Journal of Advanced Pharmaceutical Sciences and Natural Products

Journal of Advanced Pharmaceutical Sciences and Natural Products (JAPSNP)

RESPONSE SURFACES WITHOUT OPTIMA: A CROSS-STUDY REANALYSIS OF ULTRASOUND-ASSISTED EXTRACTION OF POLYPHENOLS FROM AGRO-INDUSTRIAL FRUIT WASTE

Shubham

Deepak

Akriti Singh*

Ajay Pal Singh

Lingaya's Vidyapeeth (Deemed to be University), Faridabad, Haryana, India, 121002

Corresponding author:
Akriti Singh

Email: singhakriti1522@gmail.com

ABSTRACT

Background. Ultrasound-assisted extraction is the dominant green route to recovering polyphenols from fruit processing by-products, and response surface methodology is the near-universal tool for optimising it. Individual studies report optimal conditions for a single matrix, but the fitted surfaces themselves are rarely interrogated, and the results have never been placed on a common scale. **Objective.** To refit published response surface designs for ultrasound-assisted extraction of polyphenols from agro-industrial fruit waste, establish the geometry of each fitted surface, compare factor effects across studies on a common coded scale, and test whether reported optima are consistent with the models from which they were derived. **Methods.** Five published designs covering orange by-products, apple peel, pomegranate peel, grape pomace and apple pomace, comprising 105 experimental runs, were transcribed in full from their source publications. Full second-order models were refitted by ordinary least squares in coded units, with analysis of variance, lack-of-fit testing where replication permitted, and leave-one-out predicted coefficients of determination. Every surface was subjected to canonical analysis. Linear coefficients were standardised against the mean response of their own design. Multi-response optimisation used the Derringer-Suich desirability function constrained to the experimental region. **Results.** Mean ordinary coefficient of determination across the five phenolic models was 0.9240, but the mean predicted coefficient of determination was 0.5379, falling to 0.0050 in one design, and 2 of 5 fell below one half. Canonical analysis classified 4 of 5 phenolic surfaces as saddle points with stationary points outside the studied region; only 1 possessed an interior maximum. Solvent variables dominated: solvent-to-material ratio carried a standardised effect of -0.4721 and ethanol concentration a mean of -0.2048 across two designs, whereas extraction time averaged 0.0370 across 5 designs and ultrasonic amplitude 0.0019. One reported optimum fell 2.8 per cent short of the maximum of its own refitted surface. **Conclusion.** Published optima in this field frequently derive from surfaces that possess no interior optimum, and ordinary coefficients of determination substantially overstate predictive capability. Solvent composition, not sonication intensity or duration, governs phenolic recovery across matrices.

Keywords: ultrasonic extraction; polyphenols; response surface methodology; industrial waste; antioxidants; food handling; reproducibility of results.

1. Introduction

Fruit processing generates enormous quantities of solid residue. Peel, pomace, seed and rind are separated from juice and pulp and leave the factory as waste, yet these fractions frequently contain higher concentrations of phenolic compounds than the edible portions that were retained. Recovering them converts a disposal cost into a raw material, which is why the valorisation of fruit by-products has become one of the more active areas of food and pharmaceutical process research[6,7,11].

Ultrasound-assisted extraction has emerged as the preferred technique for this recovery. Acoustic cavitation generates transient bubbles whose asymmetric collapse near a plant cell wall produces microjets and shear forces that disrupt tissue, increase permeability and accelerate the movement of solutes into the surrounding solvent. Compared with maceration or heat reflux, the technique operates at lower temperature, shortens processing time and reduces solvent consumption, all of which matter when the product is a thermolabile phenolic and the process is intended to be green [1,6,9].

Because the outcome depends jointly on several variables that interact, extraction studies almost invariably turn to response surface methodology. A Box-Behnken or central composite design is executed, a second-order polynomial is fitted to each response, and a numerical search over that polynomial returns the combination of settings predicted to maximise recovery. The approach is efficient and well founded, and the literature applying it to fruit waste is now substantial, covering mango peel[6,10], berry pomaces[7], grape seed[8], nutmeg peel [9], apple pomace[5,11] and pomegranate peel[3,12] among many others.

That literature has two characteristics which together create the gap this study addresses.

First, each study optimises one matrix in one laboratory, and the results are reported in whatever units and over whatever factor ranges that laboratory chose. A coefficient expressed in milligrams of gallic acid equivalent per litre over a solvent ratio spanning 50 to 150 mL/g cannot be compared with one expressed per gram of dry weight over an ethanol span of 0 to 100 per cent. The field therefore accumulates optima without accumulating knowledge about which variables matter generally, and practitioners approaching a new matrix have little quantitative basis for deciding which factors deserve their limited experimental budget.

Second, and more consequentially, the fitted surface is seldom examined as a mathematical object. A second-order polynomial in several variables possesses a stationary point, and that point may be a maximum, a minimum or a saddle. Only the first corresponds to an optimum in the ordinary sense. A saddle surface has no interior peak at all: it rises in some directions and falls in others, and a numerical search across such a surface will terminate somewhere on the boundary of the search region, returning a set of coordinates that looks like an optimum and is reported as one. Canonical analysis, which resolves this question by examining the eigenvalues of the matrix of quadratic coefficients, is standard in the response surface

literature yet is largely absent from applied extraction papers.

A related omission concerns model adequacy. Applied studies conventionally report the ordinary coefficient of determination, and values above 0.95 are routinely presented as evidence of a good model. A full quadratic model in four factors consumes fifteen coefficients, and a Box-Behnken design in four factors provides twenty-seven runs, leaving twelve residual degrees of freedom. Under those conditions the ordinary coefficient of determination is inflated by construction and says little about whether the model would predict a new observation. The predicted coefficient of determination, obtained by leave-one-out cross-validation, addresses precisely that question and is rarely reported.

Both omissions are testable without any new experiment, because the design matrices and observed responses are printed in the papers themselves. The present study therefore refits published designs, subjects each surface to canonical analysis, places the factor effects on a common coded scale, re-optimises by multi-response desirability within the experimental region, and tests whether the optima the original authors reported are consistent with the models they published. The objective is not to dispute individual results but to establish what the accumulated designs, analysed together and analysed properly, actually support.

2. Materials and methods

2.1 Study identification and eligibility

Studies were eligible when the material was an agro-industrial by-product of fruit processing (peel, pomace, marc, seed, stone, rind, husk or bagasse), extraction was ultrasound-assisted by bath or probe, a response surface design was applied, total phenolic content was among the responses, and the complete run-by-run design matrix with observed responses was printed in the full text. Whole fruit, pulp intended for consumption, leaves, stems and roots were excluded, as were studies reporting only an optimum without the underlying matrix, since those cannot be refitted.

Five studies met all criteria and form the analysis set: orange by-products extracted by sonotrode with aqueous ethanol[1], Ruby S apple peel extracted in an ultrasonic bath with aqueous ethanol[2], pomegranate peel extracted with a choline chloride deep eutectic solvent[3], Cabernet Franc grape pomace extracted with an aqueous Brij S20 surfactant solution[4], and apple pomace extracted in water with an ultrasonic probe[5]. Together they comprise 105 experimental runs. Four employed Box-Behnken designs and one a three-level full factorial design.

2.2 Data extraction

Every design point and every observed response was transcribed directly from the source publication. Where responses were printed as a mean with a standard deviation, the means were taken. Values printed by the original authors as model predictions were not transcribed, since the

models are refitted here from the measurements. No value was estimated, interpolated or read from a figure. Each transcribed design carries the full citation of its source, and the analysis code refuses any design supplied without one.

One transcription caveat is recorded explicitly because it affects interpretation. The orange by-products study states that its 27 runs were structured in three blocks but does not print the block allocation, so the published model cannot be reproduced exactly from the published table. That study also states that non-significant terms were discarded and the model recalculated on the significant terms alone. The refit reported here is an unblocked full quadratic, and its coefficient of determination is accordingly lower than the value the source reports.

2.3 Coding of factors

Factor settings were coded to the interval minus one to plus one about the centre of each study's own range, so that coefficients from designs using different units and different spans could be compared directly. Coding was piecewise linear through the three levels each study actually used. This distinction matters in one case: the orange by-products study set its ultrasonic pulse centre point at 50 per cent while labelling the extremes 10 and 100 per cent, so the levels are not evenly spaced, and linear coding would have placed the centre point at minus 0.11 rather than zero, unbalancing a design the authors constructed as balanced.

2.4 Model fitting

A full second-order polynomial was fitted to each response by ordinary least squares in coded units, comprising an intercept, linear, quadratic and two-factor interaction terms. Model adequacy was assessed by the ordinary coefficient of determination, its adjusted form, and the predicted coefficient of determination obtained by leave-one-out cross-validation computed from the hat matrix, together with the overall model F ratio. Where a design replicated a point, lack of fit was tested against pure error estimated from those replicates; where it did not, that limitation is stated rather than passed over, and adequacy rests on the residual and cross-validated statistics alone.

2.5 Canonical analysis

Each fitted surface was written in the form y equals the intercept plus x transpose b plus x transpose B x, where B carries the quadratic coefficients on its diagonal and half the interaction coefficients off it. The stationary point was obtained as minus one half of the inverse of B multiplied by b, and its nature was determined from the eigenvalues of B: all negative indicates a maximum, all positive a minimum, and mixed signs a saddle point. Whether the stationary point fell inside the region actually studied was tested by checking that every coded coordinate lay within the interval minus one to plus one.

2.6 Standardised effects and optimisation

To compare designs using different units and ranges, each linear coefficient from the coded

models was divided by the mean response of its own design, giving the proportional change in response produced by moving from the centre of the studied range to its upper limit.

Multi-response optimisation used the Derringer and Suich desirability approach applied jointly to total phenolic content and the antioxidant-related response of each study. Individual desirabilities were scaled between the worst and best value observed in that design, so the optimisation could not reward settings whose predicted performance lay outside the observed evidence, and the overall desirability was the geometric mean of the individual values. The search covered a regular grid of 41 levels per coded factor followed by bounded local refinement, constrained throughout to the coded interval minus one to plus one so that no recommended setting lies outside the experimental region.

Where a study reported an optimum, those settings were substituted into the refitted model and compared with the maximum of that same model located by constrained search, which tests the reported optimum against the study's own surface.

2.7 Software and reproducibility

All analyses were performed in Python 3.13.9 with NumPy 2.4.4, SciPy 1.17.1, pandas 3.0.2 and Matplotlib 3.10.9. Every analytical step recorded the tool, parameters, inputs and outputs that produced it, and those records were written to a machine-readable provenance file from which the methods description was generated. The analysis scripts, the transcribed design matrices, the provenance record and all derived tables accompany this manuscript.

3. Results

3.1 Model adequacy across the five designs

Refitted models for total phenolic content are summarised in Table 1.

Table 1. Refitted second-order models for total phenolic content.

Study	Waste matrix	Design	Runs	Factors	R2	R2 adjusted	R2 predicted	Surface type	Stationary point inside region
Orange by-products	orange peel, albedo and flavedo from juice production	Box-Behnken design	27	4	0.8265	0.624	0.005	saddle point	No
Apple peel	Ruby S apple peel	Box-Behnken design	15	3	0.9804	0.9452	0.8156	saddle point	No
Pomegranate peel	pomegranate peel	Box-Behnken design	27	4	0.8451	0.6643	0.2084	maximum	Yes

Grape pomace	Cabernet Franc grape pomace	Box-Behnken design	27	4	0.9953	0.9899	0.9799	saddle point	No
Apple pomace	apple pomace from juice production	three-level full factorial design	9	2	0.9727	0.9271	0.6804	saddle point	No

The ordinary coefficient of determination averaged 0.9240 across the five designs and exceeded 0.97 in two of them, which by the conventions of the applied extraction literature would be reported as uniformly excellent fits.

The predicted coefficient of determination tells a different story. It averaged 0.5379, ranged from 0.0050 to 0.9799, and fell below one half in 2 of the 5 designs. The orange by-products model illustrates the divergence most sharply: an ordinary coefficient of determination of 0.8265 accompanied by a predicted value of 0.0050, meaning the model as refitted retains essentially no capacity to predict an observation it has not already seen. The apple peel and grape pomace models behaved well by both measures, at 0.9804 against 0.8156 and 0.9953 against 0.9799 respectively.

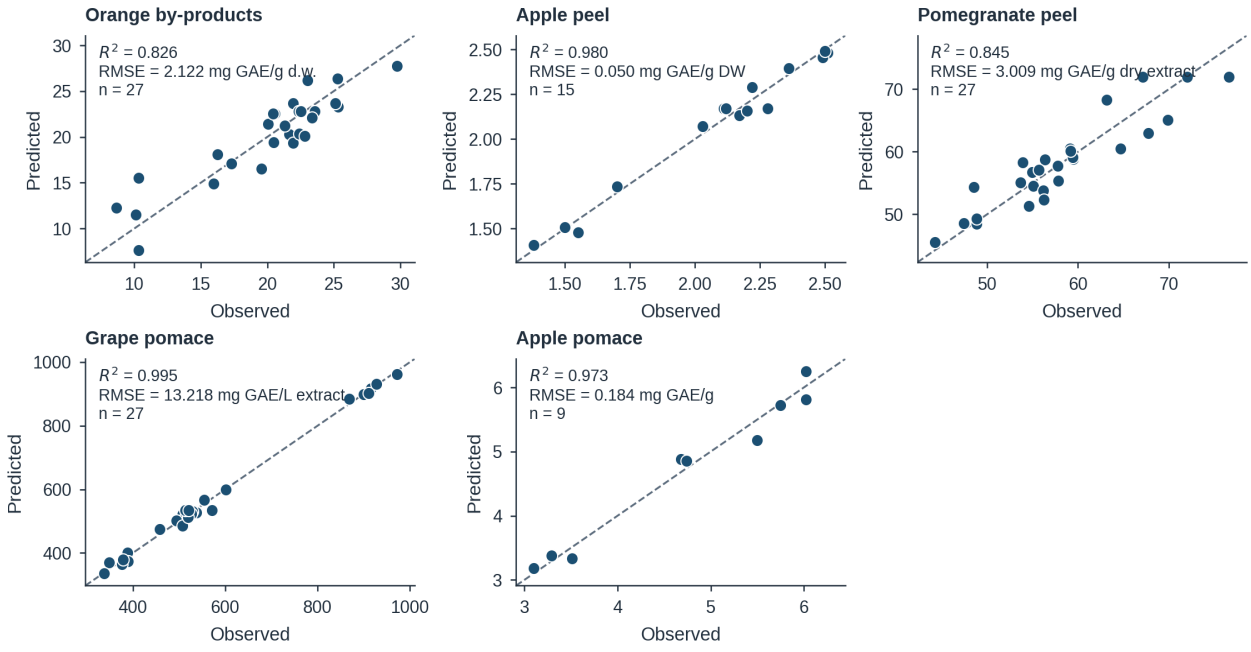

Figure 1. Observed against predicted total phenolic content for the five refitted second-order models, one panel per design. Points are the observed values reported by the original authors; predictions are from the full quadratic model refitted here in coded units. The diagonal marks perfect agreement. Coefficients of determination shown on each panel are computed from the plotted arrays. Built in Python with NumPy 2.4.4 and Matplotlib 3.10.9.

Lack of fit could be tested in four designs and was not significant in any. The apple pomace design contains no replicated point, so lack of fit cannot be separated from pure error, and its

predicted coefficient of determination of 0.6804 becomes the binding adequacy check.

3.2 The geometry of the fitted surfaces

Canonical analysis of the five phenolic surfaces produced the central result of this study. Only 1 of the 5 surfaces possesses an interior maximum. The remaining 4 are saddle points, and in every one of those the stationary point lies outside the region the study actually explored.

The pomegranate peel surface is the exception. Its eigenvalues are -10.5316, -9.4686, -5.7650 and -5.3664, all negative, defining a genuine maximum. Its stationary point lies inside the design region at 29.39 per cent water, a liquid-to-solid ratio of 53.65 mL/g, 238.89 W and 29.44 min, where the model predicts 73.50 mg GAE/g of dry extract. All four coded coordinates fall well within the interval minus one to plus one, the largest being 0.3651 for the liquid-to-solid ratio, so the maximum is interior with margin rather than marginally so.

The grape pomace surface has eigenvalues of -22.8197, -10.5775, 16.1502 and 113.8978. The two positive values, one of them an order of magnitude larger than any negative one, describe a surface that rises steeply along one direction in factor space. The orange by-products surface behaves similarly, with eigenvalues of -5.4384, -2.6314, 0.1269 and 1.8013. The apple peel surface, with eigenvalues of -0.2108, -0.0342 and 0.0662, is nearly flat along two directions and mildly saddle-shaped. The apple pomace surface, with eigenvalues of -0.3653 and 0.1787, is a saddle in two factors.

For these four designs the practical consequence is the same. There is no peak inside the studied region to find, so an optimum obtained by numerical search across such a surface is a boundary result: it reports where the search was stopped, which is the edge of the experimental design, rather than where the response is genuinely greatest.

3.3 Which variables actually govern recovery

Standardised linear effects on total phenolic content, comprising 17 factor-response combinations across the five designs, are given in Table 2 and show a consistent ordering.

Table 2. Standardised linear effects on total phenolic content.

Design	Factor	Range	Coefficient (coded)	Standardised effect	p
Grape pomace	SolventRatio	50 to 150 mL/g	-272.864	-0.4721	<0.0001
Apple pomace	Temperature	40 to 90 degrees C	1.315	0.2778	0.0021
Apple peel	Ethanol	50 to 90 %	-0.4488	-0.2163	<0.0001
Orange by-products	Ethanol	0 to 100 % v/v	-3.8833	-0.1933	0.0012
Orange by-products	Time	5 to 45 min	2.4392	0.1214	0.0210
Orange by-products	Pulse	10 to 100 %	2.2142	0.1102	0.0329

Pomegranate peel	LiquidSolid	40 to 60 mL/g	5.0042	0.0861	0.0023
Pomegranate peel	Power	120 to 300 W	3.5133	0.0605	0.0194
Pomegranate peel	Water	20 to 40 %	-2.4875	-0.0428	0.0804
Apple peel	Temperature	20 to 40 degrees C	0.0875	0.0422	0.0364
Grape pomace	pH	2 to 6 pH units	-23.4025	-0.0405	0.0015
Apple pomace	Time	10 to 20 min	0.145	0.0306	0.3469
Grape pomace	Surfactant	3 to 7 % m/V	17.5875	0.0304	0.0097
Apple peel	Time	15 to 45 min	0.0437	0.0211	0.2154
Grape pomace	Time	60 to 120 min	10.9192	0.0189	0.0806
Pomegranate peel	Time	20 to 40 min	-0.3967	-0.0068	0.7660
Orange by-products	Amplitude	20 to 100 %	0.0383	0.0019	0.9674

Solvent-related variables dominate. The solvent-to-material ratio in the grape pomace design carried a standardised effect of -0.4721, by a wide margin the largest single effect observed, and was the most statistically significant term in that model. Ethanol concentration averaged -0.2048 across the two designs that varied it, at -0.2163 in apple peel and -0.1933 in orange by-products, with both effects negative, indicating that phenolic recovery fell as the ethanol fraction rose towards the upper end of the ranges studied. In the pomegranate peel design the liquid-to-solid ratio carried an effect of 0.0861 and water content -0.0428.

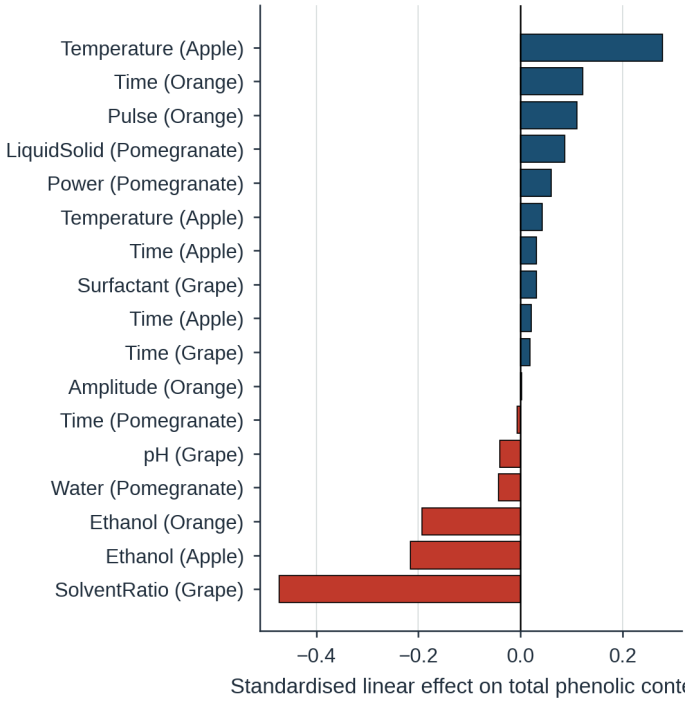

Figure 2. Standardised linear effects on total phenolic content for all 17 factor-response combinations across the five designs, ordered by magnitude. Each coded linear coefficient is divided by the mean response of its own design, giving the proportional change in response on moving from the centre of the studied range to its upper limit. Negative effects are shown in the contrasting colour. Solvent-related variables occupy the extremes; extraction time and ultrasonic amplitude cluster near zero.

Temperature ranked next, averaging 0.1600 across two designs but with wide dispersion, at 0.2778 in apple pomace and 0.0422 in apple peel.

The variables most closely associated with the ultrasound itself proved weak. Ultrasonic power in the pomegranate peel design carried a standardised effect of 0.0605. Ultrasonic amplitude in the orange by-products design carried 0.0019, the smallest effect in the entire set and far from significance. Extraction time, varied in all 5 designs, averaged 0.0370 with a standard deviation of 0.0492, ranging from -0.0068 to 0.1214.

3.4 Re-optimisation within the experimental region

Multi-response optima computed jointly for phenolic content and the antioxidant-related response of each study are given in Table 3.

Table 3. Multi-response desirability optima within the experimental region.

Study	Optimal settings	Predicted responses	Overall desirability	Factors at region boundary
Orange by-products	Ethanol 42.47, Time 37.99, Amplitude 93.96, Pulse 100.00	TPC 29.75, DPPH 23.80	0.9182	Pulse
Apple peel	Temperature 20.00, Time 26.26, Ethanol 50.00	TPC 2.45, DPPH 76.16	0.9679	Temperature, Ethanol
Pomegranate peel	Water 29.22, LiquidSolid 53.08, Power 231.67, Time 27.81	TPC 73.22, Punicalagin 117.37	0.8971	none
Grape pomace	Surfactant 7.00, Time 120.00, pH 3.63, SolventRatio 50.00	TPC 931.64, DPPH 61.36	0.9678	Surfactant, Time, SolventRatio
Apple pomace	Temperature 51.84, Time 20.00	TPC 4.32, DPPH 0.99	0.4704	Time

Overall desirability reached 0.9182 for orange by-products, 0.9679 for apple peel, 0.8971 for pomegranate peel, 0.9678 for grape pomace and 0.4704 for apple pomace.

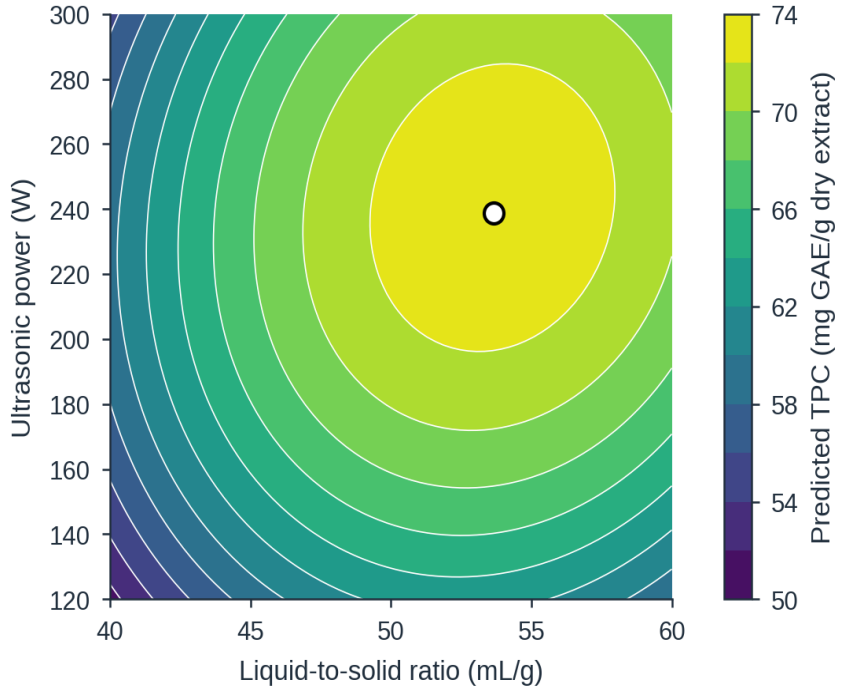

Figure 3. Predicted total phenolic content for pomegranate peel as a function of liquid-to-solid ratio and ultrasonic power, with water content and extraction time held at the centre of their studied ranges.

The low value for apple pomace reflects a genuine conflict rather than a poor model. In that study phenolic content rose with temperature while the DPPH response moved oppositely, so no setting satisfies both objectives well, and the joint optimum at 51.84 degrees C and 20 min represents a compromise predicting 4.32 mg GAE/g and 0.99 mg TE/g.

Consistent with the canonical analysis, the optima for the saddle-surfaced designs sit on the boundary of their experimental regions in one or more factors. The grape pomace optimum lies at the upper limit of surfactant concentration and time and the lower limit of solvent ratio, at 7.00 per cent m/V, 120 min, pH 3.63 and 50 mL/g. The apple peel optimum sits at the lower limits of both temperature and ethanol concentration, at 20 degrees C and 50 per cent. In each case the true optimum may lie beyond the range the original study explored.

3.5 Consistency of reported optima with published models

Two of the five studies reported an optimum in a form permitting substitution into the refitted model.

For apple pomace, the optimum reported by the original authors, 90 degrees C and 18.43 min^5, yields a predicted phenolic content 0.175 mg GAE/g below the maximum of the refitted surface, a shortfall of 2.8 per cent. The discrepancy is small in absolute terms but is a real inconsistency between a quoted optimum and the surface from which it was said to derive.

For orange by-products, the reported optimum of 45 per cent ethanol, 35 min, 90 per cent amplitude and 100 per cent pulse lies inside the

design region and is close to the re-optimised settings of 42.47 per cent ethanol, 37.99 min, 93.96 per cent amplitude and 100 per cent pulse obtained here. The agreement is reassuring, though it must be read against the blocking caveat in Section 2.2.

4. Discussion

4.1 Optima reported from surfaces that have none

The finding that 4 of 5 phenolic response surfaces are saddle points rather than maxima has a straightforward explanation and an uncomfortable implication.

The explanation is that extraction responses over the ranges typically studied are frequently monotonic. Phenolic recovery often continues to increase as solvent ratio falls or as time lengthens, without turning over inside the window the experimenter selected. A second-order polynomial fitted to such data will curve, because curvature is what the model is made of, but the curvature need not produce an interior peak. When the fitted quadratic form has eigenvalues of both signs, the stationary point is a saddle, and the numerical optimiser reports a boundary point.

The implication is that a substantial fraction of the optima in this literature are not optima in the sense readers take them to be. They mark the edge of the experimental design, not the crest of the response. This is not a computational error by the original authors, whose numerical searches were performed correctly. It is an interpretive gap: the surface was never asked what kind of surface it was. Canonical analysis answers that question in a few lines of arithmetic and is standard textbook material in response surface methodology, yet it appears in almost none of the applied extraction papers examined here.

The practical consequence is directional rather than fatal. A boundary optimum is still useful information, since it identifies the best conditions within the region tested. What it does not support is the common phrasing that the conditions are optimal without qualification, nor the implicit suggestion that further gains are unavailable. Where the optimum sits on a boundary, the correct inference is usually the opposite: the response was still improving when the experiment stopped, and a design shifted or extended in that direction would probably do better.

4.2 Coefficients of determination that describe the past

The gap between the ordinary and predicted coefficients of determination, averaging 0.9240 against 0.5379, quantifies a problem that is understood in principle and neglected in practice.

A full quadratic model in four factors estimates fifteen coefficients. A Box-Behnken design in four factors supplies twenty-seven runs. The resulting model has enough freedom to follow the data closely whether or not the underlying relationship is quadratic, and the ordinary coefficient of determination measures how well it has done so, which is a statement about fitting rather than about predicting. The orange by-products case, at 0.8265 against 0.0050, is the extreme illustration: a model that accounts for

most of the variation it was fitted to while retaining essentially none of the ability to anticipate a new observation.

Reporting the predicted coefficient of determination alongside the ordinary one costs nothing, requires no additional experiment, and would materially change how several published models are read. The two designs here that perform well on both measures, apple peel and grape pomace, demonstrate that the statistic is not merely a device for finding fault.

4.3 Solvent chemistry, not sonication, governs recovery

Placing the designs on a common coded scale produced the most transferable result of the study. The ordering of standardised effects, with solvent-to-material ratio at -0.4721 and ethanol concentration at a mean of -0.2048 against extraction time at 0.0370 and ultrasonic amplitude at 0.0019, indicates that phenolic recovery from fruit waste is governed principally by solvent composition and the solvent-to-solid ratio, and only weakly by the parameters describing the ultrasound.

This ordering is chemically coherent. The Folin-Ciocalteu response reflects the quantity of extractable reducing species that has partitioned into the solvent, and partitioning is controlled by solvent polarity and by the concentration gradient the liquid-to-solid ratio establishes. Ultrasound accelerates the approach to that equilibrium by disrupting cell walls and improving mass transfer, but it does not alter where the equilibrium lies. Once cavitation is sufficient to breach the tissue, additional amplitude or duration adds little, which is what a standardised amplitude effect of 0.0019 expresses.

There is a caveat that must accompany this conclusion. Standardised effects are comparable across studies only within the ranges each study explored, and a factor examined over a narrow range will show a small effect even when it matters. Amplitude in the orange by-products design was varied from 20 to 100 per cent, which is a wide span and strengthens the inference for that variable. Extraction time, however, spanned 10 to 20 min in apple pomace and 60 to 120 min in grape pomace, and a factor already beyond the point of diminishing returns at its lower limit will appear inert.

The practical guidance nonetheless seems robust. An experimenter with a fixed budget of runs for a new fruit waste matrix should spend them on solvent composition and solvent-to-solid ratio before spending them on sonication parameters.

4.5 Limitations

This study performed no extraction and assayed no material. Every observed value analysed here belongs to the original authors, and the conclusions inherit whatever measurement error, sampling limitation and reporting choice those studies contain.

The analysis set comprises only five designs. That reflects a strict eligibility rule, since a paper that prints an optimum without the underlying matrix cannot be refitted, and a substantial part of the literature falls into that category. Five designs support the qualitative finding that

saddle surfaces are common, but the standardised effect estimates rest on few studies per factor, with several factors appearing in only one design, and they should be read as indicative rather than definitive.

The orange by-products model could not be reproduced exactly, because the study blocked its runs without printing the block allocation and additionally refitted on significant terms alone. Its refit here is an unblocked full quadratic, and both its coefficient of determination and its very low predicted coefficient of determination should be interpreted with that in mind rather than as a direct criticism of the published model.

The optima computed here are predictions from refitted models and have not been confirmed experimentally. Total phenolic content determined by the Folin-Ciocalteu reaction is a measure of reducing capacity rather than a specific determination of phenolic compounds, and responds to ascorbic acid, reducing sugars and some amino acids, so comparison of absolute values across studies carries that interference. In vitro antioxidant capacity determined by DPPH describes electron or hydrogen transfer in a cuvette and does not establish antioxidant activity in a physiological setting. A second-order polynomial is an empirical local approximation carrying no information outside its design region, which is why every recommendation here is bounded by the region that was studied.

4.6 What should be done next

Three concrete steps follow. First, the boundary optima identified here mark directions in which the response was still improving when the original experiments stopped, and a modest confirmatory design extending beyond those boundaries, particularly towards lower solvent-to-material ratios in grape pomace and lower ethanol fractions in apple peel, would establish whether real gains remain. Second, the finding that solvent variables dominate suggests that a screening design across solvent systems applied to a single matrix would be more informative than a further response surface study of sonication parameters. Third, reporting practice would improve materially at negligible cost if extraction papers printed the full design matrix, the predicted coefficient of determination alongside the ordinary one, and the eigenvalues classifying the fitted surface.

5. Conclusions

Refitting five published response surface designs for ultrasound-assisted extraction of polyphenols from fruit processing waste, comprising 105 experimental runs, shows that 4 of the 5 fitted phenolic surfaces are saddle points whose stationary points lie outside the region studied, so the optima reported from them describe the edge of the experimental design rather than a maximum of the response. Ordinary coefficients of determination averaging 0.9240 fell to a mean of 0.5379 when computed by leave-one-out cross-validation, and to 0.0050 in one case, indicating that conventional goodness-of-fit reporting in this field substantially overstates

predictive capability. Placed on a common coded scale, solvent-to-material ratio and solvent composition governed phenolic recovery, while ultrasonic amplitude and extraction time contributed little. Canonical analysis and cross-validated model statistics cost nothing to compute and would change how a significant portion of this literature is interpreted.

Declarations

Ethics approval. This study is a secondary analysis of quantitative data published in the primary literature. It involved no human participants, no animals and no biological material, and required no ethics approval.

Funding. None.

Conflicts of interest. None declared.

References

1. Razola-Diaz MdC, Guerra-Hernandez EJ, Rodriguez-Perez C, Gomez-Caravaca AM, Garcia-Villanova B, Verardo V. Optimization of ultrasound-assisted extraction via sonotrode of phenolic compounds from orange by-products. Foods. 2021;10(5):1120. doi:10.3390/foods10051120
2. Park NY, Cho SD, Chang MS, Kim GH. Optimization of the ultrasound-assisted extraction of flavonoids and the antioxidant activity of Ruby S apple peel using the response surface method. Food Sci Biotechnol. 2022;31(13):1667-1678. doi:10.1007/s10068-022-01150-8
3. Kim HJ, Yoon KY. Optimization of ultrasound-assisted deep eutectic solvent extraction of bioactive compounds from pomegranate peel using response surface methodology. Food Sci Biotechnol. 2023;32(13):1851-1860. doi:10.1007/s10068-023-01298-x
4. Atanackovic Krstonosic M, Sazdanic D, Mikulic M, Cirin D, Milutinov J, Krstonosic V. Optimization of surfactant-mediated green extraction of phenolic compounds from grape pomace using response surface methodology. Int J Mol Sci. 2025;26(5):2072. doi:10.3390/ijms26052072
5. Egues I, Hernandez-Ramos F, Rivilla I, Labidi J. Optimization of ultrasound assisted extraction of bioactive compounds from apple pomace. Molecules. 2021;26(13):3783. doi:10.3390/molecules26133783
6. Aznar-Ramos MJ, Razola-Diaz MdC, Verardo V, Gomez-Caravaca AM. Comparison between ultrasonic bath and sonotrode extraction of phenolic compounds from mango peel by-products. Horticulturae. 2022;8(11):1014. doi:10.3390/horticulturae8111014
7. Piasecka I, Brzezinska R, Kalisz S, Wiktor A, Gorska A. Response surface methodology for optimization of ultrasound-assisted antioxidants extraction from blackberry, chokeberry and raspberry pomaces. Plants. 2024;13(8):1120. doi:10.3390/plants13081120

8. Kunjiappan S, Ramasamy LK, Kannan S, Pavadai P, Theivendren P, Palanisamy P. Optimization of ultrasound-aided extraction of bioactive ingredients from Vitis vinifera seeds using RSM and ANFIS modeling with machine learning algorithm. Sci Rep. 2024;14:1219. doi:10.1038/s41598-023-49839-y

9. Okeke UJ, Micucci M, Mihaylova D, Cappiello A. The effects of experimental conditions on extraction of polyphenols from African nutmeg peels using NADESs-UAE: a multifactorial modelling technique. Sci Rep. 2025. doi:10.1038/s41598-025-88233-8

10. Kunhilintakath A, Gada Chengaiyan J. Optimization of anthocyanin extraction from mango peel wastes using ultrasound and microwave-assisted natural deep eutectic solvents. Front Sustain Food Syst. 2026;9:1753564. doi:10.3389/fsufs.2025.1753564

11. Mantaila S, Balan N, Milea SA, Nistor OV, Andronoiu DG, Mocanu GD, Rapeanu G, Stanciuc N. Apple pomace as a source of valuable phenolics: from drying kinetics to optimization of ultrasound-assisted extraction using conventional and alternative solvents. Antioxidants. 2026;15(4):429. doi:10.3390/antiox15040429

12. Mantiniotou M, Athanasiadis V, Liakos KG, Bozinou E, Lalas SI. Ultrasound-assisted extraction of antioxidant compounds from pomegranate peels and simultaneous machine learning optimization study. Processes. 2025;13(11):3700. doi:10.3390/pr13113700