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Phenolic compound extraction from Nigerian *Azadirachta Indica* leaves: Response surface and neuro-fuzzy modelling performance evaluation with Cuckoo Search multi-objective optimization

E.O. Oke [a,*], O. Adeyi [a], B.I. Okolo [a], J.A. Adeyi [b], J. Ayanyemi [a], K.A. Osoh [c], T.S. Adegoke [d]

[a] *Chemical Engineering Department, Michael Okpara University of Agriculture, Nigeria*
[b] *Mechanical Engineering Department, Ladoke Akintola University of Technology, Nigeria*
[c] *Department of Chemistry, Akwa Ibom State College of Science and Technology, Nigeria*
[d] *Oromitope Herbal Enterprises (Ajawesola), Ogbomoso, Nigeria*

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ABSTRACT

This study is aimed at modelling and optimization of phenolic compound extraction from *Azadirica Indica* Leaves (AIL) using Response Surface Methodology (RSM), Adaptive Neuro-Fuzzy Inference System (ANFIS) and Cuckoo Search algorithm (CSA). The extraction experiments were conducted at Extraction Temperature (ET): (33.79–76.21^{o}C), Process Time (PT): (2.79–4.21 h) and Solid-Liquid Concentration (SLC): (0.007929–0.018355 g/ml) with Total Phenolic Content (TPC) and Total Flavonoid Content (TFC) as dependent variables. Predictive Regression models (RM) for AIL extraction were developed from RSM in Design Expert software and compared with ANFIS model in Matlab environment. Multi-objective optimization of AIL extraction conditions was performed using CSA and Numerical Desirability Function (NDF) techniques; while sensitivity analysis of the process was performed using Monte Carlo Simulation (MCS). RM correlation coefficients (R^2) of TFC and TPC are 0.988 and 0.949 respectively; whereas ANFIS model R^2 for TFC and TPC gave 0.997 and 0.982 accordingly. MCS sensitivity analysis show the contribution of input variables (SLC: -56.3%; PT: 39.2% and ET: -4.59%) on TPC and (SLC: -0.9%; PT: -78.6% and ET 18.5%) on TFC respectively. The CSA optimum conditions gave 2.79 h, 40.54^{0}C, 0.01 g/ml with TFC 27.7 and TPC 1.06; while NDF optimum results gave 2.79 h, 40.54^{0}C, SLC 0.01 g/ml, with TFC 26.09 and TPC 1.272. The RSM and ANFIS models are satisfactorily predicted the process. The optimum conditions results obtained from the two methodologies are analogous. Therefore, the optimum results from this study could be used for AIL extract production plant design and techno-economic evaluation.

1. Introduction

Medicines from synthetic source heal human pathological problem and leaves behind harmful additives and chemicals in human body system. Herbal medicines heal various ailments and also improve the healthy living [1]. Herbal remedies are gaining recognition in most of the developing countries due to its avoidable cost and low or no detrimental effect on human health. Over sixty percent (60%) of developing countries population is consuming natural herbs, drinks, spices and cosmetics [1,2]. Various parts of natural plants such as leaves, stems and roots have been utilized for various herbal products for human consumption [3–5].

Azadirachta Indica (AI), whose English name is neem, belongs to the Meliaceae family; it is one of the most classic plants with high worldwide importance due to its therapeutic benefits. Neem tree is found in abundance in tropical and semitropical regions; and is matured within 10 years, its bark is grey and rough [6,7]. The leaves are about 30 cm long and each leaf has 10–12 serrated leaflets that are 7 cm long by 2.5 cm wide [8]. Neem leaves are extensively utilized for treating malaria fever; the leaves extract are also used for curing allergic skin reactions, smallpox and chicken pox (Khine et al., 2013; Khan et al., 2010). The leaves show therapeutics role in health management due to high antioxidant properties found in the extract. The leaves also contain carbohydrate calcium, protein minerals, and phenolics such as flavonoids and glycosides [9,10].

A plethora of studies on biological and pharmacological activities of AI leaves extract have been reported by previous researchers [11–14]. Earlier investigators have confirmed their utilization as anti-inflammatory, antiarthritic, antipyretic, hypoglycemic, antigastric

* Corresponding author.
E-mail address: oke.olusola@mouau.edu.ng (E.O. Oke).

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ulcer, antifungal, antibacterial, and antitumour activities [15–17]. The extract from the leaves is also consumed to increase the appetite and to eliminate intestinal worms [8]. Moreover, previous reports revealed that neem leaves matrix contained high proportion of bioactive substances such as phenolic compounds [18–20].

Extraction of bioactive substances such as phenolic compounds and flavonoids from plant materials is achieved by solid-liquid separation technique. Solid-liquid Extraction (SLE) is a practical unit operation used to obtain phytochemical compounds from the biomass. SLE is based on the preferential dissolution of one or more of the compositions of a solid matrix in extraction solvent. Various extraction techniques such as maceration, soxhlet extraction, percolation, supercritical and hydro-distillation techniques have been used for bioactive compound extract production in recent years [9,21–25] and [26]. Process parameters such as extraction temperature, process time, solid-liquid ratio and extraction solvent type influence the SLE performance. Elevated extraction temperature is reported for the increase in extraction rate due to enhanced solubility and diffusion rate of solute into the extraction solvent [27]. Bioactive extraction efficiency depends on process time because as the period of extraction is increased, the mass transfer continuously increases until the process reaches equilibrium.

Modelling process system in engineering is important to process engineers due to its usefulness in process design, scale-up and control. Previous researchers showed that most of engineering processes are complex and non-linear in nature (Oke et al., 2019; [28,29,60]). Mathematical modelling of chemical processes via soft-computing model such as Artificial neural network (ANN) adaptive neuro-fuzzy inference system (ANFIS), Response surface models, support vector machine and regression trees have recently been applied for the prediction of engineering systems due to their predictive ability without prior process mechanism information. Although, mechanistic modelling techniques with analytical solutions such as Laplace transformation, separation of variables and Fourier series methods gave exact solutions; however, the solution methods are rigorous, complex and cumbersome. Shewale and Rathoa [9] studied kinetics of phenolic compounds extraction from neem leaves in a stirred batch extraction in order to investigate kinetic parameters and time dependent behaviour of total phenolic compound extract production. However, there is a dearth of information on soft-computing modelling of phenolic extraction from neem leaves biomass.

Optimization process improves performance and efficiency of process by providing optimum values for the system parameters [30–32]. Several researches have conducted in order to optimize SLE with the focus of improving extraction products and processes [33–36]. Most of engineering decisions and judgment in manufacturing industries emanated from process optimization; thus, process engineers strive to optimize process variables individually or overall as the circumstances dictate. Previous SLE shows that optimum process parameter problem were solved by Single- Objective Optimization (SOO) technique with the goal of finding the best solution for a specific criterion [35–37]. However, in some engineering processes, objectives vary and at the same time conflicting; several process variables may also be tuned in order to determine the performance of the system and therefore, it is usually desirable to seek more than one objective function of interest. Optimum process parameters are of great import in process design engineering of chemical process industries.

Multi-Objective Optimization (MOO) technique is used to solve problems having more than one conflicting objectives. Most of MOO problems are difficult and intractable to solve via convectional approaches. In contrast, soft-computational optimization techniques are robust enough to solve this sort of engineering problems. In the last decade soft-computing optimization techniques such as genetic algorithm (GA), Particle Swarm Optimization (PSO), Artificial Bee Colony (ABC) and Simulated Annealing (SA) have been used to solve various MOO problems with accurate results [38–42]. Previous researchers, from the foregoing, investigated the bioactive ingredients present in the neem extract, the phenolic content, flavonoids, anti-feedant and anti-oxidant activity in the neem extracts. However, there is no documented information relating to soft computing MOO of neem leaves herbal extract production. Therefore, this study is bridging the scientific lacuna by investigating neem leaves phenolic compound extraction modelling, optimization and Monte Carlo simulation sensitivity.

2. Material and method

2.1. Chemicals and reagents

Gallic acid, Folin-Ciocalteu and anhydrous sodium carbonate were supplied from Sigma Aldrich, Poole, England. Deionized water was obtained from Chemical Engineering Analytical Laboratory, Michael Okpara University of Agriculture, Nigeria. Rutin reagent, Aluminium chloride and methanol were procured from GFS Chemicals, Inc. USA. All the purchased chemicals were of analytical grade.

2.2. Azadirica indica preparation and solid-liquid extraction

The fresh neem leaves (*Azadirachta Indica*) were purchased from Jagun local market in Ogbomosho, Oyo state western part of Nigeria. The selected samples where sorted, washed, oven dried at 40^0C for 24 h and ground to desired size. The samples were kept in for some hours to achieve equilibrium temperature with the environment before usage. A total number of 11 experimental samples, as indicated in succeeding section, were prepared based on the design of the experiment. 1.5 g of ground AI leaves was poured into 250 ml flask and 100 ml of deionized water was added and 0.015 mg/ml (X_3) solid-liquid concentration or ratio was achieved as shown in Table 1. The mixture was heated for 3.5 (X_1) hours at temperature 55^0C (X_2). Then, the mixture was allowed to cool to room temperature and solid suspension was removed using filter paper. The same preparation protocol was used for all the experimental runs 2–11 in Table 1. The filtrate (extract) sample was stored in the freezer for further analysis.

2.3. Experimental design and statistical analysis

The Hybrid Design (HD) of Response Surface Methodology (RSM) in Design Expert was used to design AI solid-liquid extraction experiment. The design is a minimal point design for 3, 4, 6 or 7 factor levels each. The rotatable, or nearly rotatable, design is better than small central composite design. The HD is statistically randomized experimental points and gave possible lowest experimental run. Thus, the design is chosen for this study based on its ability to reduce the experimentation cost and time. Three independent variables X_1 (time), X_2 (temperature) and X_3 (solid-liquid concentration) and two responses, namely: Total Phenolic Content (TPC) as well as Total Flavonoid Content (TFC) were used for the design. The design produced a total of eleven (11) experimental runs as indicated in Table 1.

The data obtained from the experiments were used for optimization of

Table 1
AI Solid-liquid Extraction HD of RSM for three factors.

Run	A:time	B:temp	C:conc
1	3.5	55	0.0150
2	4.21	55	0.0114645
3	3.5	76.21	0.0114645
4	3.5	33.79	0.0114645
5	3.5	55	0.022071
6	3	70	0.0185355
7	4	40	0.0185355
8	4	70	0.0185355
9	3	40	0.0185355
10	2.79	55	0.0114645
11	3.5	55	0.007929

extraction parameters (independent variables) with respect to the response parameters (dependent) via numerical desirability technique. A second order polynomial equation shown below was used to determine the relationships that exist between dependent and independent variables.

$$Y = \beta_o + \sum_{i=1}^{3} \beta_i X_i + \sum_{i=1}^{3} \beta_{ii} X_i^2 + \sum \sum_{i<j\leq 1}^{3} \beta_{ij} X_i X_j \quad 1$$

where Y is the measured responses, β_o, β_i, β_{ii} and β_{ij} are the intercept, linear, quadratic and interaction coefficients, respectively of the model and X_i and X_j are levels of independent variables. The variable X_iX_j represents the first order interaction between X_i and X_j for ($i < j$).

3. Spectrophotometric analysis technique

3.1. Determination of total phenolic content (TPC)

The Total Phenolic Content (TPC) of the AI leaves was determined using Folin-Ciocalteu reagent and Na_2CO_3. as described by Adesegu et al. (2007). 1 ml of the filtrate (extract) was introduced into a clean test tube, followed by 1 ml of Folin-Ciocalteu with 2 ml of 20% Na_2CO_3, then spinned for 20 min at 4000 rpm. The mixture was incubated for 2 h at room temperature and its absorbance was taken at 756 nm against water blank. The standard curve was generated using Gallic acid as standard in water (10–50 mg/l). TPC was measured and expressed in mg Gallic Acid Equivalent (GAE) per g dry sample extract.

3.2. Determination of Total Flavonoid Content (TFC)

The flavonoid content of the sample was determined by aluminium chloride method using Rutin as standard. This method is based on formation of flavoniod-aluminum complex as established in chang et al. (2002). 1 ml of the sample (extract) filtrate was introduced into a test tube, 3 ml of methanol then 0.2 ml of 10% aluminium chloride and 0.2 ml of 1 M potassium acetate. The calibration curve was prepared by dissolving 1 g of Rutin in 1000 cm^3 and madeup with methanol to be 1000 mg/l which was used as the stock.

3.3. Gas chromatography-mass spectrometry (GC-MC) analysis

Phytochemicals of *Azadirica Indica* leaves extract were characterized using GC-MC QP2010 Plus (Shimadzu Japan). Phytochemicals identification were achieved by comparing the retention indices and peak area percentage with standard compound stored on the National Institute of Standards and Technology (NIST) digital library data of the equipment.

3.4. ANFIS model development

Artificial neural network (ANN) and Fuzzy Inference System (FIS) are combined resulting to Adaptive Neuro-Fuzzy Inference System (ANFIS) for solving and explaining imprecise as well as uncertainty problems. In this work, Takagi-Sugeno fuzzy system was applied for fuzzy inference system to model the complex system. Two input variables (x,y) and one output (Z) variable were used to symbolize ANFIS architecture as illustration. Therefore, Takagi-Sugeno fuzzy system can be shown as below: ANFIS architecture comprised 5 layers as shown in Fig. 1. In the Fig. 1, square nodes (adaptive nodes) show that the parameters in these nodes are modifiable; to be learned, while the circle nodes (fixed nodes) show that they are fixed parameters. Common rule sets with two fuzzy if-then rules are as follows:

Rule 1: If x is A_1 and y is B_1, then $f_1 = p_1\ x + q_1 x + r_1$ 2

Rule 2: If x is A_2 and y is B_2, then $f_1 = p_2\ x + q_2 x + r_2$ 3

Where A and B are linguistic terms that are user defined and representing a range of values. The sequence and functions of the layers is as follows:

Layer 1: Square node equipped with node function

$$O_i^L = \mu_{Ai}(x) \quad 4$$

Assuming x and y are the two typical input values fed at the two input nodes, which then transforms those values to the input membership functions. Where, O_i^L is the membership function of A_i and x is the input parameter to the node. $A_i$is the linguistic label connected with the node function.

Layer 2: This node increases the homeward bound signal and releases the product out of the layer.

$$w_i = \mu_{Ai}(x) \times \mu_{Ai}(y), \quad i = 1, 2 \quad 5$$

Layer 3: circle node. Node calculates the ratio of i-th rule's firing strength to the sum of all rules' firing strengths:

$$w_i^{'} = \frac{w_i}{w_1 + w_2}\ ,\ i = 1,\ 2 \quad 6$$

Layer 4: Square node with node function:

$$O_i^4 = w_i^{'} f_i = w_i^{'}(p_i x + q_i y + r_i) \quad 7$$

p, q, r – parameter set (consequent, linear parameters).

Layer 5: circle node. This node computes the overall output as summation of all incoming signals.

$$O_i^5 = overalloutput = \sum_i w_i^{'} f = \frac{\sum_i w_i f_i}{\sum_i w_i} \quad 8$$

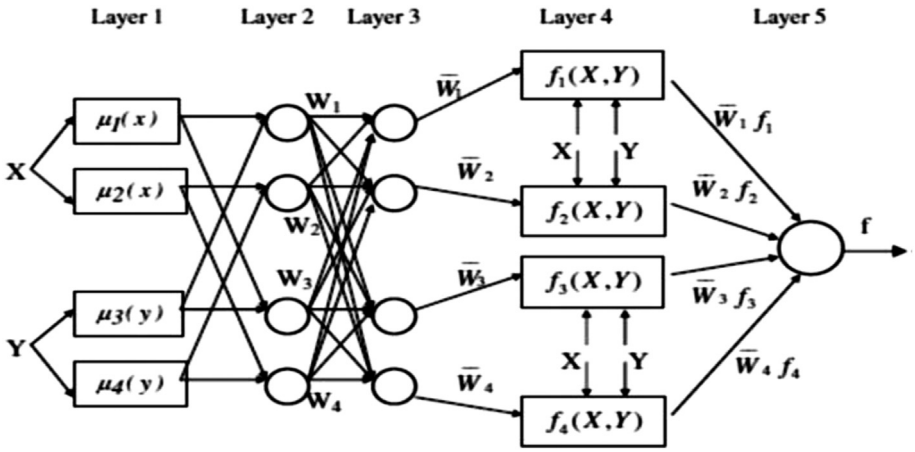

Fig. 1. A basic structure of the ANFIS(Şahin and Gök, 2016).

3.5. Performance evaluation of the developed models

Statistical parameters were applied in order to evaluate the performance of the proposed model for the prediction of TFC and TPC from AI leaves. RMSE (Root Mean Square Error), MSE (Mean Square Error) and the R^2 value (Correlation Coefficient) were used as considered below:

$$MSE = \frac{1}{P}\sum_{p=1}^{p}\left(d_p - O_p\right)^2 \quad 10$$

$$R^2 = 1 - \frac{\sum_{p=1}^{p}\left(d_p - O_p\right)^2}{\sum_{p=1}^{p}\left(O_p\right)^2} \quad 11$$

$$RMSE = \sqrt{\frac{1}{P}\sum_{p=1}^{p}\left(d_p - O_p\right)^2} \quad 12$$

$$MAD = \frac{1}{P}\sum_{p=1}^{p} d_p - O_p \quad 13$$

d_p and o_p are the desired and calculated outputs respectively. The MSE and RMSE value close to zero and the R^2 values close to one shows the good predictability and reliability of the models ([60]; Li et al., 2013) Li et al. claimed that Soft-computing Model's evaluation should be based on ranges of RMSE as given in Table 2.

3.6. Monte Carlo sensitivity and uncertainty analyses

The influence of input factors on the output of phenolic extract from *azadirical indica* leaves was investigated using Monte Carlo Simulation of Crytal Ball (CB) software (White & Porter, 2014; Arinkola et al., 2016). CB is a graphical based forecasting tool that uses Monte Carlo simulation method for sensitivity, uncertainty and risk analyses. Normal probability distribution function was considered and 20,000 simulation trials were implemented in this study. Extraction time, temperature and solid-liquid concentration were used in assumption cells of CB software, while TFC and TPC are fixed in forecast cell.

4. Optimization of solid-liquid extraction

4.1. Curcko search multi-objective optimization

CSA is a bio or naturally inspired optimization technique. The method as introduced by Yang and Deb (2009). This methodology is built on breeding behaviours and levy flights of some birds. CSA is idealized in three ways as described in Fig. 2 and Khoja et al. [43]: (1) one egg is laid randomly at a time in a chosen nest. (2) The best nest with good eggs move to the next generation. (3) The number of the host is fixed and strange egg is known via a probability parameter pa (0–1). The third proposition is assumed by a fraction probability of the n nests being substituted by new nests at new location. In this study, maximization problem of TFC and TPC is considered, then, the fitness of the solution is proportional to objective function.

Cuckoo new solution $x^{(t+1)}$ for a cuckoo i, a levy flight is implemented as described by this equation:

Table 2
Ranges of RMSE for models performance.

Ranges of RMSE	Performance
<0.009	Excellent prediction accuracy
0.009 < RMSE <0.09	Good prediction accuracy
0.09 < RMSE <0.5	Reasonable prediction
>0.5	Inaccurate prediction

Source: Li et al., 2013.

$$X^{(t+1)} = X_i^t + \propto Levy(\lambda) \quad 14$$

where superscript t is the epoch number, i is the sample size and the step size is $\propto > 0$. Levy (γ) distribution is estimated from this expression:

$$Levy(\gamma) = y = l^{\lambda} \quad 15$$

Equation (15) can be further simplified as shown in equation (16):

$$\propto Levy(\lambda) = K * \left(\frac{u}{v^{1/\beta}}\right)(x_{Best} - x_i) \quad 16$$

where K value is the Levy multiplication factor determined by the users, β is 1.5, u and v are estimated from the distribution curve.

5. RESULTS and DISCUSSION

5.1. Model analysis

The effects of the extraction temperature, time and solid-liquid concentration on TFC and TPC from the *Azadirachta Indica* herbal extract was determined using the Response Surface Methodology (RSM). The TFC and TPC result of the experiments were presented according to hybrid design of RSM are shown in Table 3. All results were statistically analyzed by Analysis of Variance (ANOVA). Statistical significance was based on the confidence level of 95% ($p < 0.05$); indicating that the model terms are significant on the response variable. ANOVA analysis suggested quadratic models to represent all experimental data. The experimental result showed that the highest and the lowest total TFC are 31.78 mg/g (55̊C, 4.21 h and 0.0114645 g/ml) and 20.1 mg/g (55̊C, 2.79 h and 0.0114645 g/ml), respectively.◦The maximum and minimum total phenolic content of 1.58 mg/g (55̊C, 2.79 h and 0.0114645 g/ml) and 0.42 mg/g (70C, 3 h and 0.0185355 g/ml) were obtained, accordingly.

Table 4 shows the ANOVA result for the Total Flavonoid Content (TFC) by RSM second order polynomial model (equation (17)). The Model F-value of 70.38 implies that the model is significant. P-value less than 0.0500 indicates model terms are significant. In this case X_1, X_2, X_1X_3 and X_1 X_3 are significant model terms. Table 5 depicts the ANOVA result for the Total Phenolic Content (TPC) by second order polynomialequation (17). The Model F-value of 86.40 indicated that the model is significant. P-values less than 0.0500 indicate model terms are significant. X_1, X_2, X_3, X_1X_2 and X_1X_3 are significant model terms.

$$TFC = +46.82955 - 13.01329X_1 + 0.65620\ X_2 - 1308.93689X_3 - 0.056667\ X_1X_2 + 689.48552\ X_1X_3 - 21.41137X_2X_3 \quad 17$$

$$TPC = +2.89524 - 0.31138X_1 - 0.12237X_2 + 242.81141X_3 + 0.034567X_1X_2 - 81.91263X_1X_3 - 0.12556\ X_2X_3 \quad 18$$

Generally, the coefficients of determination (R^2) are reliable, with R^2 values above 80% as indicated in Table 5a. Based on previous study, R^2 value less than 80% shows that the model does not well explain the relationship between the experimental variables [44,45]. On contrary, the R^2 value above 80% indicates that the model closely fit the regression line. The estimated coefficient of determination ($R^2 = 0.988$) of the model in this study shows good prediction agreement between the experiment and predicted values of the TFC. The Predicted R^2 of 0.933 is in reasonable agreement with the adjusted R^2 of 0.971 as indicated in Table 5a. The total coefficient of determination ($R^2 = 0.949$) of the model, as depicted in Table 5a, shows good prediction agreement between the experiment and predicted values of the TPC. The predicted and adjusted R^2 of TPC are 0.8621 and 0.873 respectively as shown in Table 5a. The predicted and adjusted correlation coefficient are compared for TPC and TFC models; then, it was observed that the difference is less than 0.2. The obtained difference between the adjusted R^2

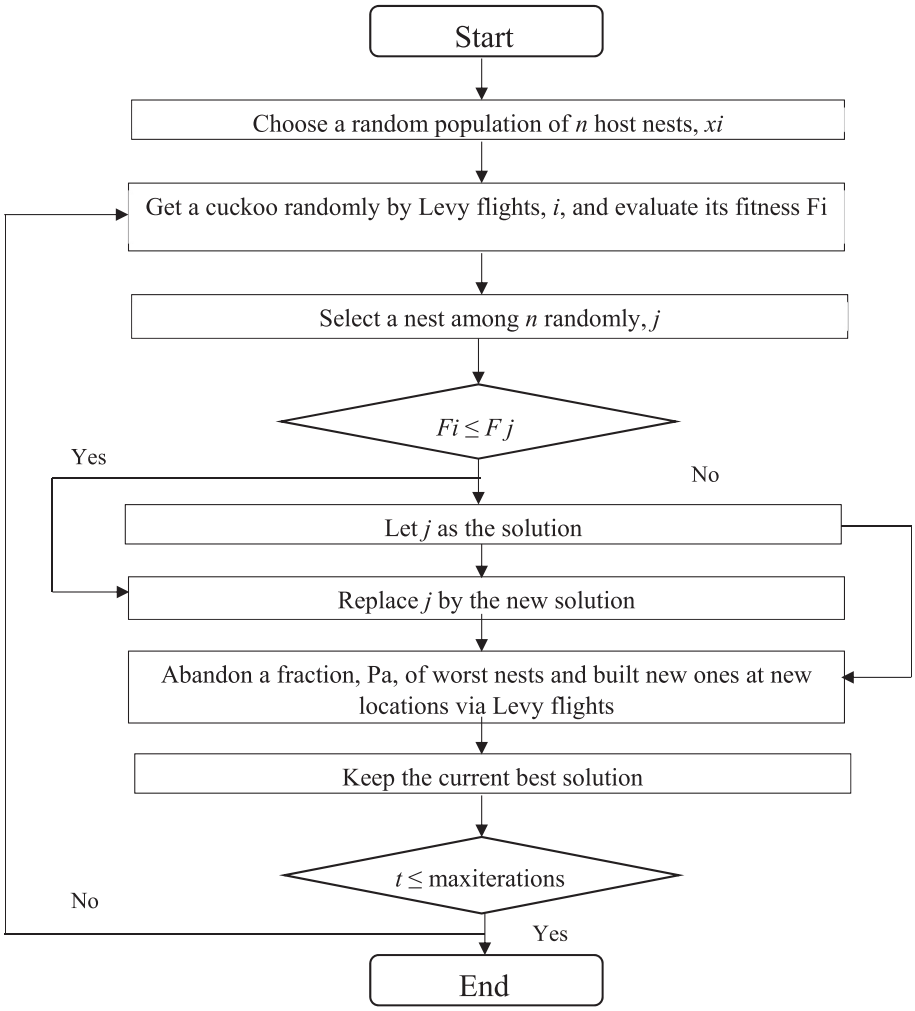

Fig. 2. Flowchart of CSA [43].

Table 3
Hybrid design of RSM for three factor and results.

Run	A:time	B:temp	C:conc	TFC	TPC
1	3.5	55	0.0150	25.27	1.01
2	2.79	55	0.0114645	20.1	1.58
3	3.5	76.21	0.0114645	30.13	1.13
4	3.5	33.79	0.0114645	21.12	1.25
5	3.5	55	0.022071	24.17	0.63
6	3	70	0.0185355	28.31	0.42
7	4	40	0.0185355	23.13	0.603
8	4	70	0.0185355	24.11	1.01
9	3	40	0.0185355	25.63	1.05
10	4.21	55	0.0114645	31.78	0.656
11	3.5	55	0.007929	25.27	1.3

Table 4
ANOVA for the TFC by response surface quadratic model.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	125.17	6	20.86	70.38	0.0005	significant
X_1	67.27	1	67.27	226.93	0.0001	
X_2	33.63	1	33.63	113.45	0.0004	
X_3	1.08	1	1.08	3.63	0.1294	
X_1 X_2	0.7225	1	0.7225	2.44	0.1935	
X_1 X_3	11.93	1	11.93	40.26	0.0032	
X_2 X_3	10.31	1	10.31	34.79	0.0041	

Table 5
ANOVA for the TPC by response surface quadratic model.

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	1.24	6	0.2061	86.40	0.0003	Significant
X_1	0.2619	1	0.2619	109.79	0.0005	
X_2	0.0193	1	0.0193	8.08	0.0467	
X_3	0.5159	1	0.5159	216.31	0.0001	
X_1X_2	0.2688	1	0.2688	112.72	0.0004	
X_1X_3	0.1684	1	0.1684	70.62	0.0011	
X_2 X_3	0.0004	1	0.0004	0.1487	0.7194	

Table 5a
Fit statistics of TC and TPC.

	TFC	TPC
Std. Dev.	0.5445	0.0488
Mean	25.37	0.9672
C.V. %	2.15	5.05
R^2	0.988	0.949
Adjusted R^2	0.971	0.8734
Predicted R^2	0.933	0.8621
Adeq Precision	26.8924	30.0807

and predicted R^2 is similar and consistent with previous investigations [46]. The predicted probability plot against the actual of TPC and TFC is also shown in Fig. 3 which further validates the models.

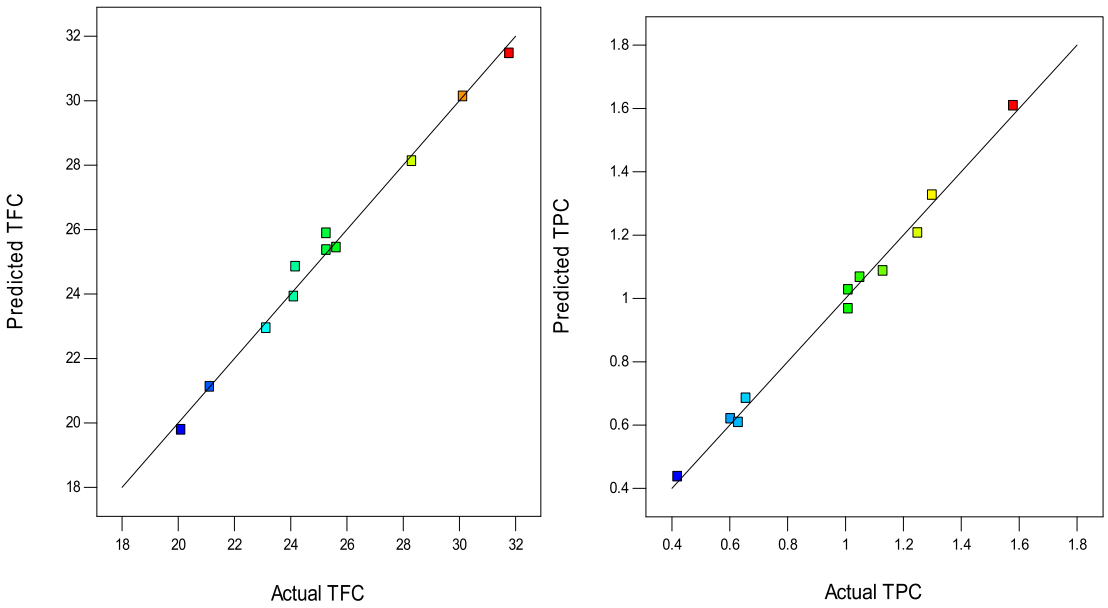

Fig. 3. Probability plot of (a) TFC and (b) TPC model.

6. ANFIS modelling results

6.1. ANFIS architecture simulation for TFC and TFC

Best ANFIS prediction for TFC and TPC of neem leaves extracts was simulated at various input mfs (gbell, trap,tri, gauss, gauss2, pi, psig and disg) and output mfs (constant and linear) with constant 2000 epoch number, step size 0.01. MSE and correlation coefficient (R^2) of the checking data were applied to validate the degree of predictability of the models. Tables 6 and 7 show TFC and TPC ANFIS model simulations at different input and output mfs. R^2 values of linear and constant output mfs in Table 6 range from 0.967 to 0.999 and 0.966 to 0.998 respectively, for varying input mfs. It was noticed that highest R^2 value and minimum MSE were observed using gbell input mf and linear output mf as highlighted in Table 6. However, R^2 values for TPC ANFIS model ranging from 0.97 to 0.9829 as shown in Table 7. MSE values for TPC ANFIS models lie from 0.1 to 0.16 as shown in Table 7. With the results obtained in Table 7, gauss and gauss2 mfs of linear output mf gave the best prediction of the TPC. The present results obtained from this study are similar and comparable with previously related investigation (Oke et al., 2019; [47]).

Fig. 4 shows ANFIS model architecture characteristics for TFC and TPC. The network consists of three input mf, 27 linear parameters and 27 nonlinear parameters with 27 fuzzy rules as also evident in Fig. 4. The network architecture is not clumsy and congested and therefore, the computational time (50 s) is relatively low. The network in Fig. 4 obtained in this study is similar to Betiku et al. [47]; Oke et al. (2019) with the same number of input variable but different mf type. Fig. 5a and b depict ANFIS predicted and experimental results for TFC and TPC respectively. The closeness of experimental and predicted data as shown in Fig. 5 further confirmed the goodness of ANFIS model fitting.

Table 6
TFC ANFIS Model Simulation at Different Input and Output mfs.

Ouput membership function	MSE (linear)	R^2 (linear)	MSE (constant)	R^2 (constant)
Gauss	0.25	0.992	0.26	0.966
Gauss2	0.25	0.99	0.255	0.966
Gbell	**0.157**	**0.997**	0.256	0.997
Tri	0.268	0.967	0.257	0.998
Trap	0.253	0.993	0.258	0.996
Pi	0.25	0.99	0.257	0.996
Dsig	0.256	0.991	0.357	0.996
Psig	0.257	0.996	0.357	0.996

Table 7
TFC ANFIS Model Simulation at Different Input and Output mfs.

Ouput membership function	MSE (linear)	R^2 (linear)	MSE (constant)	R^2 (constant)
Gauss	**0.1**	**0.9829**	0.11	0.976
Gauss2	**0.1**	**0.9829**	0.1	0.9729
Gbell	0.1	0.9829	0.11	0.9721
Tri	0.13	0.98	0.112	0.975
Trap	0.12	0.981	0.15	0.976
Pi	0.1	0.982	0.16	0.97
Dsig	0.14	0.98	0.12	0.975
Psig	0.12	0.9829	0.11	0.976

6.2. ANFIS results compared with RSM

The results of ANFIS and RSM were compared in this work in order to ascertain the reliability of the models that predicted both TPC and TFC of neem leaves extract. It was observed that both correlation coefficients (R^2) of RSM (TFC: 0.988, TPC: 0.949) and ANFIS (TFC: 0.997, TPC: 0.9829) were very close to one; showing the correlation as well as closeness between experimental and predicted results. The MSE of both models were also matched and it was noticed that both MSEs of RSM (TFC: 0.49, TPC: 0.05) and ANFIS (TFC: 0.1, TPC: 0.1) were less than one. These showed that both models are capable of predicting and estimating TFC and TPC from neem leaves extraction. However, the R^2 of ANFIS model is slightly higher than RSM; demonstrating the higher correlation of the predicted with the experimental data.

6.3. Monte Carlo sensitivity analysis

The quantitative influence of extraction time, temperature and solid/liquid ratio on TPC and TFC was achieved by Monte Carlo simulation using Crystal Ball (CB) software. The uniform distribution was assumed for assumptions cells in Crystal Ball environment based on the fact that the range (minimum and maximum) of the variables was known from RSM experimental design data. TPC and TFC values were put into forecast cell of the software. 1000 runs were used for Monte Carlo simulation, then, CB software ranked the assumption parameters according to their

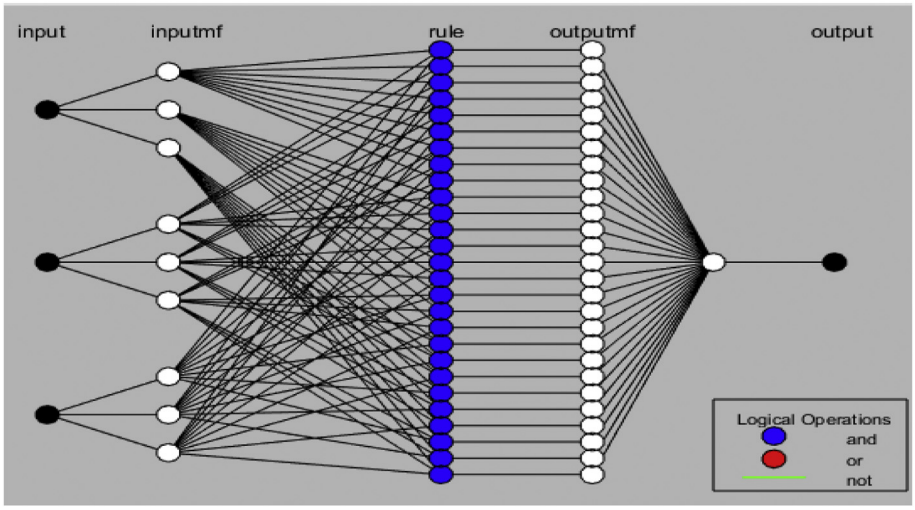

Fig. 4. ANFIS model Architecture for Phenolic Extraction Model.

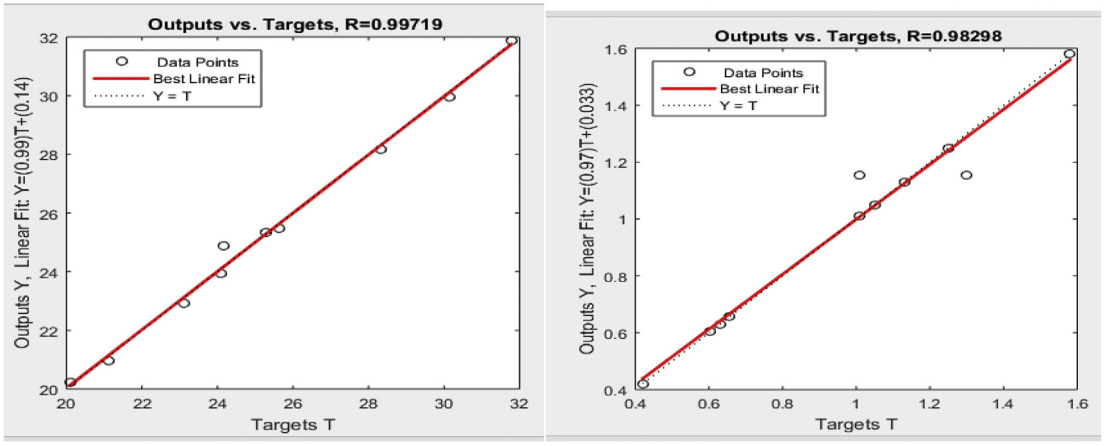

Fig. 5. (a) TFC predicted versus experimental data (b) TPC predicted versus experimental data.

influence on the respective forecast variables. Fig. 6a and b shows the contribution of each input (solid/liquid ratio: -56.3%; extraction time: 39.2% and temperature: 4.59%) variable on TPC and (solid/liquid ratio: -0.9%; extraction time: -78.6% and temperature 18.5%) TFC respectively. For TPC, solid/liquid ratio has most influence on the response; followed by extraction time and temperature. However, extraction time has the highest contribution on TFC; followed by temperature and solid/liquid ratio as shown in Fig. 6a and b.

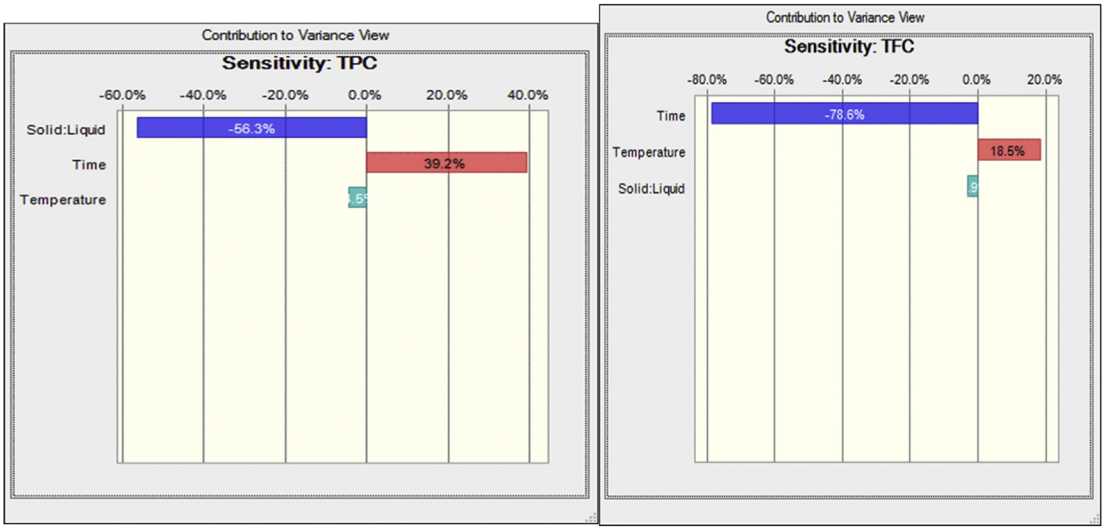

Fig. 6. aContribution of input Variables on TPC 6a: Contribution of input Variables on TFC.

6.4. Multi-objective optimization (MOO) results

The objective of this study is to simultaneously maximize TPC and TFC of neem leaves extract with two multi-objective optimization techniques namely, Curkco search and numerical desirability of RSM. MOO problem is formulated and mathematically written for TFC or TPC objective functions as shown in equation (17)–(20):

$$Maximize\{f_1(k), f_2(k), f_3(x), \ldots\ldots\ldots f_k(k)\} \quad 17$$

$$Subject\ to\ k^L \leq k \leq k^U \quad 18$$

$$\mathrm{I}\ (\mathrm{k}) = 0 \quad 19$$

$$\mathrm{J}\ (\mathrm{k}) = 0 \quad 20$$

Where k is the decision variables, $k^L$and k^U are vector of lower and upper limit of the variables accordingly; I and J are the equality constraints as shown in equations (19) and (20). Weighted sum conventional technique was first applied to covert MOO into Single Optimization Problem (SOO) which can be then solved by bio-inspired curcko search optimization approach as applied in previous study [48]. Thus, the two objectives were combined together in the weighted objective function in equation (21):

$$Maximize\ z = wTFC + (1-w)TPC \quad 21$$

W stands for weight coefficient for a range of 0 and 1 values.

6.5. Curcko search multi-optimization results

Curkco search algorithm seeks the suitable decision variables such as extraction time, temperature and solid-liquid ratio which simultaneously maximize the performance criteria (TPC and TFC) as well as satisfying the extraction constraints in equation (20) -22.

$$2.79 \leq k_1 \leq 4.21 \quad 22$$

$$33.79 \leq k_2 \leq 76.21 \quad 23$$

$$0.01 \leq k_3 \leq 0.02 \quad 24$$

Integrated Curcko search and weighted sum algorithms were coded in MATLAB 2015 environment and implemented with tuning input parameters such as the probability value (0.25), number of nest (25), number of iteration, step size and user beta (1.5) were considered in this study. The parameters were considered based on what is obtainable in previous studies [43,49]. Table 8 shows different optimal solutions with varying weight coefficient for TPC and TFC extraction from neem leaves. It was observed from Table 8 that as the weight coefficient increases from 0.1 to 0.6, the algorithm provided the same set of solution with extraction time (2.79 h), process temperature (33.79^{0}C), solid-liquid concentration (0.01 g/ml), TFC (26.26) and TPC (1.29). Maximized conditions were obtained at weighted coefficient 0.9 with extraction time (2.79 h), process temperature (40.54^{0}C), solid-liquid concentration (0.01 g/ml), TFC (27.7) and TPC (1.06). It was noticed that TFC values from weighted coefficient 0.7 inclined till 0.9 and declined at weighted coefficient 1; however, minimum TPC (1.06) was achieved at weighted coefficient 0.9. Generally, it was noticed that the Cuckoo search algorithm solutions of maximization of TFC and TPC were obtained at lower limit of decision variables (extraction time, process temperature, solid-liquid concentration).

6.6. Numerical desirability MOO result

Numerical optimization of RSM was also used to obtain optimum conditions for maximization of TPC and TFC. Table 9 shows the numerical optimization criteria such as lower and upper boundary, weight coefficient, variable importance and optimization objective goal for phenolic maximization. For maximization of TPC, weighted coefficients 1,1,1,0.1 and 0.9 for time, temperature, solid-liquid concentration, TFC and TPC as depicted inTable 9, respectively. Lower boundary values were chosen as decision (target) variables optimization objective goal as it was obtained in cuckoo optimization results. This was done in order to compare both optimization methodology results.

Table 8
10 Cuckoo Search multi-objective optimal solutions for TPC and TFC extraction.

Weight	Time (hrs)	Temperature	S/L ratio (g/ml)	TFC	TPC
0.1	2.79	33.79	0.01	26.26	1.29
0.2	2.79	33.79	0.01	26.265	1.29
0.3	2.79	33.79	0.01	26.265	1.29
0.4	2.79	33.79	0.01	26.265	1.29
0.5	2.79	33.79	0.01	26.265	1.29
0.6	2.79	33.79	0.01	26.265	1.29
0.7	2.79	36.09	0.01	26.556	1.22
0.8	2.79	38.5	0.01	27.266	1.13
0.9	2.79	40.54	0.01	27.7	1.06
1	2.79	33.79	0.01	26.265	1.29

Fig. 7 presents numerical optimization result ramp as follows: extraction time (2.79 h), process temperature (40.54^{0}C), solid-liquid concentration (0.01 g/ml), TFC (26.09) and TPC (1.272) with total desirability 0.971. Fig. 8 present individual parameter desirability of the optimized conditions for maximization of TFC and TPC. It was observed that 0.999, 0.999, 0.999, 0.935 and 0.758 were desirabilities for extraction time, process temperature, solid-liquid concentration, TFC and TPC respectively as shown in Fig. 8. Earlier reports showed that the desirability value close to one (1) gives excellent optimum conditions [50–52]. The obtained desirabilities in this study are not dissimilar to previous optimization studies in Ref. [53–55].

Laboratory experiment was conducted in order to validate the degree of accuracy of the two multi-objective optimization techniques applied in this work. Confirmatory laboratory experimental results are presented in Table 10 as follows: extraction time (2.79 h), process temperature (33.79), solid-liquid concentration (0.01 g/ml), TFC (26.21) and TPC (1.24). Moreover, Table 10 also compared curckoo search algorithm and numerical optimization of RSM with laboratory experimental results as error values presented in Table 11. Both MOO methodologies are comparable with confirmatory results as noticed and indicated in Table 11. Cuckoo optimization error indices are MAD, MSE, RMSE and MAPE are 0.0038, 0.0002, 0.0139 and 0.01, as depicted in Table 11 respectively. Numerical RSM error indices (MAD, MSE, RMSE and MAPE) also gave 0.009, 0.0011, 0.0324 and 0.03 respectively as further shown in Table 11. It was noticed from the table that Cuckoo error indices gave the lowest error value as compared in Table 11. Thus, the optimum conditions obtained from this investigation could be used for pre-construction and fabrication processes such as computer aided simulation, design and process scale up for neem leaves extract production commercialization.

6.7. GC-MS characterization results

Fig. 9 presents GC-MS result of neem leaves extract. The chromatogram shows five prominent bioactive compounds as indicated in Fig. 9. The compounds are as follows: Isobutylamine, Silanamine, Aziridine, Thiirane and Guanidine. Previous researches revealed that these compounds, in the extract, possess biological and medicinal activities [56, 57]. Exising study reported that thiirane and guanidine are widely used to combat cancer, microbial activities [58,59].

7. Conclusion

The present study investigated RSM and ANFIS modelling performance evaluation with Cuckoo search and desirability function algorithm multi-objective optimization of phenolic extraction from azadirica

Table 9
Numerical optimization criteria for TFC and TPC.

	Time (hrs)	Temperature	S/L ratio (g/ml)	TFC	TPC
Upperlimit	4.21	76.21	0.02	31.78	1.58
Lower limit	2.79	33.79	0.01	20.01	0.42
Weight	1	1	1	0.1	0.9
Importance	5	5	5	5	1
Objective/ Goal	target = 2.79	target = 33.79	target = 0.01	Maximize	Maximize

indica leaves. The correlation coefficient results of RSM (TFC: 0.988, TPC: 0.949) and ANFIS (TFC: 0.997, TPC: 0.9829) models were compared. Furthermore, the MSE of both models RSM (TFC: 0.49, TPC: 0.05) and ANFIS (TFC: 0.1, TPC: 0.1) were less than one. These showed that both models are reasonably capable of estimating TFC and TPC of neem leaves extract production. But, the R^2 of ANFIS model is slightly higher than RSM. The CBMCS showed that solid/liquid concentration has the highest influence on TPC; followed by extraction time and temperature. However, extraction time has the highest contribution on TFC; followed by temperature and solid/liquid ratio. The optimized extraction was obtained at weighted coefficient 0.9 with extraction time (2.79 h), process temperature (40.54^{0}C), solid-liquid concentration (0.01 g/ml), TFC (27.7) and TPC (1.06). Moreover, numerical optimization result revealed that extraction time (2.79 h), process temperature (40.54^{0}C), solid-liquid concentration (0.01 g/ml), TFC (26.09) and TPC (1.272) with total desirability 0.971. GC-MS results showed that the following compounds were present in the extract: Isobutylamine, Silanamine, Aziridine, Thiirane and Guanidine. Thus, the soft-computing models developed from this study could be used for dynamic equation in fuzzy controller of *Azadirica Indica* leaves extraction. In addition, optimum extraction parameters obtained from the investigation can also be used as a precursor for process *Azadirica Indica* leaves production design and scale-up.

Table 10
Optimization results comparison and validation.

Optimization Type	Time (hrs)	Temperature	S/L ratio (g/ml)	TFC	TPC
RSM Numerical	2.79	33.79	0.01	26.093	1.273
Cuckco	2.79	33.79	0.01	26.26	1.29
Experimental	2.79	33.79	0.01	26.21	1.24

Table 11
Error Index Estimation for MOO methodologies.

Optimization method	MAD	MSE	RMSE	MAPE
Cuckoo	0.0038	0.0002	0.0139	0.01
Numerical RSM	0.0090	0.0011	0.0324	0.03

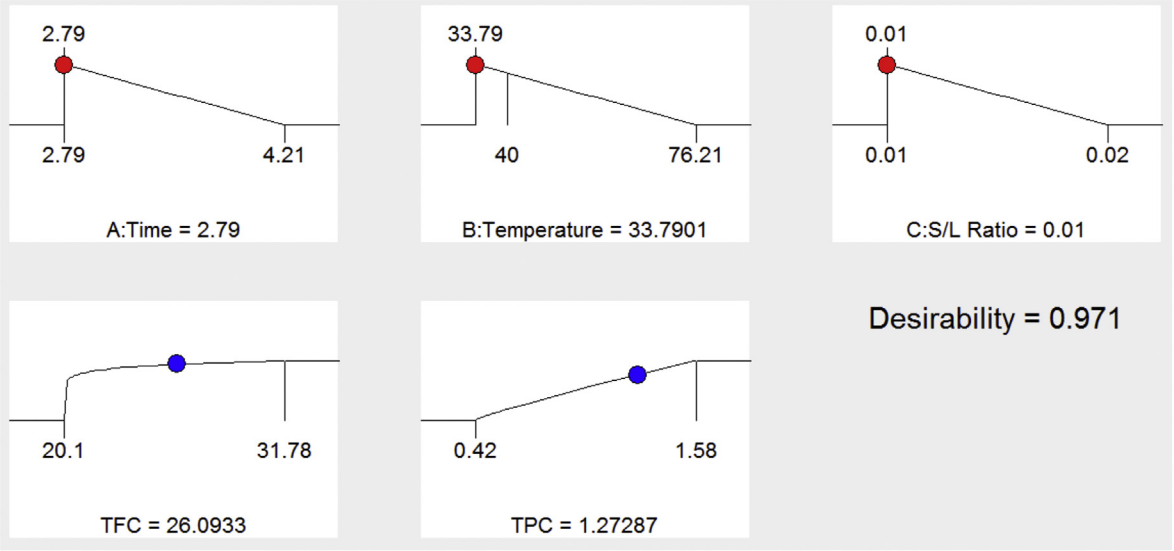

Fig. 7. Numerical multi-optimization result ramp.

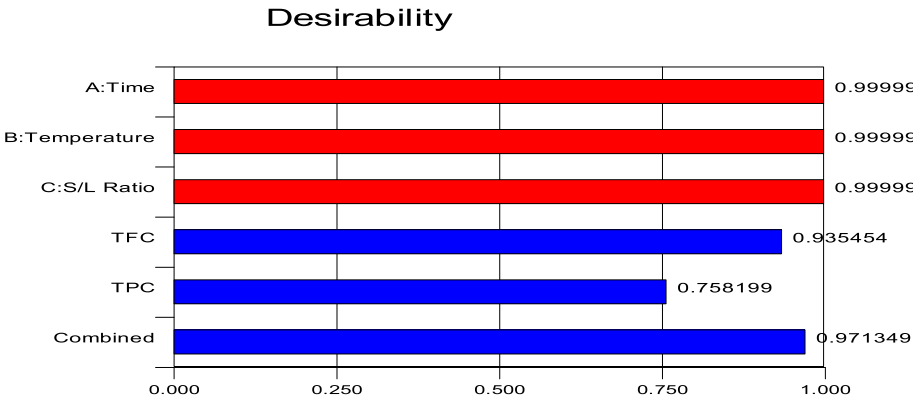

Fig. 8. Desirability value for multi-objective individual optimal parameter.

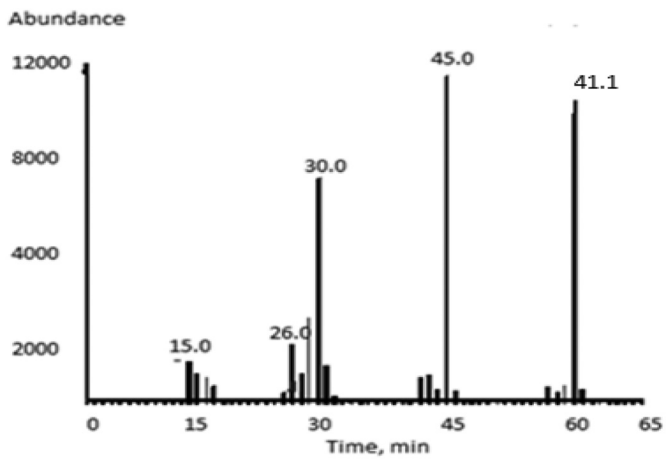

Fig. 9. GC-MS chromatogram of neem leaves extract.

Authours contributions

Oke E.O: Conceptualization, Methodology, Supervision, Investigation, Formal analysis, Writing - original draft, Writing - review & editing, Resources, Project administration. Adeyi O: Conceptualization, Methodology, Supervision. Okolo B.I: Conceptualization, Investigation, Resources, Project administration. Adeyi J.A: Resources, Project administration Investigation, and Conceptualization. Ayanyemi J.O: Formal analysis, Writing - original draft, Resources, Project administration. Osoh, K. A: Formal analysis, Writing - original draft, Resources, Project administration. Adegoke. T.S: Conceptualization, Resources, Project administration

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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