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AN OVERVIEW OF THE *Gynura procumbens* LEAVES EXTRACTION AND POTENTIAL OF HYBRID PREDICTIVE TOOLS APPLICATION FOR PREDICTION AND SIMULATION IN SUPERCRITICAL FLUID EXTRACTION

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ABSTRACT
Supercritical Fluid (SCF) technology has been applied in many areas, such as the pharmaceutical and food sectors due to its outstanding features. It is an efficient technology that performs extraction and leaves none or less organic residues compared to conventional processes. Recently, the simulation and prediction of process output from supercritical fluid extraction (SFE) have been determined using intelligent system predictive tools, such as artificial neural networks. The prediction of the set of results from SFE for designing and scale up purposes is because apart from reducing the usage of extraction solvent, and the energy and time of the process, it can also generate a solution for problems that a complex mathematical model cannot solve. For example, the prediction of solubility is important because this particular fundamental value contributes to the optimizing process. A neural network is considered as one of the artificially intelligent systems, and furthermore a key technology in Industry 4.0. Moreover, the use of hybrid predictive tools is also a developing area in the prediction and simulation of supercritical fluid extraction (SFE), which would be discussed further in this paper. Currently, a limited number of studies related to the analysis of processing technology on extracting *Gynura procumbens* leaves can be found. Most of the research was focused on pre-clinical studies of *Gynura procumbens* extracts using conventional methods to prove the effectiveness of the herbal product application. Therefore, this overview will discuss and describe previous studies using *Gynura procumbens* and several recommendations for subsequent analysis.
Keywords: **I**ntelligent System, Extraction, Supercritical Fluid, Simulation, Prediction, Neural Network, Optimization.

INTRODUCTION

Malaysia has an abundant supply of valuable traditional herbs that are yet to be discovered. In 2017, five traditional herbs had been emphasized on by the government, namely *Tongkat Ali, Kacip Fatimah, Misai Kucing, Hempedu Bumi* and *Dukung Anak*. Intensive clinical studies and testing had been done to identify their respective valuable components and validate the claims positioned by traditional folks regarding the health effects. However, there are still so much more herbs that can be discovered; for this overview, the *Sambung Nyawa* plant or *Gynura Procumbens* was selected. Based on the traditional uses of *Gynura procumbens*, the leaves seem to have a high therapeutic potential for treating various diseases, rendering it targeted by many researchers aiming to confirm and provide scientific evidence in support of such claims. *Sambung Nyawa* or *Gynura procumbens* is one of the potentially valuable herbs, which can be found in Malaysia, Thailand, and Indo-China. The leaves are lancelote, with dimensions of 3.5 to 8 cm long and 0.8 to 3.5 cm wide. It has a narrow yellow-coloured flowering head and panicled at 1 to 1.5 cm long[1].

Extraction of the leaves has been conducted by many researchers to identify the potential of anti-diabetic/anti-hyperglygemic[2,3], anti-hypertensive[4,5], anti-microbial[6], anti-oxidant[7–9], anti-imflammatory[10], anti-ulcer[11], anti-cancer[12], anti-herpes[13] and immunomodulatory[14] properties. They have extracted the valuable compounds using the solvent extraction and maceration technique, focusing on the isolation and characterization of the active compounds found in the extract.

Currently, SCF technology has successfully attracted the interest of many researchers in positioning the replacement of the conventional process that utilizes organic solvent as the working fluid. The advantages of using the technology compared to the conventional process are abundant; it is energy-saving and environmentally friendly, offers better efficiency, easily tuneable and controlled, suitable for heat-liable substances, and achieves the simple separation of solvent from solute with none or less solvent residues left in the extract. SCF technology is widely used in many areas, including in chemical processing, as well as food and pharmaceutical sectors. It utilizes the unique property of the SCF, namely the pressure-dependent dissolving power so as to alter the process performance. The supercritical fluid offers the exclusive behavior of a fluid's dual characteristics of gas and liquid. Gas has low mass transfer resistance and consequently high diffusivity and penetrability, whereas the higher density of liquid enables it to dissolve materials. Among the SCFs available, carbon dioxide is a commonly used fluid as it is inexpensive and safe, available in high purity, and can be used under mild conditions. Moreover, it is a small-sized molecule with a linear structure that offers fast diffusion compared to other solvents. The critical temperature and pressure for carbon dioxide are 31.3°C and 71.9 bars, respectively; the combination of these mild conditions and its non-toxic behavior has offered various benefits to many food and health-related processes[15].

To apply the SCF technology, fundamental knowledge, such as solubility is crucial to control, design, and initiate a more efficient and environmentally friendly extraction process. For prediction purposes, in addition to having the appropriate mathematical model, the values of the experimental data and the thermodynamic properties of the sample and the extract are required. Traditional mathematical modeling approaches for SCF extraction are various, which determine the solubility; they can be developed from differential mass balance equations for the packed solid bed and if possible, represent the overall extraction process. Some of the examples include hot ball diffusion, broken and intact cells, shrinking cores, and desorption models. Assumptions and simplifications of a mathematical model are sometimes required, causing the model to not be reliable. However, many conventional mathematical models have been both challenging and impractical. Therefore, predicting the effects of temperature and pressure towards the yield and solubility of the SCF extraction process using relevant tools is now developing due to time and cost concerns. Predictive tools using the intelligent systems are used to model and simulate a chemical process, as well as to compute, classify and optimize a process for process control. There is an increasing number of studies on the prediction of SCF extraction using predictive tools via intelligent systems. Intelligent systems apply the ability to learn, observe and memorize in a situation full of factors and important data. The main advantage of intelligent systems is that the predictions can be performed easily, quickly, and accurately for systems that are difficult to simulate using physical models. Intelligent systems address imprecision, uncertainty, partial truth, and approximation to achieve tractability, robustness and, more importantly, low solution cost. Examples of intelligent systems include neural networks, fuzzy systems, and evolutionary algorithms. Thus, there is an increasing number of studies on the solubility of different compounds in SCF using intelligent systems. Nevertheless, such a wealth of information is not well summarised. Therefore, this paper discusses several works involving the utilization of intelligent systems-based hybrid predictive tools for the simulation and prediction of the yield and solubility of various parts of plant extracts, using the SCF extraction process.

Gynura procumbens: A Plant

Gynura procumbens is a plant commonly found in tropical countries in Asia, such as China, Thailand, Indonesia, Malaysia, and Vietnam[16]. *Gynura procumbens* has been listed as one of the 10 commonly available medicinal plants in Malaysia for the treatment of diabetes[1]. Its common name is *Sambung*

Nyawa, which is grouped under the umbrella of the Asteraceae family. The genus name *gynura* is derived from the Greek and Latin words *gyne* meaning female, and *uora* meaning tail in reference to the long stigmas and shape of the flowers. It is widely cultivated for its leaves, which are edible and offer medicinal benefits. The leaves are green in color, odorless, and oval-shaped with alternate arrangements. They can be eaten raw; they have a slightly pungent smell, flavourless, and have a mild raw taste. Freshly picked leaves can also be blended in juices or smoothies, while some cook them as stir-fried vegetables or added in an omelette. The vernacular names include leaves of Gods, longevity spinach, mollucan spinach (English), *dewa raja, akar sebiak, kacham akar* (Malay), *daun dewa* (Indonesian), *Man san qi cao*, *lam fei yip*, *ping wo ju san qi*, *jianfengwei* (translated into pointed phoenix tail) (Chinese), *bai bing ca* (the Philippines), *Paetumpung* (Thai), *Kim That Tai, Cay Tieu Duong, Tiem Vinh* (Vietnamese), *Ci Angkam* (Cambodia), and *ngokilo* (Java).

Extraction can be done at various parts of a plant, for example, its leaves[17], roots[18] and flowers [19]. To date, there are many extraction and isolation processes that have been done by researchers from the pharmaceutical and biomedical areas on *Gynura procumbens* extract. As many traditional folks use the various parts of the *Gynura procumbens* plant due to its wonders, some of the claims are not underpinned by scientific evidence. The leaf extracts are claimed to possess anti-diabetic, anti-cancer, anti-inflammatory, anti-hypertension, anti-herpetic, anti-ulcerogenic, anti-oxidant, anti-hyperglycemic properties, among others. These properties have been identified and isolated after the extraction process and upon further experimental works and clinical testing that was conducted to prove the claims[2,7,12,13,20].

In 2016, a group of researchers from the Institute of Bioproduct Development, Universiti Teknologi Malaysia (UTM) undertook an extraction process of *Gynura procumbens* using the maceration technique[21]. They performed an extensive experiment starting from the preparation of the sample by drying and grinding. The sample was then divided into two types of particle size, namely A (coarse: <3 mm diameter) and B (fine: <100 µm diameter). Various parameters were tested for the extraction process, including different raw material to solvent ratios and different extraction time. The solvent used was water. Different raw to solvent ratios were found to affect the yield of *Gynura procumbens* extract, with the highest yield obtained for particle B with 1:30 solvent to raw material ratio. Moreover, slight changes in production yield were seen between the extraction times (1-3 hours) of particle size B, hence the conclusion that one hour is the best production of extract in this study. It can shorten the time of extraction besides reducing the amount of energy used.

A modern technique has since been applied to extract *Gynura procumbens* extracts, whereby a researcher of Universiti Malaya (UM) had applied the Microwave-Assisted Extraction (MAE) technology to extract the anti-diabetic active ingredient of quercetin-3-*O*-glucoside from the leaves[22]. It has served as a preliminary study for comparing the yield of quercetin-3-*O*-glucoside from MAE and Soxhlet methods. By fixing the amount of sample to 5 g and ethanol solvent amount to 150 ml, the extraction time was set to 5 min for MAE and 180 min for Soxhlet. Under optimized conditions, MAE required much shorter extraction time (5 min vs. 3 hr) and generated better quercetin yield (1.60 mg/g vs. 1.40 mg/g) compared to the Soxhlet extraction. Additional custom-made temperature controlled extraction apparatus was fabricated to allow better control of the extraction process, as well as an improved extraction yield.

Optimization has been conducted by the researchers of Universiti Putra Malaysia (UPM) by extracting chlorophylls a and b in *Gynura procumbens* at an optimum condition[23]. The extraction process varied at different temperatures (40 to 80 ˚C), solid/liquid ratio (1:5 to 5:5 g/ml), solvent (i.e. methanol, ethanol, and water) and time (5 to 120 min). Based on the results, the highest yield of chlorophyll was extracted by ethanol at 80 ˚C with solid to solvent ratio of 2:5 mg/ml for 90 minutes. Finding the mathematical model for the extractions called for the use of the Response Surface Methodology (RSM) software, based on the obtained results for the extraction of chlorophyll at different solid to solvent ratio, temperature, and extraction time (three parameters).

Previous studies have shown that no research on *Gynura procumbens* has been done using SCF extraction, while optimization studies are limited to chlorophyll extracts and analysis of yield that are compared at different conditions is limited to the conventional method (i.e. solvent extraction and maceration) and MAE.

Supercritical Fluid Extraction

Supercritical Fluids (SCFs) are fluids that are above their critical properties of temperature and pressure. Supercritical fluid extraction (SFE) is a process in which solid or liquid matter is processed with SCF to obtain soluble compounds from the mixtures[24,25]. SCFs have been successfully used as solvents in extraction processes, which can be attributed to their unique tunable physical properties, such as changeable density, liquid/gas-like viscosity, and high diffusivity. The high solvating power of SCFs is the major argument for laboratories to be interested in developing SFE methods for routine analyses in their innovative research[26]. The recent decade has resulted in a number of laboratories replacing their conventional extraction methodologies with SFE-based technologies to minimize the consumption of organic solvents[27,28]. Various solvents and gases are available for use as SCFs, namely carbon dioxide, ethane, nitrous oxide, propane, ammonia, fluoroform, *n*-pentane, sulphur hexafluoride, and water. Reviews done by previous research show that among the wide variety of the above-mentioned compounds, carbon dioxide is the primarily utilized supercritical solvent (Table-1).

Table-1: Compilation of Works on the SFE of Different Types of Samples and its Parameters.

Sample	Extract	Pressure	Temperature	CO_2 flowrate	Extraction time	Particle size	Mass of sample	The volume of the extract or vessel
Mentha spicata L. (Labiatae)[29]	Essential oils	85–120 bar	38–50 °C	0.059–0.354 g/min	20–120 min	0.177–2 mm	30 g	n.a
Odontonemas trictum leaves[30]	Flavonoids	200 and 250 bars	55 and 65 °C	15 g/min	210 and 270 min	0.6 mm	10 g	100 ml
Salvia officinalis L. leaves[31]	Oxygenated monoterpenes, α-humulene, viridiflorol and manool	10 to 30 MPa	40 to 60 °C	1 to 3 kg/h	90 mins	0.478 mm	50 g	n.a
Radish leaves[32]	Bioactive compound	300 and 400 bars	35, 40 and 50 °C	0.6 kg/h	n.a	710 μm	5 g	n.a
Lupinusalbescens[33]	Bioactive compound	150,200 and 250 bars	40, 50 and 60 °C	4 g/min	n.a	n.a	10 g	100 ml
Piper auritum and *Porophyllumruderale*[34]	Essential oils	10.34 and 17.24 MPa	40 and 50 °C	126.4 ml/min	180 mins	n.a	25 g	0.526 l
Basil leaves[35]	Essential oils	100 and 300 bars	40 °C	0.2kg CO_2/h	30, 60, 90, 120, 180 and 240 min	n.a	50 g	n.a

SFE separates one component (the extractant) from another (the matrix) using SCF as the extracting solvent[36]. SFE works based on the solvating properties of the supercritical fluid (SF), by utilizing pressure and temperature above the critical point of a compound, mixture or element. SFE is considered as an eco-friendly process because it does not utilize chemical solvents with severe environmental impacts[37]. SFE of plant herbs has been increasingly reported in the literature[38–41]. Numerous review papers have been written on the topic of SCF of plants and herbs, for instance on their experimental design[37], sample preparation, extraction condition, SFE modelling[42], effects of SFE conditions[43], factors influencing SFE efficiency[44], and extractions of nutraceuticals and other phytochemicals from plant material[26]. These reviews and studies indicate that most of the herbs are possibly extractable using the SFE method. Table 1shows several prior SFE processes with their operating conditions.

Predictive Tools

Predictive tools have been used to save time, money and energy. Experimental studies of SFE in the laboratory require high usage of solvents, energy and time to produce sets of data for simulation and prediction purposes. Among the predictive tools from intelligent systems that have been applied, the Artificial Neural Network (ANN) is the common tool used for prediction as it is easily referenced and applied. The ANN is based on the biological nervous system, which consists of a large number of neurons in an architecture inspired by the brain. Neural networks learn by example; therefore, they are trained by known examples of a problem to attain knowledge about it. After being properly trained, the network can be put to effective use in solving unknown parameters of the problem[45]. Over the years, neural network systems have evolved. The architectures of neural networks can be identified by three types: single layer feedforward networks, multilayer feedforward networks, and recurrent networks. There are various types of learning methods for neural networks, whereby one of the most applied methods is the backpropagation learning rule. Neural networks have been applied to several SFE processes in predicting the yield of extraction[46–51], initial slope[49], and solubility[52–54]. Table-2 lists some of the works that applied ANNs in the SFE of plants.

Table-2: Compilation of Works on the Types of Models of ANNs Applied in SCF Extraction.

Model	Sample	Extract	Network Data
Feedforward multilayer backpropagation[48]	*Cuscutareflexa*	Coumarin	Input: Temperature, time and pressure Output: Coumarin yield (µg/g)
Back-propagation neural network, a radial basis function neural network[55]	Pomegranate seed	Pomegranate oil	Input: Temperature and pressure Output: Extraction yield (%w/w)
Multi-Layer Perceptron[56]	*Glycyrrhiza glabra* (liquorice) root	Glycyrrhizic acid (GA)	Input: Temperature, pressure, CO_2 flow rate and dynamic time Output: Glycyrrhizic acid recovery
Back-propagation neural network[47]	Iranian green tea	Epigallocatechin-3-gallate (EGCG)	Input: Temperature, pressure, CO_2 flow rate and dynamic time Output: Epigallocatechin-3-gallate recovery
Levenberg- Marquardt backpropagation[46]	*Galega officinalis L.* leaves	Galegine	Input: Temperature, pressure, CO_2 flow rate and dynamic time Output: Galegine recovery
Levenberg–Marquardt backpropagation[57]	*Rosa damascene* (Persian rose)	Quercetin	Input: Temperature, pressure, CO_2 flow rate and dynamic time Output: Quercetin extraction recovery
Back propagation network with Marquardt Levenberg algorithm[58]	*Ferulagoangulata*	Essential oil	Input: Temperature, pressure, particle size and dynamic time Output: Essential oil extraction recovery

The inputs for the network are mostly the most critical factors in the SFE process, namely the temperature and pressure (Table-2). Meanwhile, other inputs can be time, flow rate and particle size. These inputs are basically the factors affecting the yield and recovery of sample extracted in SFE. The simulated output from the network that is yielded or recovered need to be compared to those from the experimental data and simulated output from other mathematical model or network.

Hybrid Predictive Tool Systems

Hybrid denotes the integration of two or more systems. Prediction using predictive tools with intelligent systems is a system integrating two or more technologies. The combined use of technologies has resulted in effective problem-solving in comparison with each technology being used individually and exclusively. As illustrated in Fig.-1, each of these technologies individually and in combination can be employed to solve problems. For example, when neural networks are combined with fuzzy systems, a neuro-fuzzy hybrid model is developed; when neural networks and evolutionary algorithms are combined, a neuro-evolutionary model is developed.

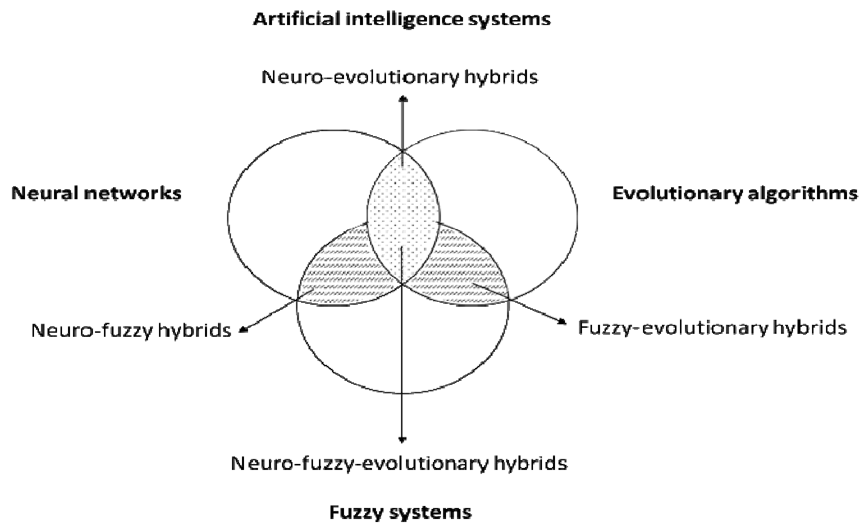

Fig.-1: Integration of Neural Networks, Fuzzy Systems and Evolutionary Algorithm Technologies[45].

Adaptive Neuro-Fuzzy Inference System (ANFIS)

The Adaptive Neuro-Fuzzy Inference System (ANFIS) is considered as a type of hybrid model since it combines the ANN and Fuzzy Inference System (FIS) system. The ‘black-box’ nature of the ANN models and unsatisfactory extrapolation by ANN models have led to the development of hybrid neural network models that combine ANNs with simple models. These hybrid neural network models are expected to perform better than ANNs in terms of process identification tasks since generalization and extrapolation are confined only to the uncertain parts of the process, and since the basic model is always consistent with the first principle[59].

Generally, the ANFIS architecture consists of five layers, as shown in Fig.-2. The architecture of ANFIS in Fig.-2 maps the inputs through the input membership functions (MF) and fuzzy rules. Similarly, output mapping is achieved through output membership functions with its fuzzy rules. The number of membership functions assigned to each input variable is chosen by trial and error. Fig.-2 shows the general architecture of ANFIS for the SFE system.

The hybrid of a neural network and fuzzy logic in ANFIS allows it to have both the low-level learning and computational power of neural networks, as well as the advantages of the high-level human-like thinking of fuzzy systems. Therefore, this neuro-fuzzy model is capable of overcoming the individual disadvantages of individual models as they can complement each other[60]. Table-3 describes the advantages and disadvantages of applying the ANN model independently.

There are several studies that utilized ANFIS to predict the solubility[61] and mass of the extract[62,63]. Some studies even compare the results of ANN and ANFIS implementation to identify the best system that can represent the data and is reliable for optimization processes[53–55, 63]. A detailed description of the prior research that applies ANFIS and its hybrid for yield and solubility predictions is shown in Table-4.

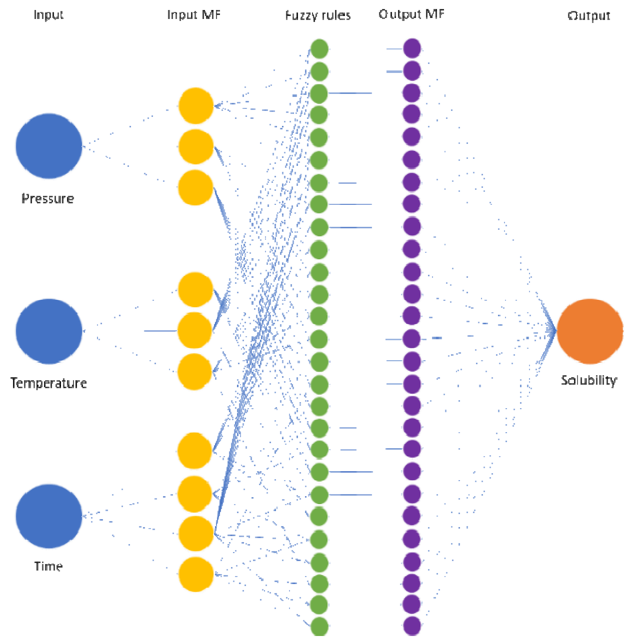

Fig.-2: ANFIS Architecture

Table-3: Advantages and limitations of ANN-based Models[65].

Advantages	Limitations
Simple for the correlation of data, although lacking suitable function	Difficult to interpret and analyze the output
The model can easily be developed and takes less time to be developed compared to other models	The training of the data might take a lot of time, even days
No theoretical knowledge of process and literature parameters needed to develop the model	A large set of experimental data covering wide operating conditions is required as the training of an ANN uses experimental data
It can handle noise, and incomplete and inconsistent data whenever the over-fitting is avoided	The architecture depends on the variation of conditions when trained and cannot be predicted

Table-4: Compilation of Research Applying ANFIS Tools for Predicting the Yield and Solubility of SFE.

Sample	Extract	Purpose	Remarks
Pimpinellaanisum L. Seed[62]	Seed oil	Prediction of mass of extract	Independent variables: pressure, solvent mass flow rate, and extraction time Dependent variable: mass of extract
Pomegranate[55]	Pomegranate oil	Simulation of oil yield	Independent variables: Temperature and pressure Dependent variable: Extraction yield

			(%w/w)
Glycyrrhiza glabra L. [56]	Glycyrrhizic acid (GA)	Modeling the recovery of extraction	Independent variables: dynamic time (t), pressure (P), temperature (T) and flow rate of $SCCO_2$ (Q) Dependent variable: Recovery of GA
Rosa damascene Mill[57]	Quercetin	Modeling the recovery of extraction	Independent variables: dynamic time (t), pressure (P), temperature (T) and flow rate of $SCCO_2$ (Q) Dependent variable: Recovery of quercetin

Mathematical Model-Neural Network Hybrid

Hybrid models can combine both physical laws and observed measurements, as well as include all available knowledge regarding the process. This model can be arranged in series or parallel; in the series approach, the heuristic model estimates the unmeasured process parameters of mathematical modelling, such that the first principle constraints are satisfied. In contrast, the parallel approach describes the hybrid model prediction that is combined with the outputs of the mathematical and initial heuristic models, thereby allowing residuals between the process and mathematical model to be compensated[66]. This type of hybrid can solve the black box issues of neural networks for which the knowledge of the process is lacking. By combining both processes, the model will become more reliable and represent the data well.

In 2003, a group of researchers from Canada proposed a hybrid model of the Radial Basis Function-Peng Robinson (RBF-PR) model. Its formulation was initiated by first developing a simple RBF model, which consisted of the three inputs of T, p and other factors; with one output, which is yield rate. This model had no knowledge of the whole process. To overcome the black box problem of the RBF model, the model was correlated with the Peng-Robinson equation to becoming a hybrid RBF-PR model (Fig.-3). In the Peng-Robinson equation of state, there is an unknown interaction parameter k_{12} for a binary mixture, whereby the predicted solubility is sensitive. The k_{12} can be obtained from the physical property data for the mixture, but it requires trial and error processes to obtain it. Moreover, the parameters are all temperature dependent, which does not fit the data compared to pressure. The proposed hybrid model (Fig.-3) can resolve the black box problem[67]. The proposed model revealed well-fitting outcomes with the experiment data while also effectively retaining the physical meaning of the whole SFE process.

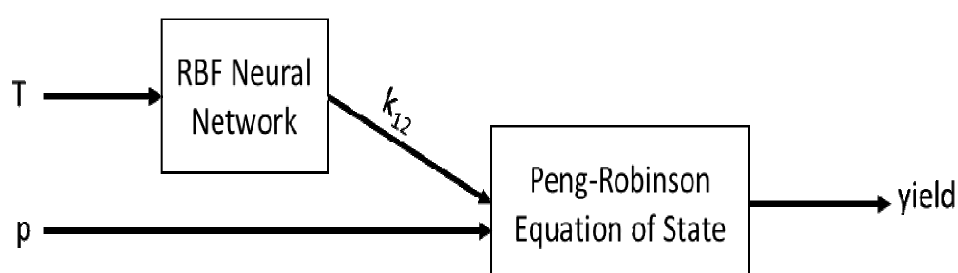

Fig.-3: Proposed Hybrid Model Schematic Diagram [67].

Ten years later, a hybrid model arranged in parallel was developed by researchers from Iran for the prediction of the epigallocatechin gallate extract of supercritical extraction[63]. It combined conventional mathematical modelling based on the differential mass balance in solid and mobile phases with ANFIS (Fig.-4). By using an analytical model in this structure, the accuracy of ANFIS is increased in non-training domains and capable of solving the problem of unknown analytical parameters. In other words, the hybrid model can simulate any extraction system with the random values of adjustable parameters for any mathematical modelling specified[66].

To date, only a few studies have approached the application of a hybrid model between neural networks and mathematical models. As a result, it is recommended to venture into this area of study in terms of the prediction of values, other than the yield and recovery of extracts.

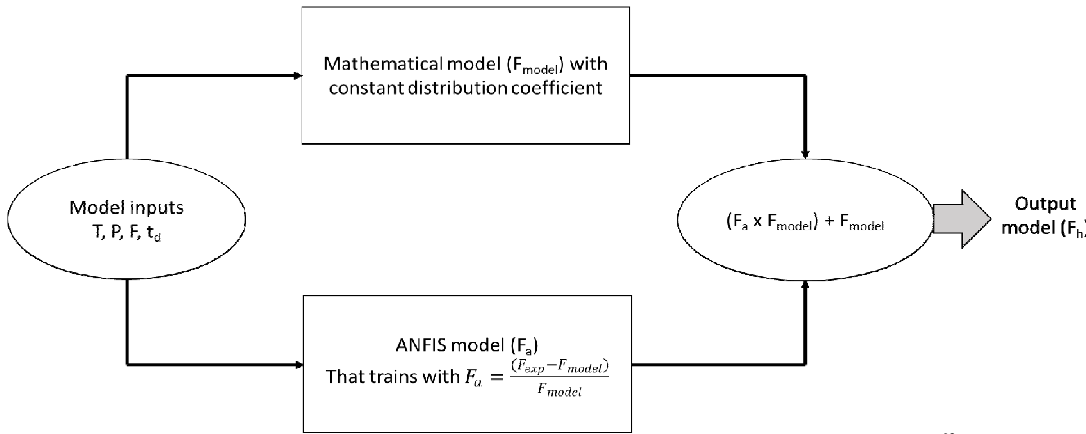

Fig.-4: Parallel hybrid of the mathematical model and the ANFIS network[63]

RESULTS AND DISCUSSION

Existing literature review reveals the limited number of studies related to the analysis of processing technology on extracting *Gynura procumbens* leaves. Most of the research was conducted mainly by pharmaceutical researchers that focused on the pre-clinical studies of *Gynura procumbens* extracts using conventional methods to prove the effectiveness and safety effect for the herbal product application[2–5,12,13]. For this reason, this study explored the application of a modern and green technology known as SFE to extract *Gynura procumbens* leaves, which included further analysis regarding their yield at different conditions of material preparation. Based on the literature analyzed, the yield and solubility data were lacking still; to date, no experiment had been done on producing one. Solubility data is important for chemical engineers to design a system for chemical separation and purification process calculations. Besides, no study was performed for analysing the effect of operating conditions, such as temperature, pressure, time, and flow rate of solvent towards the process. Therefore, a model to represent the experimental data is recommended to be generated. There are several mathematical models that can correlate the solubility data, such as the empirical correlations density-based model and theoretical model thermo-based equation of state (EOS). However, mathematical modelling of the SFE process is not always possible as these models usually require an excessive number of parameters, such as the critical properties of the extract, porosity of particles, void fraction of extractor, and internal and external mass transfer coefficients[68]. Besides, simplifying assumptions in the mathematical modelling of SFE decreases the accuracy and validity of the model[46].

In both ANN and ANFIS, the correct and optimum structures were the most important problems during training. For ANN, the performance of the network would not be satisfied when the number of the neurons in the hidden layer was small or excessive. Too many neurons may lead to a long length of training, and it may be compromised by over fitting. For ANFIS, whenever the number of input membership functions was increased, the structure became more complex, requiring more iterations to achieve the convergence to the target error. Thus, the training process became very lengthy. However, the predictive tools can ultimately solve the problem; the acceptance of the model highly depends on the values of the coefficient of determination (R^2) and absolute average deviation (AAD). The correlation was therefore meaningless as the model did not contain any meaning to the process.

The hybrid of the mathematical modelling and neural network was very promising because it overcame the aforementioned problem. The hybrid model combined the application of the mathematical model derived from the theory with the intelligent system. The limitation of solving the complex mathematical model could be resolved by applying the predictive tools, resulting in generating a much more meaningful model to be used in the prediction of yield and solubility values in the SFE processes.

As seen in Table-4, the prediction for extract recovery and yield is the top application for ANFIS. In addition, a hybrid of the mathematical model with the neural network was mostly applied for the prediction of extract yield. In ANN application, other than recovery and yield, two other crucial predictions that could also be made: solubility and initial slope. Therefore, the hybrid between the mathematical model and intelligent system may be applied for predictions other than the yield and recovery. Such an approach would be an interesting effort as the correlation with solubility was different from that of the extraction yield mathematical model.

CONCLUSION

Overall, the application of an intelligent system to model and simulate a chemical process was achieved in the SFE process. The intelligent system models generalized the experimental results and presented the process behavior, while also predicting and estimating the problem. The model could be applied individually or by combining two or more models rendering it called as a hybrid model for achieving the best estimation and prediction data. The appropriate model would be particularly beneficial in the development of new products by offering experimental time and cost-saving measures. However, no research has been performed prior regarding the solubility of SFE using a hybrid model; thus, a comparison between a mathematical model and an intelligent model is recommended for further research. Besides, further study on the kinetics of *Gynura procumbens* is recommended via SFE, as these data are still lacking in the literature.

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