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The effect of ethanolic leaves extract of *Hymenodictyon floribundun* on inflammatory biomarkers: a data-driven approach

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Abstract

Background: Medicinal plants are used to manage pain and inflammatory disorders in traditional medicine. A scientific investigation could serve as a basis for the determination of molecular mechanisms of antinociceptive and anti-inflammatory actions of herbal products. In this work, we used both artificial intelligence (AI) based models inform of adaptive neuro-fuzzy inference system and artificial neural network (ANN) as well as a linear model, namely; stepwise linear regression in modelling the performance of four different inflammatory biomarkers namely; interleukin (1L)-1 β , 1L-6, tumour necrosis factor (TNF)- α and prostaglandin E2 (PGE₂). This modelling was done using number of abdominal writhes, the reaction time of paw licking in mice and paw oedema diameter as the input variables.

Results: Four different performance indices were employed, which are determination coefficient (DC), root mean squared error (RMSE), mean square error (MSE) and correlation co-efficient (CC). The results have shown the superiority of the AI-based models over the linear model.

Conclusions: The overall quantitative and visualized comparison of the results showed that adaptive neuro-fuzzy inference system outperformed the ANN and SWLR models in modelling the performance of the four inflammation biomarkers in both the calibration and verification phases.

Keywords: Medicinal plants, Antiinflammatory, Inflammatory biomarkers, Artificial intelligence, Stepwise linear regression

Background

Pain is a disturbing sensation associated with emotional experience due to actual or possible tissue injury and usually manifest as a typical symptom in the diagnosis of various disorders (Abdulmalik et al. 2011). Inflammation could serve as a body's response to tissue damage, cellular death, tumour, ischemic and degenerative diseases (Azab et al. 2016). It helps the body to eliminate injurious agents by serving as immunity (Rafieian-kopaei et al. 2017). Several endogenous substances including tumour necrosis factor α (TNF- α), interleukins (IL), and

prostaglandins play a role in the pathogenesis of of pain and inflammation (Azab et al. 2016).

Non-steroidal anti-inflammatory drugs (NSAIDs) as the most common drugs used to manage pain and inflammation elicit analgesic and antiinflammatory action by inhibiting cyclooxygenase (COX) enzyme, which interferes with PG synthesis (Adedayo et al. 2019). The opioids have also been employed to manage severe pain. However, they are associated with some serious side effects including gastrointestinal irritation, bleeding, gastric ulceration, tolerance, dependence, respiratory depression, drowsiness, nausea and vomiting (Abdulmalik et al. 2011; Ezeja et al. 2011). Besides, the NSAIDs are also associated with liver diseases, risk of myocardial infarction (Kearney et al. 2006), erectile dysfunction (Shiri et al. 2006) and renal toxicity (Schneider et al. 2006). Steroids are commonly used to treat

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inflammation (Rafeian-kopaei et al. 2017). However, they are also associated with adverse effects such as cardiovascular effects (fluid retention, hypertension), hyperglycaemia, insomnia, irritability, psychotic-like symptoms, rashes, gastric and oesophageal ulcerations, weight gain, immunosuppression, increased risk of osteoporosis, impaired wound healing and many more (Kapugi and Cunningham 2019).

The pharmacological investigations of medicinal plants have encouraged the search for newer and more efficacious therapeutic agents (Akindele et al. 2012). Some important analgesic agents, such as acetylsalicylic acid and morphine, were sourced from medicinal plants (Abubakar et al. 2020). Therefore, there is increasing interest in developing effective anti-inflammatory and analgesic drugs from herbal preparations in managing pain and inflammation (Adedayo et al. 2019).

The use of different pharmacological and machine learning methods is essential to investigate the molecular pathogenesis of human diseases and serve as a basis for developing novel therapeutic agents (Xu et al. 2020). For instance, Zihad et al. (2018) used a computational approach to identify bioactive compounds with activity against COXs as a basis for treating pain and inflammation. Also, Chagas-Paula et al. (2015) predicted the anti-inflammatory activity of natural compounds from Asteraceae species using an artificial neural network (ANN) model. Furthermore, Pandya et al. (2020), in their study, reported the use of computational approaches to predict the antiinflammatory action of bioactive compounds from *Murraya koenigii* and their pharmacological effects on COX-1 and COX-2.

The *Hymenodictyon floribundum* (Rubiaceae) is a small tree that is widely available in tropical Africa. The trunk bark of the plant has been utilized to treat fever in African countries (Borges et al. 2010). Previous research has shown that the trunk of the plant contains scopolin, scopoletin, 3-O- β D-glucopyranosyl- β -sitosterol and hymeselsin (Borges et al. 2010).

The leaves of *Hymenodictyon floribundum* is claimed to have antinociceptive and anti-inflammatory potentials by the ethnic people of Zaria, Kaduna State, Nigeria. However, no documented scientific investigation was conducted to ascertain its effect on inflammatory biomarkers. Therefore, this article aims to investigate the effect of ethanolic leaves extract of *Hymenodictyon floribundum* on inflammatory biomarkers using data driven-approach.

Methods

Collection and identification of *Hymenodictyon floribundum*

The *Hymenodictyon floribundum* was collected from Kargil Hill along Birnin Gwari road, Zaria Local Government of Kaduna State, Nigeria, in October 2019. The

identification of the plant was done by a taxonomist, Mallam Namadi Sambo, at the Herbarium unit of the Department of Botany, Ahmadu Bello University, Zaria, Kaduna State, Nigeria. The plant was compared with an existing specimen already deposited in the herbarium. The plant's voucher number (ABU900124) was obtained.

Experimental animals

We obtained adult Wistar rats (150–200 g) and Swiss albino mice (18–25 g) from the Department of Pharmacology and Therapeutics, Ahmadu Bello University, Zaria, Nigeria. The experimental animals were housed in an adequately-ventilated cages, and provided with rodent diet (Vital feed, Jos, Nigeria) with water provision ad libitum. They were maintained under appropriated laboratory conditions (room temperature 22 ± 3 °C, relative humidity 30–70% with 12-h light and 12-h dark). The animals were kept in polypropylene cages for two weeks and allowed to acclimatise to the laboratory environment prior to the commencement of the experiment. The permission to conduct the experimental procedures were granted by the Ahmadu Bello University Ethical Committee on Animal Use and Care (approval number: ABUCAUC/2020/011) and carried out based on the guidelines of ARRIVE (Animal Research: Reporting of In Vivo Experiments). After completing the experimental procedures, all the animals were anaesthetized with chloroform and quickly euthanized by cervical dislocation. They were immediately buried deeply according to the institutional guideline for proper disposal of laboratory animals remain.

Drugs and chemicals

The drugs and chemicals used in this studies are ethanol, carrageenan, chloroform (Sigma Aldrich, St. Louis Mo, USA), morphine sulphate (Martindale Pharmaceuticals, UK), piroxicam (RotexMedica, Germany), glacial acetic acid (May and Baker limited, Dagenham, England), normal saline and distilled water.

Extraction procedure

The leaves of *Hymenodictyon floribundum* were allowed to dry under shade and size-reduced into a fine powdered form with the aid of mortar and pestle. 700 g of the powdered leaves were extracted exhaustively with ethanol using the soxhlet apparatus for 72-h. The solvent was removed by placing the extract on a water bath set at 45 °C.

Finally, the extract was weighed and kept in a well-closed and labelled container. It was then called as "ethanolic leaves extract of *Hymenodictyon floribundum*" (EEHF).

Acute toxicity determination

We investigated the acute toxicity study of EEHF in rats and mice based on the guideline specified by the Organization of Economic Co-operation and Development (OECD) 423 (OECD 2001). The oral median lethal dose (LD₅₀) was investigated following administration of the extract to nulliparous and non-pregnant female rats and mice. Two groups containing three animals were fasted before dosing (food was withheld overnight for rats and 3 h for mice with adequate access to water). In the initial phase, a dose of 2000 mg/kg of the extract was administered to each animal and observed for 48-h for any sign and symptom of toxicity, including death. The same procedure was done in the second phase but at 5000 mg/kg and the animals were observed for signs and symptoms of toxic effects of the extract, including tremor, convulsion, salivation, lacrimation, diarrhoea, lethargy, sleep, respiratory, behavioural pattern, time of onset of toxicity if any, and length of the recovery period as well as the time of death one time after every 30 min within the first 4-h and then subsequently for 14-days consecutively.

Acetic acid-induced writhing test

We adopted the procedure previously used by Okpo et al. (2001). Thirty mice were divided randomly into 5 groups containing six animals in each group (n=6). Group I received distilled water (10 ml/kg), groups II, III, IV received graded doses of EEHF (250, 500, and 1000 mg/kg), respectively and the group V received morphine (10 mg/kg). One hour after the treatment, 0.6% v/v of

acetic acid (10 ml/kg) was orally administered to each mouse. Subsequently, after 5 min of acetic acid injection, the number of abdominal constriction observed in each mouse was counted for 10 min.

Hot plate test

The method previously described by Okolo et al. (1995) was used. 30 mice were randomly divided into 5 groups containing six mice (n=6). Group I received distilled water (10 ml/kg). Group II, III and IV were administered the graded doses of EEHF (250, 500 and 1000 mg/kg), respectively, while group V received morphine (10 mg/kg). The animals were placed individually on a hot plate set at a temperature of (45±1 °C) for 15 s. The pain latency was observed and recorded at 0, 60, 90, 120 and 150 min when the animals licked their paws or jumped from the hot plate.

Carrageenan-induced paw oedema

The method previously described by Winter et al. (1962) was used. 30 male rats were randomly grouped into 5 different groups (n=6). Group I received distilled water (10 ml/kg), while group V received piroxicam (10 mg/kg). Group II, III and IV received EEHF (250, 500 and 1000 mg/kg), respectively. 30 min after the treatment, 1% of freshly prepared suspension of carrageenan (0.1 ml) was injected into the sub-plantar surface of rat right hind paw. The diameter of the oedematous paw was measured

Table 1 Correlation analysis performance of the variables

Variables	ABD	NPL (Min.)					POD (Min.)					IB				
		0	60	120	180	240	0	60	120	180	240	300	IL-1B	IL-6	TNF-α	PGE2
ABD	1															
0	0.1	1.0														
60	-0.6	0.2	1.0													
120	-0.7	0.1	0.8	1.0												
180	-0.7	0.1	0.7	0.6	1.0											
240	-0.4	0.1	0.2	0.1	0.2	1.0										
0	-0.3	0.3	0.0	0.1	0.2	0.2	1.0									
60	0.3	0.0	0.2	0.2	0.4	0.0	0.1	1.0								
120	0.7	0.1	0.6	0.6	0.7	0.1	0.1	0.4	1.0							
180	0.7	0.3	0.4	0.4	0.4	0.2	0.1	0.4	0.6	1.0						
240	0.8	0.2	0.6	0.6	0.6	0.2	0.2	0.3	0.8	0.8	1.0					
300	0.8	0.1	0.5	0.5	0.5	0.3	0.1	0.2	0.7	0.7	0.9	1.0				
IL-1B	0.1	0.1	0.1	0.1	0.3	0.1	0.4	0.3	0.2	0.2	0.2	0.0	1.0			
IL-6	-0.1	0.2	0.1	0.0	0.3	0.2	0.3	0.1	0.3	0.2	0.1	0.2	0.4	1.0		
TNF-α	0.3	0.0	0.3	0.2	0.3	0.2	0.1	0.0	0.3	0.4	0.4	0.3	0.6	0.3	1.0	
PGE2	0.6	0.1	0.4	0.5	0.4	0.2	0.2	0.7	0.5	0.5	0.5	0.5	0.2	0.1	0.1	1

ABD: Number of abdominal writhes, NPL: Number of paw licking, POD: Paw oedema diameter, IB: Inflammatory Biomarkers, n=6

using a vernier caliper and recorded at 0, 1, 2, 3, 4 and 5 h.

Investigation of the inflammatory biomarkers in the antiinflammatory properties of *Hymenodictyon floribundum*

In another separate experiment, the carrageenan-induced paw oedema previously described above was adopted. This time, the hind paw oedema was measured and recorded at different time intervals (0, 1, 2, and 3 h) with the aid of the vernier caliper. The rats were immediately anaesthetised using chloroform, euthanized by cervical dislocation, and the blood was collected from the orbital sinus into the ethylenediamine tetraacetic acid (EDTA) containing bottle. The blood collected was centrifuged at 3000 revolutions per minute (rpm) for 15 min which was used to estimate the levels of pro-inflammatory biomarkers (PGE2, IL-1β, IL-6, and TNF-α) according to the manufacturer’s instructions.

Adaptive—neuro-fuzzy inference system (ANFIS)

ANFIS serves as a general estimator, which responds to various complications. It was originated from feed-forward networks and adaptive multi-layer. It constitutes input variables together with the fuzzy rule that consist of input–output variables along with fuzzy rule based on the Takagi–Sugeno type. The main components of the fuzzy database are fuzzier and defuzzifier. The fuzzy logic converts the input parameters into fuzzy values by the use of membership functions.

Nodes play a role as a membership function (MFs), which allowed the modelling of the association between the input and output parameters. Its membership function includes trapezoidal triangular, sigmoid, and Gaussian (Elkiran et al. 2019).

Based on the assumption Eqs. 1 and 2 are derived.

$$\text{Rule 1 : if } \mu(x) \text{ is } A_1 \text{ and } \mu(y) B_1 \text{ then } f_1 = p_1x + q_1y + r_1 \tag{1}$$

$$\text{Rule 2 : if } \mu(x) \text{ is } A_2 \text{ and } \mu(y) B_2 \text{ then } f_2 = p_2x + q_2y + r_2 \tag{2}$$

A_1, B_1, A_2, B_2 . parameters are membership functions for x and y , and inputs $p_1, q_1, r_1, p_2, q_2, r_2$, are output function data. The structure of ANFIS and its formulation is in line with a neural network configuration of five layers. Refer to (Khademi et al. 2016) for more information about ANFIS.

Multi-layer perceptron (MLP) neural network

Multi-layer perception (MLP) neural network is among the typical examples of ANN that could manage a non-linear system. Therefore, researchers recognize it as a universal approximator compare to other forms of ANN (Choubin et al. 2016). The structural features of MLP include an input layer, a hidden layer and an output layer, in a similar manner to other distinguished ANNs (Kim and Singh 2014; Pham et al. 2019). On a general note, the nodes of the independent layers are connected to the hidden and output layers. The transduction of the signal are then transferred from the input layer into e output layer with the help of biases and weights through mathematical procedures. The MLP comprises of an input together with one or more hidden layers and output layers in its structural framework much similar to ANN (Committee 2000; Kim and Lee 2017).

$$y_i = \sum_{j=1}^N w_{ji}x_j + w_{i0} \tag{3}$$

N denotes the total number of nodes within the node’s top layer; i ; w_{ji} is the weight between the nodes, i and j in the upper layer; x_j defines the output that is derived from node j ; w_{i0} is the bias in the node i , and y_i defines the input signal of node i which crosses via the transfer function.

Step-wise-linear regression (SWLR)

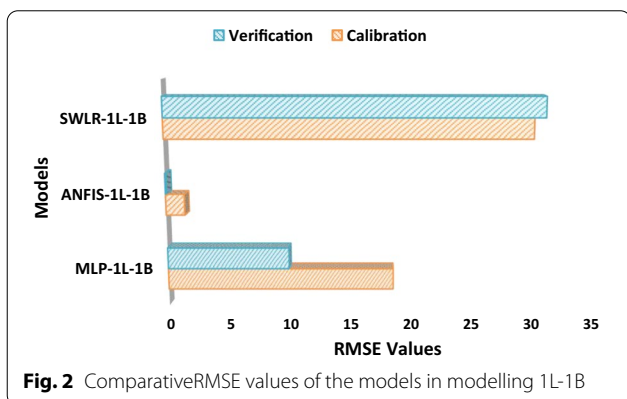
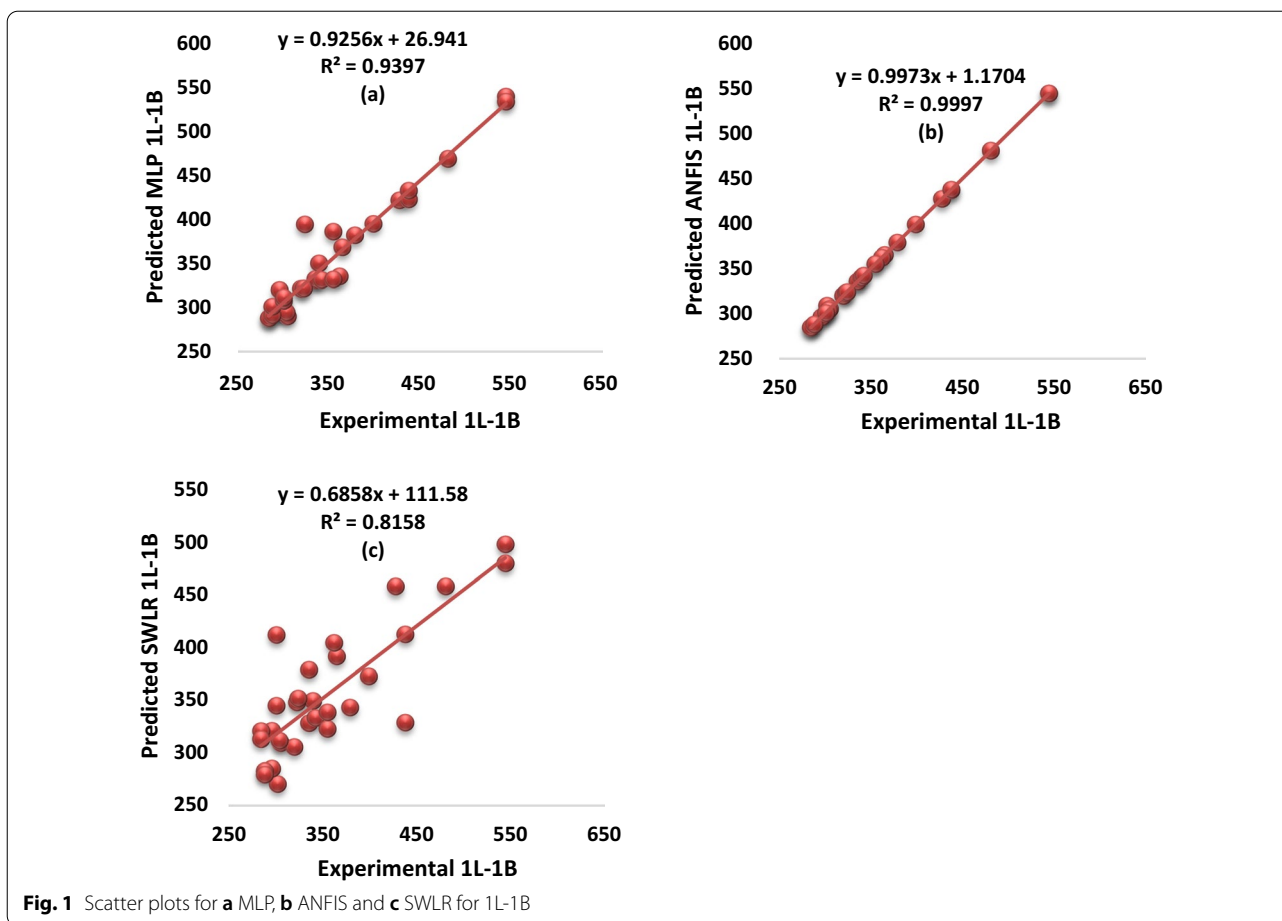
Generally, linear regression (LR) is among the main computational approaches in modeling a lot of input and output variables. It is necessary to note that there has been a correlation between single and multiple variables in finding the optimal set of the parameters that

Table 2 Performance of 1L-1B inflammatory biomarker

Models	Calibration				Verification			
	DC	CC	RMSE	MSE	DC	CC	RMSE	MSE
MLP-1L-1B	0.9419	0.9705	18.5051	342.439	0.92760	0.96313	9.95155	99.0326
ANFIS-1L-1B	0.9996	0.9998	1.52768	2.33380	0.99999	0.99996	0.10699	0.01147
SWLR-1L-1B	0.8488	0.9213	29.8442	890.676	0.8346	0.91354	30.786	947.778

The best performing model are written in bold

DC = Determination co-efficient, CC = Correlation co-efficient, RMSE = Root mean square error, MSE = Mean square error, $n = 6$



give the highest prediction efficiency, which is related to the output variable (Abba et al. 2020a, b, c). Various modellers described the systematic regression as an advancement selection that utilizes the optimal set of the input data by deleting or adding the variables through the influence of the residual sum of the squares (Abba et al. 2020a, b, c).

The SWLR abides by the systematic changes of the variables by checking their impacts. Any variable that fails to contribute and satisfy the process of the model would be deleted in a step-wise manner in order to eliminate its impact (Mohammadhassani et al. 2013). MLR could be used to demonstrate the theory of SWLR (Lee et al. 2017). The systematic regression is the procedure of adding or removing an input in constant from LR (Gaya et al. 2020).

Evaluation metrics of the models

The performance skills are checked with the help of various parameters based on comparison between the expected and calculated value for any type of data-driven approach.

In the present work, we used two statistical errors namely; root mean-squared error (RMSE) and mean-squared error (MSE) for determination coefficient (DC) as a goodness-of-fit, correlation coefficient (CC) and evaluation of the two models.

Table 3 Performance of 1L-6 inflammatory biomarker

Models	Calibration				Verification			
	DC	CC	RMSE	MSE	DC	CC	RMSE	MSE
MLP-1L-6	0.7971	0.8928	77.6708	6032.766	0.6450	0.8031	89.8350	8070.327
ANFIS-1L-6	0.9999	0.9999	0.21906	0.047991	1.0000	1.0000	0.00000	0.0000
SWLR-1L-6	0.7382	0.8591	88.2317	7784.8414	0.61340	0.78319	91.23550	8323.9164

The best performing model are written in bold

DC = Determination Co-efficient, CC = Correlation co-efficient, RMSE = Root mean square error, MSE = Mean square error, n = 6

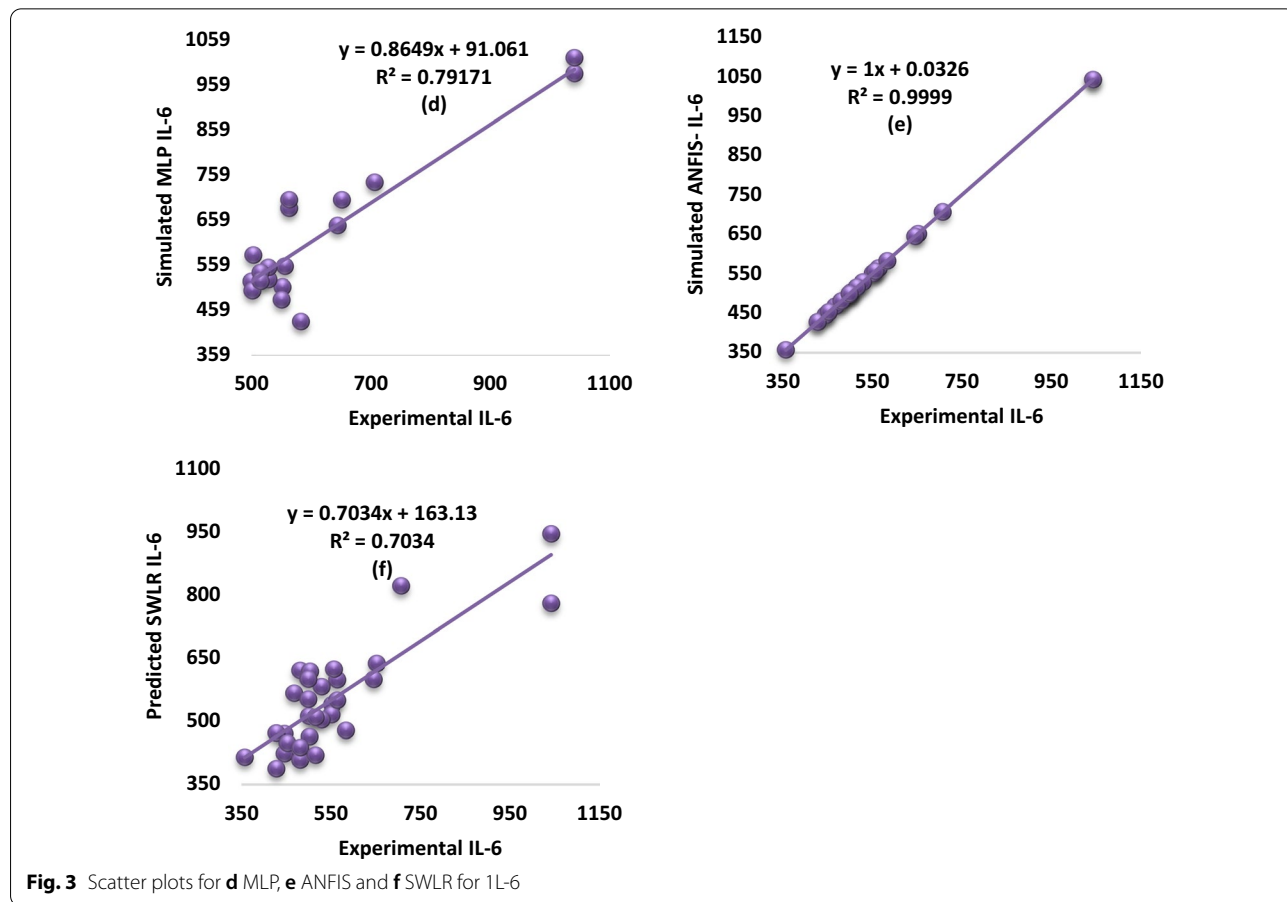


Fig. 3 Scatter plots for **d** MLP, **e** ANFIS and **f** SWLR for 1L-6

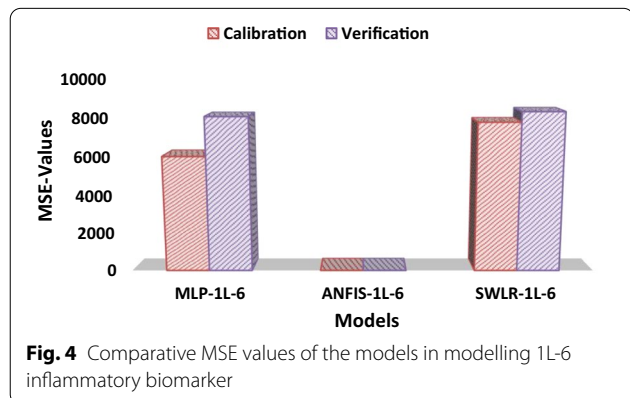


Fig. 4 Comparative MSE values of the models in modelling 1L-6 inflammatory biomarker

$$DC = 1 - \frac{\sum_{j=1}^N [(Y)_{obs,j} - (Y)_{com,j}]^2}{\sum_{j=1}^N [(Y)_{obs,j} - \overline{(Y)}_{obs,j}]^2} \tag{4}$$

$$CC = \frac{\sum_{i=1}^N (Y_{obs} - \overline{Y}_{obs})(Y_{com} - \overline{Y}_{com})}{\sqrt{\sum_{i=1}^N (Y_{obs} - \overline{Y}_{obs})^2 \sum_{i=1}^N (Y_{com} - \overline{Y}_{com})^2}} \tag{5}$$

$$RMSE = \sqrt{\frac{\sum_{i=1}^N (Y_{obs,i} - Y_{com,i})^2}{N}} \tag{6}$$

Table 4 Performance of PGE2inflammatory biomarker

Models	Calibration				Verification			
	DC	CC	RMSE	MSE	DC	CC	RMSE	MSE
MLP-PGE2	0.65	0.80	75.96	5770.56	0.72	0.85	31.40	986.05
ANFIS-PGE2	1.00	1.00	0.00	0.00	1.00	1.00	0.22	0.05
SWLR-PGE2	0.85	0.92	49.63	2463.26	0.85	0.92	23.26	540.84

The best performing model are written in bold

DC=Determination co-efficient, CC=Correlation co-efficient, RMSE= Root mean square error, MSE= Mean squared error, n=6

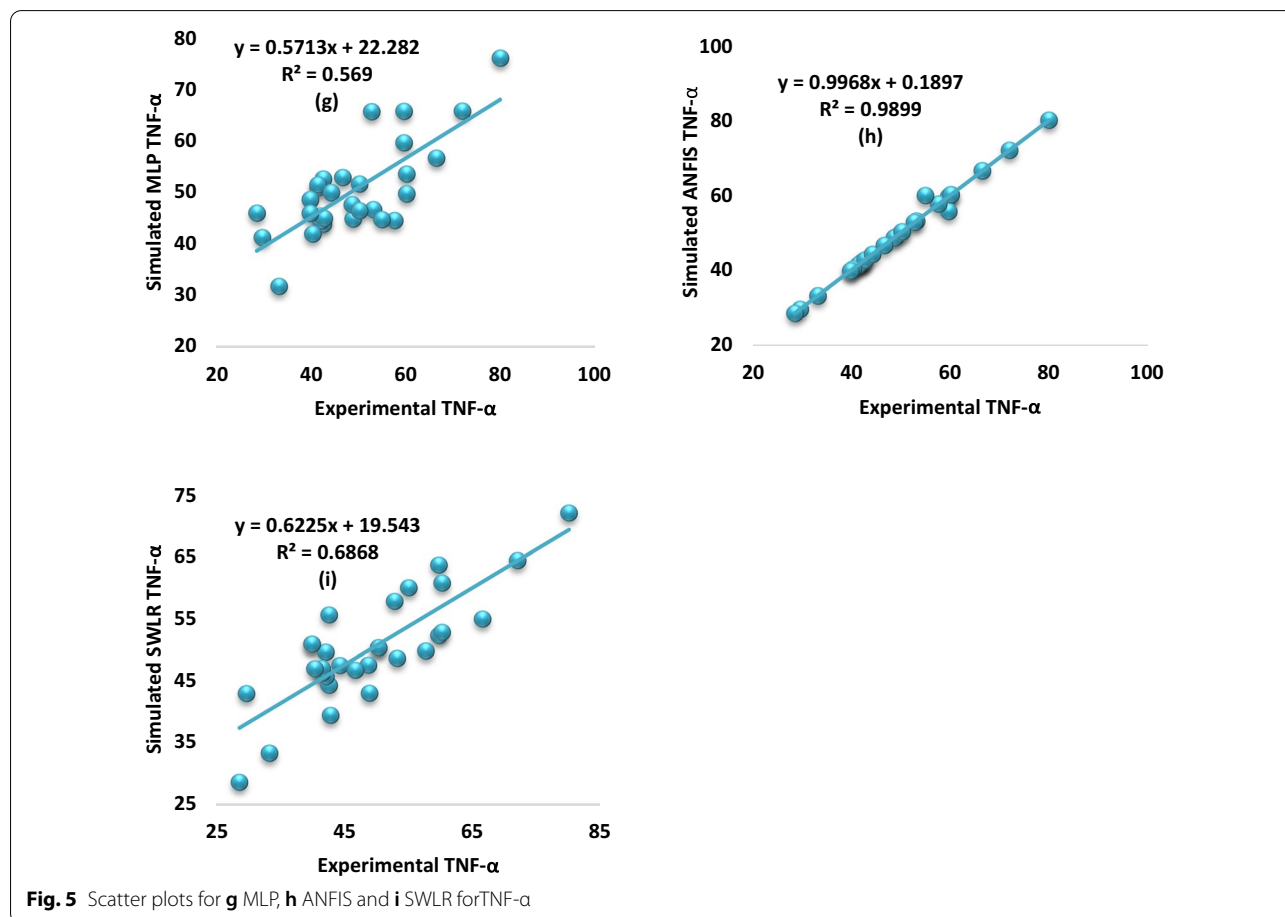


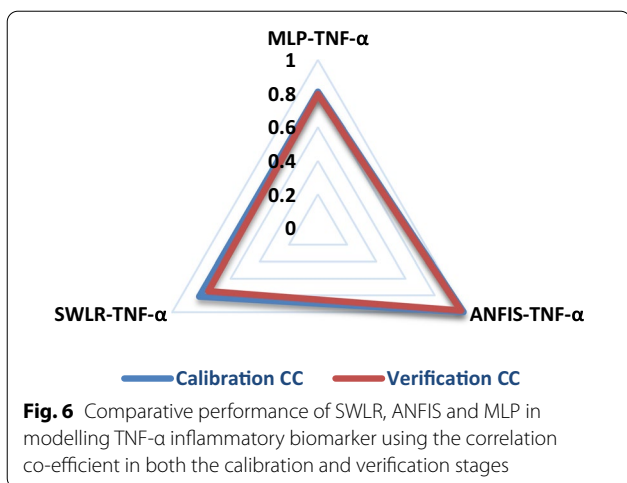
Fig. 5 Scatter plots for **g** MLP, **h** ANFIS and **i** SWLR for TNF-α

$$MSE = \frac{1}{N} \sum_{i=1}^N (Y_{obsi} - Y_{comi})^2 \tag{7}$$

where N , Y_{obsi} , \bar{Y} and Y_{comi} are data number, data observed, average value of the data observed and computed values, respectively.

Data set description and validation of the models

For effective data-driven approaches, the main objective is to make the model to provide a set of data from the indicators in use as a basis to reliably predict the unknown variables. Looking at the fact that some limitations examples overfitting, the satisfactory training performance do not consistently comply with the testing performance. Different validation approaches such as k-fold cross-validation, holdout, leaving one out,



and many more. The most important benefit of the k fold cross-validation procedure is because the validation and training sets are independent (Selin and Abba 2020). Therefore, in this work, we have categorized the data into 75% for the calibration (training) and 25% for the testing (verification) stage, based on the k-fold cross-validation. Therefore, it is essential to know that other models of validation could be applied to the data set (Abba et al. 2020a, b, c). Besides, the data set were obtained over two months, where the data set comprised of 64 instances for each of the variables.

The proposed methodology

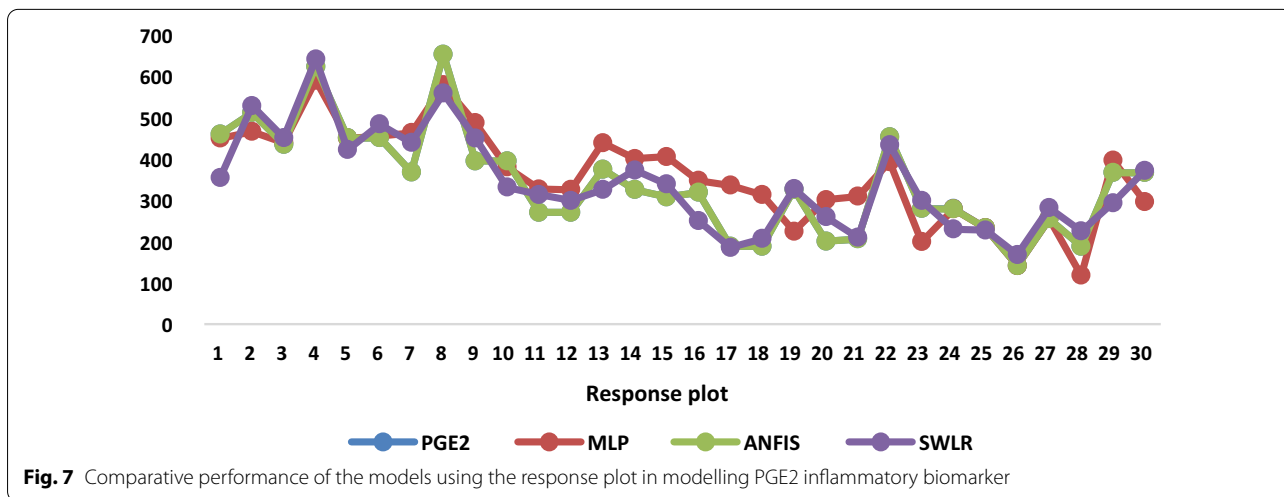
It is significant to understand the science and knowledge of the data used during any data-driven technique (Barm-palexis et al. 2018). The data employed in this study was generated from our experimental studies. This research employed the use of three data-driven approaches MLP, ANFIS and SWLR models, for modelling four different

inflammatory biomarkers; IL-6, IL-1B, TNF- α and PGE2 using number of abdominal writhes, number of paw licking and paw oedema diameter (mm) as independent variables.

One of the significant objectives of using different modelling methods is due to the limitation in understanding the model that has higher prediction performance skills than the others in practice (Abba et al. 2020a, b, c). Therefore, selecting a particular model for a specific data set is challenging.

Results

The main enthusiasm of this study is to comparatively develop various data-driven techniques for the modelling of four inflammatory biomarkers; IL-1B, IL-6, TNF- α and PGE2. In this section, the obtained results are shown both quantitatively and in a visualized form. Table 1 demonstrates the correlation analysis of the variables involved in the study (Ghali et al. 2020), namely, number of abdominal writhes, number mean reaction time of paw licking and paw oedema diameter. Acetic acid-induced abdominal writhes result from the stimulation of the release of arachidonic acid to form PG that plays a critical role in pain mechanism. The model depicts a peripheral analgesic mechanism (Ofuegbe et al. 2014). The measurement of the mean reaction time in mice in the hot plate test of algnesia is used to investigate the analgesic action of centrally acting agents via an increase in pain threshold in mice. It also predicts the potential involvement of narcotic analgesic agents (Ibrahim et al. 2012). Injection of carrageenan into the paw of the rats causes the release of inflammatory mediators including bradykinin, histamine, serotonin and prostaglandins that subsequently stimulate the production and release of TNF- α . The cascade of the event causes the release of other pro-inflammatory



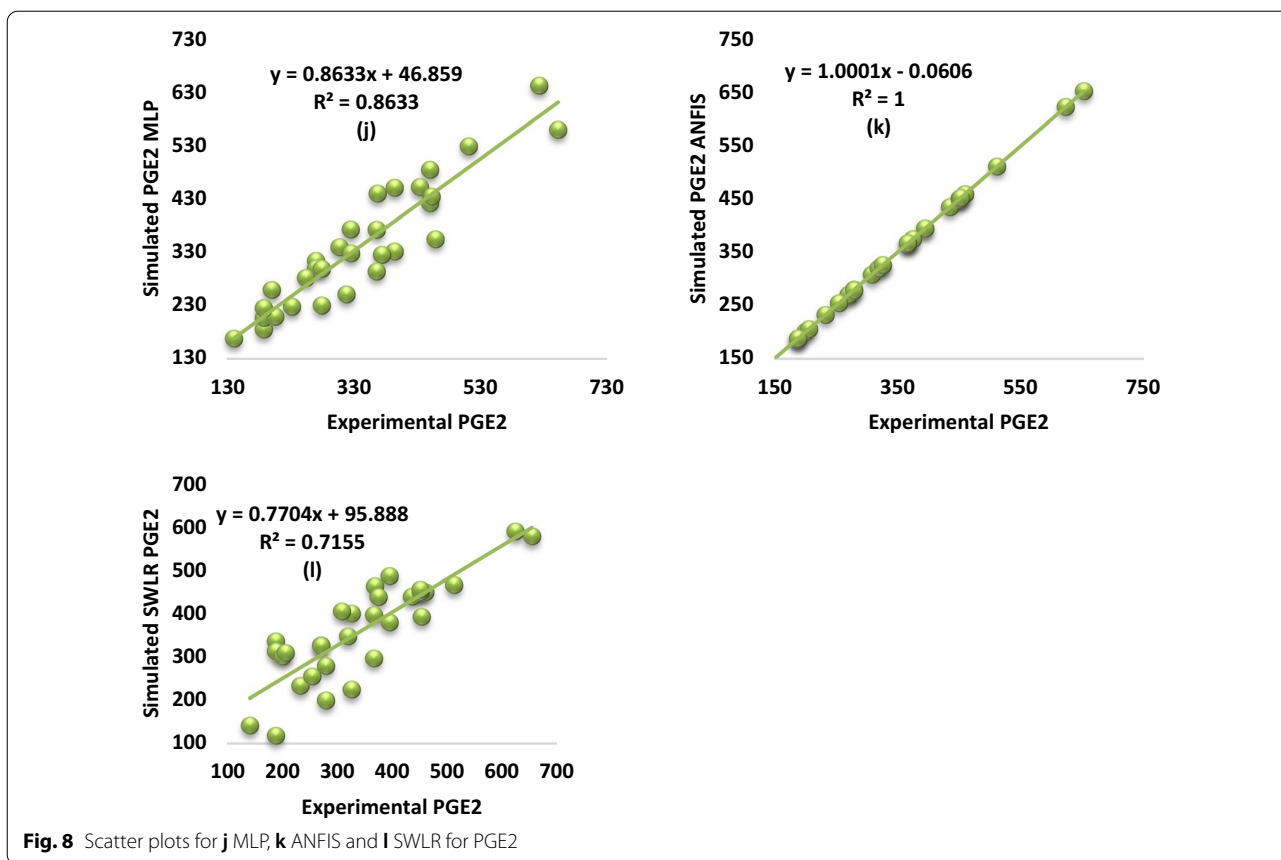


Fig. 8 Scatter plots for j MLP, k ANFIS and l SWLR for PGE2

Table 5 Performance of PGE2inflammatory biomarker

Models	Calibration				Verification			
	DC	CC	RMSE	MSE	DC	CC	RMSE	MSE
MLP-PGE2	0.65	0.80	75.96	5770.56	0.72	0.85	31.40	986.05
ANFIS-PGE2	1.00	1.00	0.00	0.00	1.00	1.00	0.22	0.05
SWLR-PGE2	0.85	0.92	49.63	2463.26	0.85	0.92	23.26	540.84

The best performing model are written in bold

DC = Determination co-efficient, CC = Correlation co-efficient, RMSE = Root mean square error, MSE = Mean square error, n = 6

cytokines such as IL-1β. The cytokines enhance the production of PG from arachidonic acid by the action COXs (Kumar and Jitendra 2009).

To improve the methodologies of the models, assurance of the correlation co-efficient conducted are presented in Table 1, Where the guiding symbols (+ or -) shows the connection among the variables (Usman et al. 2020a, b). The correlation analysis helps us in determining the highest and lowest parameters related to one another (Khalid and Usman 2021). More also, it helps in understanding the science and the mechanism of the data prior to dwelling into the modelling method by showing

the input parameter with the highest correlation with the output variable (Usman et al. 2020a, b).

Performance of the data-driven techniques

As described in the methodology section, the simulation was conducted using MATLAB 9.3 (R2020a).

Discussion

For the MLP and ANFIS models, the best architecture was optimized and selected using the trial and error technique. The results of the simulation were checked and evaluated using DC and CC to check for the fitness

between the experimental and predicted values, while RMSE and MSE were employed in order to determine the error depicted by the models in both the training and testing phases.

A comparative analysis of three different data-driven techniques (MLP, ANFIS and SWLR models) were depicted in Table 2 for the simulation of IL-1 β inflammatory biomarker. The obtained results showed that ANFIS-IL-1 β and MLP-IL-1 β AI-based models demonstrated higher prediction skills as compared to the SWLR-IL-1 β (linear model). It is not surprising that the ANFIS-IL-1 β showed the highest prediction, which is considered as a hybrid emerging system for modelling highly complex data. The models' performance efficiency can be demonstrated based on the hierarchical order ANFIS-IL-1 β > MLP-IL-1 β > SWLR-IL-1 β . This can be shown visually using a scatter plot, which indicated the fitness between the experimental and predicted values (see Fig. 1).

It is evident that the AI-based models are superior to the classical linear model SWLR-IL-1 β by depicting lower error values as shown in Fig. 2. This is in line with the performance of the models shown in Table 2 in both the training and testing phases.

As shown in Table 3, it can be observe that only the emerging non-linear AI-based model ANFIS was able to capture the performance of the IL-6 biomarker with a fitness performance of more than 80% using its determination co-efficient in both the calibration and verification phases. Therefore, ANFIS has the ability to boost the performance skills of both MLP and SWLR models by 20.28% and 26.17% in the calibration and 35.5% and 38.66% in the verification stage respectively. The performance skills of the models can be graphically illustrated using the scatter plot (see Fig. 3).

The performance accuracy of these models can equally be comparatively determined using their respective MSE, and this can be graphically demonstrated using the bar chart plot (see Fig. 4).

Based on the chart, it can be seen that the increasing order of the models' performance can be as follows SWLR-IL-6 < MLP-IL-6 < ANFIS-IL-6.

The performance indices for the data-driven approaches used in modelling TNF- α inflammatory biomarker are shown in Table 4. The comparative performance of the models showed that only ANFIS has the ability to model TNF- α inflammatory biomarker with a minimum of 80% fitness in both the training and testing stages, respectively. Therefore, this proves the ability of AI-based models in capturing highly chaotic and complex system. Furthermore, the performance of these models can be graphically demonstrated using the scatter plot (see Fig. 5).

Moreover, the performance of the models can be equally shown graphically using a radar plot. This plot generally demonstrates the comparative performance fitness of data-driven techniques using either their DC or CC. Whereby, in this current research, the performance of the models were checked using the CC evaluation metric in both the calibration and the verification phases (see Fig. 6).

The performance accuracy of three data-driven techniques for modelling PGE2 inflammatory biomarker. Based on the obtained results, it can be observed that the two non-linear AI-based models outperformed the classical linear model SWLR-PGE2. Furthermore, both MLP-PGE2 and ANFIS-PGE2 were able to simulate the PGE2 inflammatory biomarker with a minimum fitness of 80%, whereby the SWLR-PGE2 failed in both the calibration and verification stages. The overall performance of the models showed that ANFIS-PGE2 outperformed both MLP-PGE2 and SWLR-PGE2, which increased their performance skills by 15% and 28% in the verification stage, respectively. The response plot can be used to graphically illustrate the comparative performance of the models (see Fig. 7).

Based on Fig. 7, it can be observed that ANFIS-PGE2 showed the highest fitness in capturing the oscillation of the experimental values. Moreover, the performance of the models can equally be depicted using the scatter plot (see Fig. 8).

Conclusion

In this research, three different data-driven approaches, MLP, ANFIS and SWLR models, were employed for the simulation of four different inflammatory biomarkers; IL-1 β , IL-6, TNF- α and PGE2. The performance indices used in the work, namely DC, CC, RMSE and MSE, proved the ability of the AI-based models (ANFIS and ANN) over the classical linear model (SWLR) in modelling the four inflammatory biomarkers in both the calibration and verification stages (see Table 5).

Overall, the comparative performance of the models demonstrates that ANFIS exhibited higher performance skills in modelling the performance of the inflammatory biomarkers in both the training and testing stages. It is recommended that other models and optimization algorithms such as support vector machine (SVM), extreme learning machine (ELM), Harris Hawks' optimization (HHO) technique, genetic algorithms (GA) and particle swarm optimization (PSO) to be employed in order to boost the prediction ability of the inflammatory biomarkers.

Abbreviations

AI: Artificial intelligence; ANFIS: Adaptive neuro-fuzzy inference system; ANN: Artificial neural network; CC: Correlation co-efficient; COX: Cyclooxygenase; DC: Determination coefficient; EDTA: Ethylenediaminetetraacetic acid; EEHF: Ethanolic leaves extract of *Hymenodictyon floribundum*; IL: Interleukins; LD₅₀: Median lethal dose; MSE: Mean square error; N: Number of abdominal writes; NSAIDs: Non-steroidal anti-inflammatory drugs; OECD: Organization of Economic Co-operation and Development; RMSE: Root mean squared error; SWLR: Stepwise linear regression; TNF- α : Tumour necrosis factor α .

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Authors' contributions

AU: Conceptualization, data analysis, writing the manuscript and review. MHA: Conceptualization, writing original draft and review. RND: Conceptualization, data curation and conducting the pharmacological investigation. SIA: Supervised and critically revised the manuscript. All the authors read and approved the manuscript.

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The data are provided in the main manuscript.

Declarations

Ethics approval and consent to participate

The experimental protocols were approved by the Ahmadu Bello University, Ethical Committee on Animal Use and Care Zaria (ethical approval number: ABUCAUC/2020/011).

Consent for publication

Not applicable.

Competing interests

The authors declared that there is no any personal or financial competing interest to declare.

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