32
13	1:20	30	50	77.65 ± 0.35	5.31 ± 0.12
14	1:30	10	20	67.66 ± 3.31	7.29 ± 0.4
15	1:20	10	50	68.91 ± 0.76	5.09 ± 0.11

Results and Discussions

UAE and conventional extraction of almond hull

UAE and conventional solvent extractions were used for the extraction of TPC. The conventional extraction resulted in TPC and %DPPH inhibition of 2.67 ± 0.17 mg GAE/g of raw almond hull and 63.89 ± 0.45%, respectively after 24 h of extraction, whereas, after 48 h of extraction the TPC and %DPPH inhibition were 2.56 ± 0.27 mg GAE/g and 64.34 ± 1.97%, respectively. UAE extraction of almond hull was optimized by using Box-Behnken design (Table 1). The optimal extraction conditions were 1:40 sample to solvent ratio, 80% ethanol and 20 min of extraction time which corresponded to TPC and %DPPH inhibition of 11.31 ± 0.19 mg GAE/g and 86.03 ± 3.41%, respectively. As compared to conventional solvent extraction, UAE was found to be more effective and rapid for TPC extraction. The reported difference in yield of TPC by conventional and UAE extractions

might also be influenced by different extraction conditions such as extraction time, sample to solvent ratio and extraction temperature. UAE is based on the application of sound waves to disrupt plant membranes, which facilitates the solvent penetration and enhance the high extraction yield (Mala *et al.*, 2021). Similarly, He *et al.* (2016) found high yield of TPC and antioxidant activity in blueberry wine pomace after UAE in comparison to conventional extraction.

Effect of UAE extraction parameters on TPC

TPC of almond hull extract was in the range of 4.92 ± 0.5 to 11.31 ± 0.19 mg GAE/g of raw material. Quadratic model was used to evaluate the effect of extraction parameters on response variables. The sample to solvent proportion significantly effect ($p < 0.05$) TPC in comparison to solvent concentration and UAE extraction time. The polynomial equation for TPC is presented as equation 1.

$$TPC = +7.78 + 2.60 \times X1 - 7.500E - 003 \times X2 + 0.11 \times X3 - 0.057 \times X1X2 + 0.27 \times X1X3 + 0.028 \times X2X3 + 0.20 \times X1^2 - 0.50 \times X2^2 + 0.31 \times X3^2 \ldots . (1)$$

X1: Sample to solvent ratio; X2: Extraction time; X3: Solvent concentration.

The p-value of 0.0042 and R^2 (coefficient of determination) value of 0.9641 indicated that the model was significant. Ingawale *et al.* (2018) reported that the hydroalcoholic solvent was more effective for the extraction of TPC than alcohol alone and increase in concentration of alcohol resulted in an increase in TPC. Simsek *et al.* (2012) reported that TPC was increased with an increase in extraction time of sour cherry pomace to optimal time and further increase in time, decreased the TPC. Extended extraction time might enhance the exposure of phenolics to oxygen and light, which resulted in degradation of the antioxidants. The extraction of TPC from *Murtus communis L.* leaves and milled berries was reported to increase with an increase in sample to solvent ratio (Cacace *et al.*, 2003; Dahmoune *et al.*, 2015). The increase in sample to solvent proportion results in an increase mass transfer, hence extraction yield is improved (Pinelo *et al.*, 2007).

Effect of UAE extraction parameters on %DPPH inhibition

Antioxidant activity of almond hull extract was in the range of 67.54 ± 0.51 to 86.03±3.41%. Quadratic model was used to evaluate the effect of extraction parameters on %DPPH inhibition. All the extraction parameters (sample to solvent proportion, extraction time and solvent concentration) had significant effect ($p < 0.05$) on %DPPH inhibition. The sample to solvent proportion, extraction time and concentration of solvent were reported to significantly influence the antioxidant activity (Belwal *et al.*, 2016; Chavan and Singhal, 2013). The polynomial equation for %DPPH inhibition is presented as equation 2.

$$TPC = +74.08 + 2.78 \times X1 + 3.90 \times X2 + 5.14 \times X3 - 0.20 \times X1X2 + 0.16 \times X1X3 + 0.82 \times X2X3 + 2.71 \times X1^2 - 0.30 \times X2^2 + 0.28 \times X3^2 \ldots . (2)$$

X1: Sample to solvent ratio; X2: Extraction time; X3: Solvent concentration.

The p-value (0.0420) and R^2 (coefficient of determination) value of 0.9035 indicated that the model was significant.

Optimization of UAE extraction

UAE extraction conditions were optimized by using optimization function of Design expert and optimized extraction conditions (1:40 g/ml, sample to solvent ratio, 22.5 min extraction time and 80% ethanol) with desirability of 0.994 were used for TPC extraction. The optimized extract was evaluated for its bioactive potential.

Characterization of optimized extract

TPC and DPPH inhibition: TPC of optimized extract was 110.17 ± 3.44 mg of GAE/g of dried extract. Sfahlan *et al.* (2009) reported TPC of almond hull extract as 78.2 mg GAE/g, which was lower than the current investigation. Prgomet *et al.* (2019a) reported TPC of almond hull extract in the range of 91.76-138.9 mg GAE/g of extract. The reported variations in TPC depends on plant species, environmental conditions, postharvest processing, maturity of fruit and collection season (Sadiq *et al.*, 2015). The antioxidant activity increased with concentration and the highest DPPH inhibition (87.45 ± 1.28%) was observed at 2000 µg/ml, whereas, the lowest DPPH inhibition (44.17 ± 1.91%) was observed at 31.25 µg/ml (Figure 1). Positive control (vitamin C) exhibited 95.03 ± 0.81% DPPH inhibition at 2000 µg/ml. The corresponding IC_{50} values for almond hull and vitamin C were 51. 64 and 180 µg/ml, respectively. Qureshi *et al.* (2019) reported IC_{50} value of almond hull extract as 167.11 and 76.04 µg/ml for 70% ethanol extract and n-butanol fraction, respectively. FRAP values of optimized almond hull extract and vitamin C were 3625.5 ± 66 and 3530 ± 96 µM of Fe (II)/g, respectively. Tlili *et al.* (2019) reported that

almond hulls contain bio-antioxidants which can be used in food and feed industries.

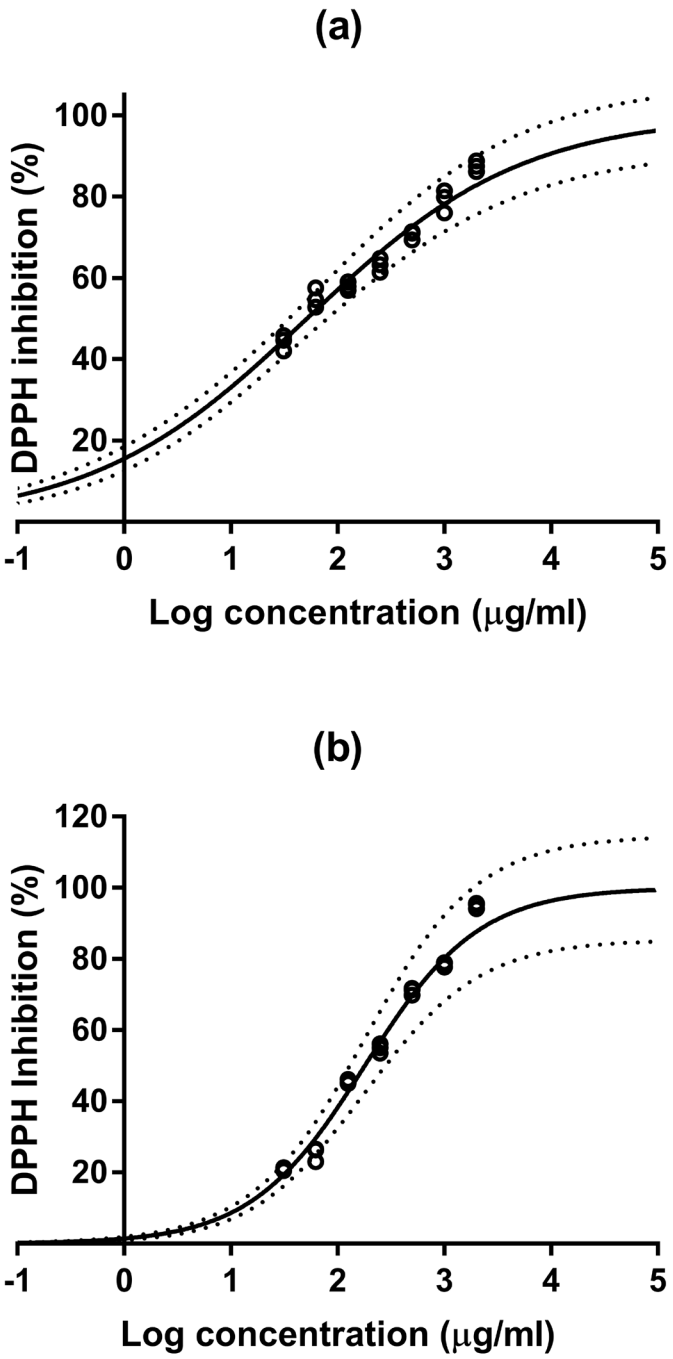

Figure 1: *DPPH inhibition (%) of almond hull extract (a) and vitamin c (b) at different concentrations, using nonlinear regression. The circles present observations, the solid lines represent the estimated means curves, and the broken lines represent the 95% confidence intervals of the mean estimates.*

Antimicrobial activity: The antimicrobial activity of almond hull extract was increased with the increase in extract concentration (Table 2). The maximum diameter of inhibition zones was 19.66 ± 0.58, 19.67 ± 0.58 and 19.33 ± 1.15 mm against *E. coli*, *S. typhimurium* and *S. aureus*, respectively, at the highest test concentration (50 mg/ml). MIC value of almond hull extract was 12.5 mg/ml against all test bacteria. MBC value of almond hull extract was 12.5 mg/ml for *E. coli* and *S. aureus*, whereas it was 25 mg/ml for *S. typhimurium*. Polyphenolic compounds present in almond hull were reported to exhibit antimicrobial potential (Prgomet *et al.*, 2019b). Antibacterial mechanism of polyphenolic compounds is associated with their ability to form hydrogen bonding with cell membrane proteins, destruction of electron transport chain and disruption of membranes (Liaqat *et al.*, 2019).

Table 2: *Antimicrobial activity of almond hull extract.*

Concentration	Diameter of zone of inhibition against pathogens		
mg/ml	*Escherichia coli* (mm)	*Salmonella typhimurium* (mm)	*Staphylococcus aureus* (mm)
50	19.66 ± 0.58^{a}	19.67 ± 0.58^{a}	19.33 ± 1.15^{a}
25	18.33 ± 1.53^{a}	15.33 ± 1.53^{b}	16.33 ± 1.53^{a}
12.5	12.66 ± 1.15^{b}	13.67 ± 1.53^{bc}	15.33 ± 1.53^{ab}
6.25	10.66 ± 1.53^{b}	11.33 ± 2.08^{c}	11 ± 2.65^{b}
3.12	-	-	-
1.56	-	-	-

Where, - indicate that there was no inhibition. Different superscript letters (a-c) indicate significant differences ($p < 0.05$) among mean observations within columns.

FTIR analysis of almond hull extract

FTIR spectrum of extract was summarized in Table 3 and Figure 2. The peaks in the range of 2936-2913 cm^{-1}, 1618-1498 cm^{-1}, 1377-1233 cm^{-1}, 900-700 cm^{-1} and 1040-1030 cm^{-1} were attributed to aliphatic compounds, aromatic compounds, carboxylic acid, aromatic hydrocarbons and aliphatic ethers, respectively (Geetha *et al.*, 2019). The presence of several hydroxyl groups on aromatic ring provides ability to polyphenolic compounds to donate a proton to a radical and act as an antioxidant or chain breaking molecule upon secondary oxidation (Franco *et al.*, 2008).

GCMS analysis of almond hull extract

The major phytoconstituents identified in almond hull extract were β-sitosterol (44 %), diisooctyl phthalate (12%), benzene, 1,3-bis (1,1-dimethylethly) (9.9%), phenol, 2,4-bis (1,1-dimethylethly) (8.7%), n-hexadecanoic acid (8%), 9-octadecenamide, (Z) (7%), spirost (5.20%) and lupeol (4.9%). β-sitosterol and its glucoside derivatives were reported for lowering cholesterol, cancer prevention, antimutagenic and anti-inflammatory effects (Villasenor *et al.*, 2002). Lupeol and hexadecanoic acid were previously reported as strong antioxidants (Jiang et al., 2017; Srivastava et al., 2013).

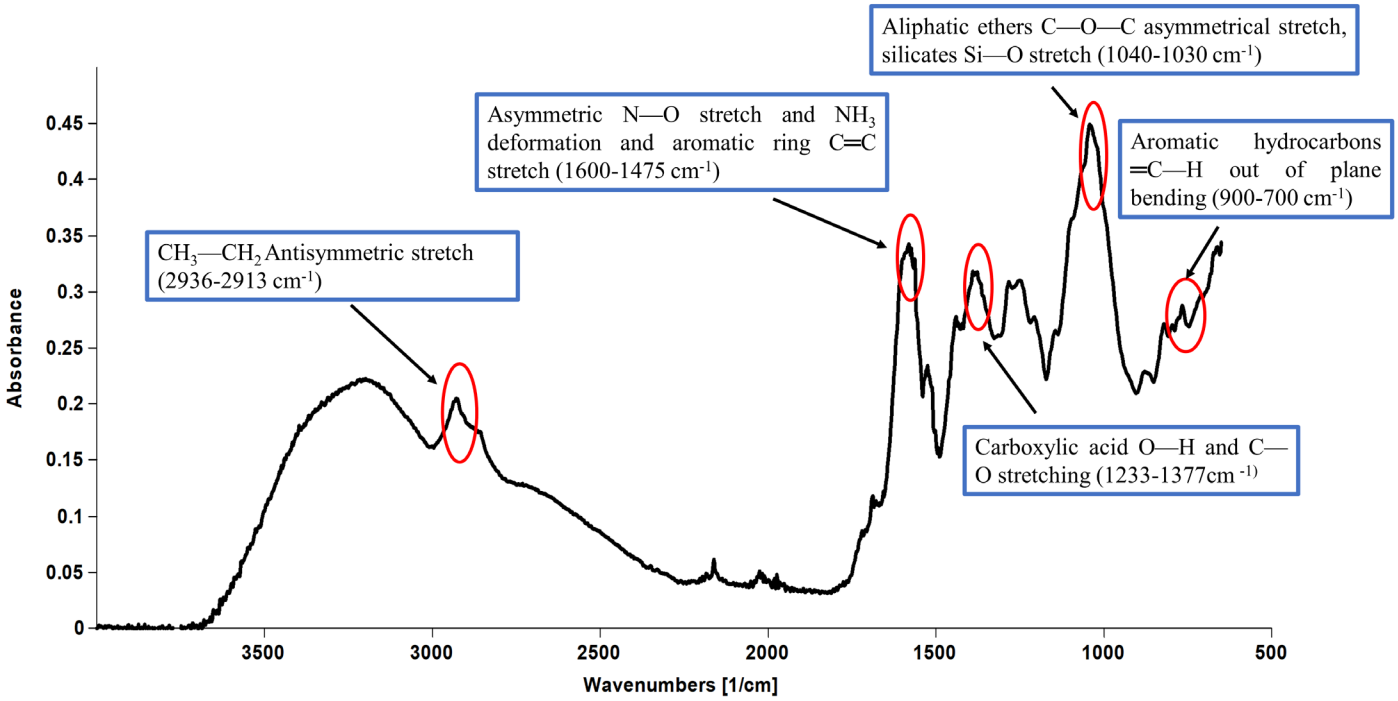

Figure 2: *FTIR spectrum of optimized almond hull extract.*

Table 3: *Assignment of FTIR peaks to the functional groups present in almond hull extract.*

Range (cm^{-1})	Group and class of compound	Assignment and remarks	Almond hull extract (cm^{-1})
2936-2913	CH_3—CH_2 In Aliphatic compounds	CH_3—CH_2— Anti-symmetric stretch	2929.7
1697	C=O	—C=O stretch	1688.5
1600-1520	NH_3^+ In NH4OH	NH_3 Deformation	1580.4, 1524.5
1618-1498	Benzene ring in aromatic compounds	C=C Aromatic ring stretch	1580.4, 1524.5
1550-1475	N—O Nitro compounds	N—O Asymmetric stretch	1524.5
1427	O—H In carboxylic acid	O—H stretch	1440.6
1233-1377	C—O In carboxylic acid	C—O stretch	1390.3, 1284.1
1246.92	O—H In carboxylic acid	O—H stretch	1248.7
1040-1030	C—O—C In aliphatic ethers, Si—O In silicates	C—O—C Asymmetric stretch, Si—O stretch	1041.8
900-700	=CH In aromatic hydrocarbons	=C—H out of plane bending	877.79, 820.01, 765.97

Parvez *et al.* (2018) reported that phytoconstituents such as β-sitosterol and lupeol exhibit antimicrobial and antioxidant potential.

Conclusions and Recommendations

This study was aimed to optimize the conditions that provide the maximum yield of TPC and high DPPH inhibition of almond hull extract. The optimized ultrasonic assisted extraction conditions for almond hull extract were with 80% ethanol for 20 min and 1:40 solid to solvent ratio to achieve the maximum output response. Almond hulls were found good source of phenolics, exhibited high DPPH inhibition

and showed considerable inhibition of food borne pathogens. Due to antioxidative and antimicrobial potential, almond hull extract can be used as a natural source of preservative for food and feed applications.

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The manuscript has not been submitted or published anywhere. All authors agree contribute significantly and agree to submit manuscript to Sarhad Journal of Agriculture.

Novelty Statement

The research study highlights the importance of almond hull which is byproduct of almond processing, as a potential functional ingredient in food and feed.

Authors' Contributions

Nabila Khan: Performed all the experiments.
Muhammad Bilal Sadiq: Supervised the research and designed the experimental plan.
Imran Ahmad: Performed data analysis and manuscript drafting.

Conflicts of interest
The authors have declared no conflict of interest.

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