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En vue de l'obtention du diplôme

MASTER

Thème

Optimisation des conditions d'extraction des composés phénolique à partir de la peau d'amande en utilisant les réseaux de neurones et les réponses de surfaces

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Dédicace

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Liste of abbreviations

AA : Antioxydant **A**ctivity

ANN : Artificial **N**eural **N**etworks

ANOVA : Analysis Of Variance

APG : **A**ngiosperm **P**hylogeny **G**roup

BBD : Box-**B**ehnken **D**esign

°C : Selcus degrees

CCD : Central **C**omposite **D**esign

CV : Coefficient Of **V**ariation

DNS : Dinitrosalicylic acid

DPPH : Diphenylpicrylhydrazine

DW : Dry **W**eight

GAE : Gallic **A**cid **E**quivalent

HO : hydroxyl radical

H_2O_2 : hydrogen peroxyde

M : Molar

MAE : Microwave **A**ssisted **E**xtraction

Mg : Milligram

min : Minute

ml : Milliliter

nm : Nanometer

R^2 : Coefficient Of Determination

ROS : Reactive **O**xygenic **S**pecies

RSM : Response **S**urface **M**ethodology

TPC : Total **P**henolic **C**ompounds

UV : Ultra-**V**iolet

µl : Microliter

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Introduction

Introduction

According to the International Nuts & Dried Fruits Statistical Yearbook 2018/2019, almonds are the most consumed nut in high-income economies, accounting for 39% and followed by walnuts, cashews and hazelnuts**(Beltrán Sanahuja et al., 2021).** Almond production has increased significantly in the last years, with a worldwide production of about 3 million tons in 2022. Food applications of almonds such as confectionary items and bakery, snack formulations, cereals, and marzipan, require the almonds without the seed coats. The external coating of almonds is industrially removed from hot water blanching process, with the brown skin contributing to around 6.0-8.4% of the seed weight. Almond skin agricultural by products are produced upon almonds processing in large amounts. Industries are forced to consider ways of treating or using these residues, since most of them are just incinerated or dumped without control causing several environmental problems or used as animal feed **(Valdés et al., 2015)**

In recent years, phenolic compounds have received a lot of interest due to their ability to promote benefits for human health as well as their industrial use as natural antioxidants, colorants, food preservatives, and in the manufacturing of paints, paper, and cosmetics. Because of these numerous beneficial properties, researchers have increased their efforts to identify fruits, vegetables, plants, agricultural and agro-industrial residues as sources of bioactive phenolic compounds. **(Martins et al,. 2011)**

Microwave assisted extraction (MAE) is a novel extraction technique that provides better extraction yield, improves extract quality, and reduces extraction time and solvent consumption when compared to traditional extraction techniques. MAE provides for quick extractions without the destruction of thermolabile chemicals, resulting in significant time and energy savings, and this approach is already being utilized to extract bioactive molecules of interest to the food and pharmaceutical industries. Another significant advantage of the microwave is its ability to be used in the laboratory, on a pilot scale, and on an industrial basis **(Karabegovic et al 2013).**

To obtain an accurate analysis, the extraction of phenolic chemicals must be optimized. RSM (response surface methodology) is a powerful technique for optimizing this process. It is a set of statistical and mathematical techniques for establishing, enhancing, and optimizing processes in which a response of interest is influenced by a number of factors (independent variables). RSM provides a mathematical model that describes the chemical or biological processes in

addition to defining the impacts of the independent variables. (Alberti et al 2014) in case of large numbers of input parameters, a higher number of interactions will take place in between responses and input parameters thus increase the complexity of the system, which is one of the major drawbacks of RSM technique. Also, RSM technique is not capable to express non-linear biological interaction deploying second-order polynomial equation

Artificial Neural Networks (ANNs) are one of the powerful methods in dealing with non-linear relationships. Many authors have underlined the interest of using ANNs instead of linear statistical models **(Muriel Gevrey 2003).** To mitigate all these problems much-enhanced modelling and technique like ANN is introduced which can optimize multivariable nonlinear interaction in a very easy way **(Tanmay Sarkar).**

The objectives of this study were to examine MAE as a method applicable for the extraction of polyphenolic compounds from the almond skin, to estimate the influence and combined effects of the main extraction parameters (microwave power, ethanol concentration and extraction time), as well as to optimize operational parameters in order to obtain a maximal possible content of polyphenolic compounds in extracts using RSM and ANN.

To the best of our knowledge, this is the first study comparing RSM and ANN with several statistical parameters, in microwave assisted extraction technology of phenolic compounds from almond skin.

CHAPTER I: Almond and its by-products and Microwave assisted extraction

Section 1. Almond and its by-products

1. Origin and history

The almond (*Prunus dulcis*) is an important nut native to Central Asia, but today is produced worldwide in hot-arid Mediterranean climate regions. (**Barreca et al., 2020)** Almonds are the most popular nut, according to the International Nuts & Dried Fruits Statistical Yearbook 2018/2019. With over 66% of the global production, the USA currently produces the most almonds, followed by Spain **(Figure 1)**. **(Beltrán Sanahuja et al., 2021).** The worldwide production of almonds has been noticeable increased in the last years **(Table 1)** because they greatly enrich many recipes and desserts in Mediterranean culinary such as nougat, marzipan, pralines, or ice cream. Also, they can be used in different forms : natural or salty, fresh or dried, roasted or fried.**(Beltrán Sanahuja et al., 2021)**

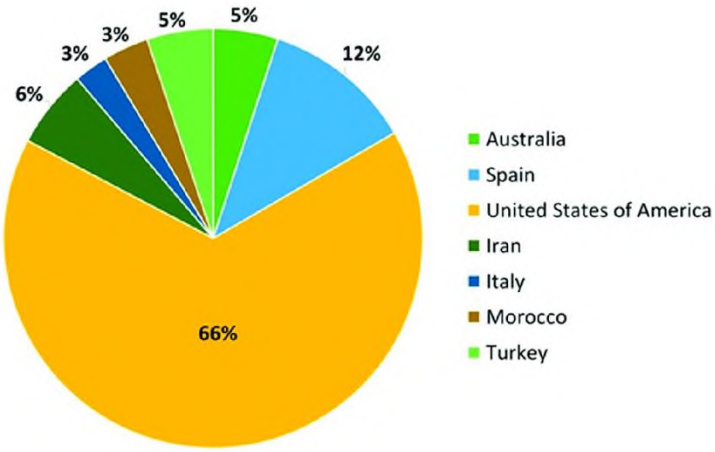


Figure 1. Worldwide almond production (2019)**(Beltrán Sanahuja et al., 2021)**

2. Description.

The almond is a deciduous tree, growing 4- 10 m in height, with a trunk of up to 30cm in diameter (**figure2**). The young twinges are green at first, becoming purplish where exposed to sunlight, then grey in their second year. The leaves are 7-2 cm long with a serrated margin and 2.5 cm petiole **(figure3)**. The flowers are white to pale pink, 3-5 cm with five petals, produced singly or in pairs and appearing before the leaves in early spring **(figure4)**. Almond is also the name of the edible and widely cultivated seed of the almond tree **(figure5)**.

Figure 2. a. Almond tree, b. Almond leaves, c. Almond flowers, d. Almond fruits.

3. Classification

Almonds (*Prunus dulcis*), which belong to the rosacea family that also includes apples, pears, prunes and raspberries, are one of the most popular tree nuts on a wide basis and rank number one in tree nut production. Taxonomically, almond trees belong to the subgenus amygdalus **(Esfahlan et al., 2010)**

Table I. Systematic classification of *Peunus amygdalus* according to APG III **(Tela Botanica, 2011).**

Class	**Scientific name**	**Illustration**
Kingdom	Plantae	
Order	Rosales	
Family	Rosacea	
Genus	Prunus	
Subgenus	Amygdalus	
species	*Peunus amygdalus*	

4. Different parts of almond

Almond fruit consist of tree or correctly four portion: Kernel or meat, middle shell, outer green shell cover or almond hull and a thin leathery layer known as brown skin of meat or seed coat

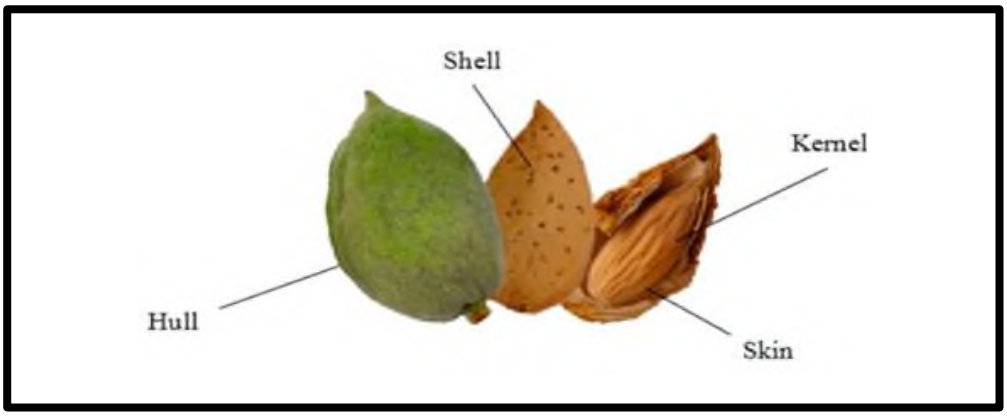


Figure 3. Different parts of almond fruit **(Iva Prgomet et al., 2017)**

4.1. Almond's meat

Edible nuts are grown in a range of climates and growth circumstances, and they are prized for their sensory, nutritional, and health benefits on a worldwide scale.**(Esfahlan et al., 2010)**

Almond, with or without the brown skin, is consumed as the whole nut or used in various confectionaries **(wijeratne et al,. 2006).** It is well known that fruits and nuts contain a wide variety of phenolic acids and flavonoids that are predominantly conjugated with sugars or other polyols via O-glycosidic bonds are ester bonds **(Mibury et al,. 2006)** and its consumption has been associated with reduced risk of chronic diseases **(Pellegrini et al,. 2006).**

4.2. Almond's meat brown skin

The flesh of almond seed is encased in a brown leathery coating, called the seed coat, which protects the almond from oxidation and microbial contamination. Almond skins, resulting from hot water blanching process, are ground and used as animal feed or burned as fuel in processing plants (Harrison and were 2007). The skins constitute about 4% of the almond fruit, and are a readily available source of phenolic **(Esfahlan et al., 2010).**

Figure 4. Almond's skin

4.3. Almond's green shell cover

The mesocarp of almond becomes dry, and astringent to the taste, reflecting the fact that mature almond mesocarp has unusually a high concentration of flavonoids compared to its botanical relatives, as well as to other fruits. This is thought to be a consequence of the length of time that the mesocarp is subjected to intense heat, ultraviolet radiation, and pest infection, as the flavonoids play protective roles against all of these stress factors. The extended maturation period of the mesocarp, flowing into remarkably stable senescence period, also allows for biosynthesis of lignans in the mesocarp, compared to the near absence of these compounds in other fruits **(Esfahlan et al., 2010).**

Figure 5. Almond's hull (anonym 1)

4.4. Almond's shell

Almond's shell is the name given to the ligneous material forming the thick endocarp or husk of the almond tree fruit. When the fruit is processed to obtain the edible seeds, big ligneous fragments are seated. The high xylene content of almond shells makes them a suitable

substrate for the production of xylose, furfural or for fractionation into cellulose, pentosanes and lignin **(Martinez et al ,.1995, Pou-Ilinas et al,. 1990, Quesada et al,. 2002)**

Figure 6. Almond's shell (anonym 2)

5. The use of almond by-products (hull and skin)

After blanching, the almond skin (seed coat) can be removed and discarded. Total dietary fiber (47.5 and 45.1 g/100 g of blanched and natural skin, respectively), soluble dietary fiber (2.7 and 3.8 g/100 g blanched and natural skin, respectively), lipids (22.2 and 24.2 g/100 g of blanched and natural skin, respectively), and proteins (12.8 and 10.3 g/100 g of blanched and natural skin, respectively) are all present in almond skin. In addition to the fundamental chemical composition, although skin accounts for just around 4.0% of total almond weight and has a relatively low economic worth, a number of recent studies have found that it includes approximately 60.0-80.0% of total phenolic chemicals found in the nut. It is critical to emphasize that phenolic **(Prgomet et al., 2017)**

6. Definition of phenolic compounds

Phenolic chemicals are aromatic secondary plant metabolites that are one of the most abundant categories of plant metabolites. In various plant species, over 8000 polyphenol chemicals have been found. These substances are classified into two groups based on the amount of phenol rings and how these rings interact with metabolites: flavonoids and non-flavonoids.

They are derived from two major synthetic pathways: the sikimate pathway and the acetate process. Polyphenols are a vast heterogeneous collection of chemicals defined by hydroxylated phenyl moieties, an aromatic ring having one or more hydroxyl groups, and

structures that can range from a simple phenolic molecule to a complex high-molecular wright polymer.**(Balasundram et al,. 2006, Martin et al,. 2011, pandey and Rizvi 2009, Cardona et al,. 2013).**

These compounds may be classified into different groups as a function of number of phenol rings that they contain and of the structural elements that bind these rings to one another **(Pandey and Rizvi 2009)**. The main groups of polyphenols are: flavonoids, phenolic acids, tannins (hydrolysable and condensed), stilbenes and lignans. Flavonoids naturally occurring phenolic compounds **(Martins et al,. 2011b).**

7. Role of phenolic compounds

7.1. In plants

Phenolic compounds are important in plants because they act as UV light protectors, participate in growth and reproduction, are components of pigments, essences, and flavors, and contribute to the color, astringency, and bitterness of fruits and vegetables. They also serve as a plant's chemical defense mechanism against infections caused by microorganisms and injuries caused by insects. **(Soto et al,. 2011, Hurtado-Fernandez et al,. 2010)**

7.2. In nutrition and human physiology

Reactive oxygenic species (ROS) in the form of superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (HO) are naturel by-products of human metabolism. However when present in excess, they can attack biological molecules such as lipids, proteins, enzymes, DNA and RNA, leading to cell or tissue injury associated with degenerative diseases **(Barreira et al,. 2008)**. Although the human body has some defense mechanisms to battle and lessen oxidative damage, epidemiological research suggests that eating foods rich in antioxidant phytonutrients, particularly flavonoids and other polyphenols, is beneficial to health. The antioxidant activity of phenolic compounds has been related to their beneficial benefits. In recent studies, there has been an increasing interest in biology and medicine in oxidative stress. Antioxidant supplementation has been shown in studies to be the most effective technique of reducing oxidative stress.**(Esfahlan et al., 2010).** Antioxidants are substances that can delay or limit the oxidation of lipids or other molecules by inhibiting the beginning or propagation of an oxidizing chain reaction. The food sector is quite interesting since it improves the quality and nutritional content of foods. Antioxidants, when added to foods, reduce rancidity, delay the generation of hazardous oxidation products, maintain nutritional quality, and extend shelf life. **(Antolovich et al,. 2002, Proestos and Komaitis 2008).**

8. Phenolic compounds of almond skin

In the industry, almond skin is obtained by blanching or roasting. Upon these processes, the entire almond is subjected to high temperatures (around 100 ◦C for blanching and up to 200 ◦C for roasting) to obtain skinless almond kernels. Even though the almond skin represents just around 4.0% of the total almond weight, 60.0–80.0% of the almond phenolic compounds are distributed within the almond skin. However, thermal processes in the food industry may affect the stability of polyphenols and promote the degradation and loss of bioactive compounds. For instance, albeit subjected to lower temperatures compared to industrial roasting, almond skin polyphenols are easily lost by hot water blanching and demonstrate a lower phenolic content. Furthermore, results from one study suggested that the majority of the phenolic compounds in the kernel itself does not consist of flavonoids. **(Prgomet et al., 2017)**

Recovery of a wide range of compounds. Microwave assisted extraction typically exhibits clear advantages over traditional reflux extraction and soxhlet extraction, including faster extraction times, higher extraction yields, improved selectivity, and better quality of the target extract. When compared to rapid solvent extraction, microwave aided extraction is more cost effective. **(Veggiet al,.2013)**

The MAE system is viewed as a potential method for extracting plants because it uses distinct physical and chemical phenomena than those used in traditional extractions. **(Veggiet al,.2013).**

Section 2. Microwave assisted extraction

1. History

In the past few years, interest in using microwave energy to treat samples has increased**. (Camel, 2000)**. The use of microwave radiation for heating was discovered in 1946, and the first home microwaves were released in 1950 **(Mallakpour and Rafiee, 2011)**. In 1975, Abu-Samra et al. Performed the first experimental trace analysis of metals from biological material using a microwave home oven **(SparrEskilsson and Björklund, 2000).** In 1978, the first commercial microwave for use in laboratories was recognized **(Mallakpour and Rafiee, 2011).** There have been many publications on microwave-assisted extraction of plant secondary metabolites since microwave irradiation was first used to recover significant components from plant materials in 1986. (**Zhang et al., 2011).**

These days, this method is used in a variety of sectors, including organic synthesis, inorganic processes, the creation of catalysts, and analytical chemistry **(Nóbrega et al., 2002).**

2. Microwave

Microwave is an electromagnetic radiation with a wave length from 0.001 m to 1 m (i.e. with a frequency from 3 ×1011 Hz to 3 × 108 Hz), which can be transmitted as the wave **(Zhang et al., 2011).** The wave lengths between 0.01 and 0.25 m are typically used for radar transmissions, and the remaining wavelengths are used for telecommunications. All home microwave ovens and microwave reactors for chemical synthesis run at a frequency of 2.45 GHz, or a wavelength of 12.25 cm. This is done to prevent any cellular phone and telecommunications frequencies from being interfered with. **Fig. 10** displays the microwave portion of the electromagnetic spectrum. As indicated in this figure, this region lies between the infrared and radio frequencies **(Motasemi and Ani, 2012).**

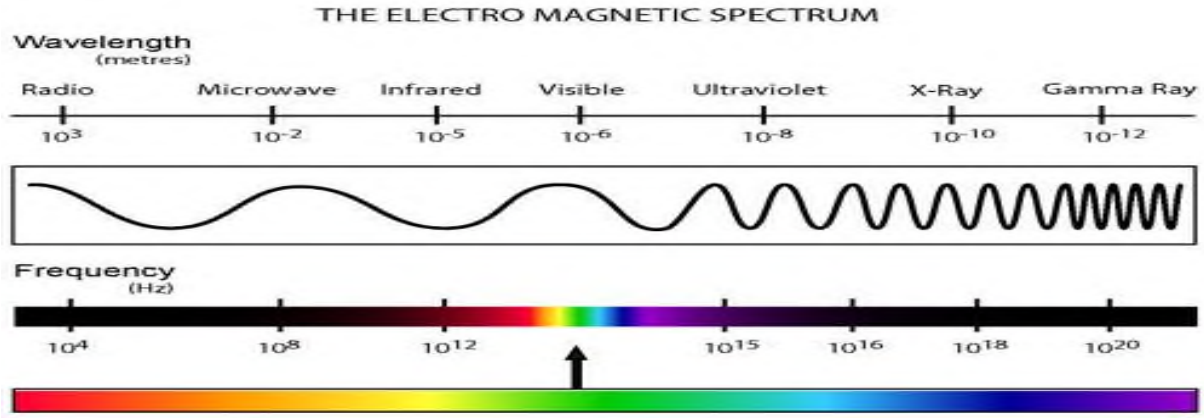


Figure 7. The electromagnetic spectrum **(Motasemi and Ani, 2012).**

3. Principe

Each microwave system consists normally of three basic parts: the microwave source, the wave guide and the applicator **(Routray and Orsat, 2012)** Before the mixture is fed into the equipment, the powdered sample is combined with an exact amount of extraction solvent.. (**Routray and Orsat, 2012)** Process parameters such as solvent choice, temperature, microwave power, and extraction time are crucial influences in MAE. Generally, extraction yields in MAE increase as microwave power increases due to localized heating, which contributes to the rupture of the matrix. However, there is a limit above which microwave power can cause a decrease in extraction yield **(Osorio-Tobón, 2020)**. The direct impact of microwaves on molecules through ionic conduction and dipole rotation is the foundation of the microwave heating theory. Both of these mechanisms operate at the same time. Ions move electrophoretically when an electromagnetic field is applied, which is known as ionic conduction. The solution will become heated as a result of the friction caused by the solution's resistance to the ion movement. Rotating a dipole implies realigning it with the applied field.

The dipoles align and randomize 4.9310 times per second at 2450 MHz, the frequency utilized in commercial devices, and this forced molecular movement causes warmth. **(Eskilsson and Björklund, 2000).** MAE can efficiently extract phenolic compounds from solvents like water, ethanol, methanol, acetone, and their combinations. The most often used method for recovering phenolic compounds from them is a mixture of water and ethanol. **(Osorio-Tobón, 2020)**

Table II. Physical constants and dissipation factors for some solvents commonly used in MAE **(Eskilsson and Björklund, 2000).** In **Table 2,** selected physical parameters, including dielectric constants and dissipation factors, are shown for solvents used in extractions

Solvent	**Dielectric constant ε'**	**Dipole moment**	**Dissipation factor tanδ ($X10^{-4}$)**	**Boiling point (C°)**	**Closed-vesseltemperature**
Acetone	20.7			56	164
Ethanol	24.3	1.96	2500	78	164
Methanol	32.6	2.87	6400	65	151
Water	78.3	2.3	1570	100	156

4. Factors influencing the performance of MAE

The efficiency of MAE strongly relies on the selection of the operating conditions and the parameters affecting the extraction mechanisms and yield. The factors that may influence the performance of MAE are solvent nature, solvent to feed ratio, extraction time, microwave power, temperature, sample characteristic, effect of stirring ....etc. Understanding how these elements affect and interact with the MAE processes is crucial **(chan *et al*,.2011).**

5. Instrumentation

The rapid development in MAE processes has prompted various suppliers to provide improved microwave systems and related instruments for the extraction process. Most of the microwave extractors available are laboratory-built systems based on domestic microwave oven **(chan*et al*,.2011)**

Microwave furnaces consist of three major components; the source, the transmission lines, and the applicator. The microwave source generates the electromagnetic radiation, and the transmission lines deliver the electromagnetic radiation, and the transmission lines deliver

the electromagnetic energy from the source to the applicator in which is the sample to treat **(Cendres 2010).** Moreover, many elements can be added and adapted according to the needs for the experiment **(Cendres 2010).**

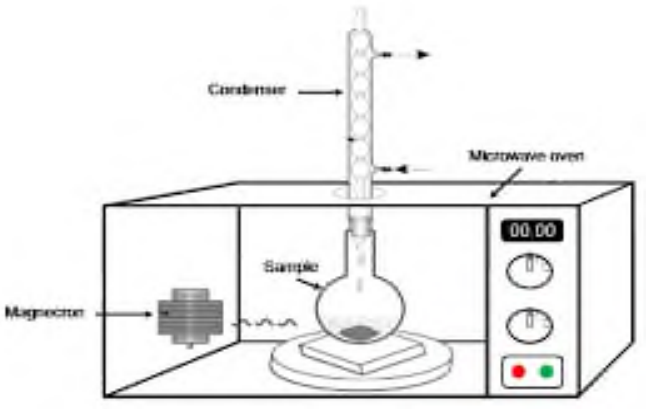


Figure 8. Microwave equipment **(Cendres, 2010).**

6. Advantages of microwave assisted extraction

As previously mentioned, microwave assisted extraction is recognized as a flexible and effective method for extracting secondary metabolites from plants.

CHAPTER II: Response surface methodology and Neural network

Section 1: Response surface methodology

1.1. General information

In analytical chemistry, the phrase optimization is frequently used to describe the process of identifying the variables to apply to a technique in order to get the optimal answer. Response surface methodology (RSM) is one of the most crucial multivariate methods employed in analytical optimization **(Bezerra et al., 2008)**

Response surface methodology (RSM), which was first introduced by Box and Wilson (1951), is a useful approach for process optimization when numerous variables and interactions affect intended production process response **(Sun et al. 2010).**

The analysis of many input variables that affect the performance and quality attributes of the product or process under investigation can be done effectively with the use of the response surface methodology (RSM) technique. In order to analyze relationships between one or more answers (dependent variables) and a variety of factors, the approach offers mathematical and statistical procedures (independent variables). RSM makes it possible to get information faster and for less cost **(Karazhiyan et al. 2011).**

RSM is a group of statistical and mathematical methods for creating, developing, and optimizing procedures **(Şahin and Şamlı, 2013).**

1.2. Terminology

It is important to introduce and define a few essential terminology before starting the discussion on the uses of response surfaces in the optimization of analytical methods.

- **Experimental design**

An experimental design is a particular set of experiments that are defined by a matrix made up of the various level combinations of the variables under study **(Bezerra et al. 2008).**

- **Coded factor levels**

Coded variables are frequently used to describe experimental design **(Hibbert, 2012**). The elements in screening design are typically looked at at two levels (-1, +1). The levels are chosen based on information from the literature or prior knowledge, and the range between them represents the broadest period in which the factor can be altered for the system under

study.**(Vera Candiotiet al. 2014).** Whenever there are multiple variables, each has its own range of variation All values are theoretically feasible inside the field of a continuous factor. In light of the study's requirements, one can however select two, three, or more levels**(Goupy and Creighton, 2006).**

- **Experimental domain**

The experimental domain is the area that needs to be looked into. The minimal and maximal values of the investigated experimental variables serve as its definition **(Bezerra et al. 2008).**

- **Responses or dependent variables**

The measured values of experiment findings are called responses or dependent variables. The analytical signal (absorbance, net emission intensity, and electrical signal), analyte recovery, chromatographic peak resolution, residual carbon percentage, and ultimate acidity are examples of typical reactions.

- **Residual**

For a specific set of conditions, residual is the difference between the calculated and experimental result. A successful mathematical model must have low residual values when it is fitted to experimental data **(Bezerra et al. 2008).**

- **Response surface designs**

With the experimental results of a response surface design, a polynomial model, describing the relation between a response and the considered factors, is build. Usually a second-order polynomial model is constructed.

Afterwards, the model can be interpreted graphically and/or statistically. Graphically, the model is visualized by drawing 2D contour plots or 3D response surface plots. A 2D contour plot (Figure.12a) shows the isoresponse lines as a function of the levels of two factors, while a 3D response surface plot (Figure.12b) represents the response in a third dimension. From such plots, often the best or optimal conditions are derived. However, one should be aware that, in case three or more factors are considered, a plot as in Fig. 5 only represents a part (occasionally a very small) of the entire response surface in the examined domain. The fit of the model to the data can be evaluated statistically applying either. Analysis of Variance (ANOVA), a residual analysis, or an external validation using a test set. One also can

determine the significance of the b coefficients and then eliminate the non-significant ones, for instance, sequentially.

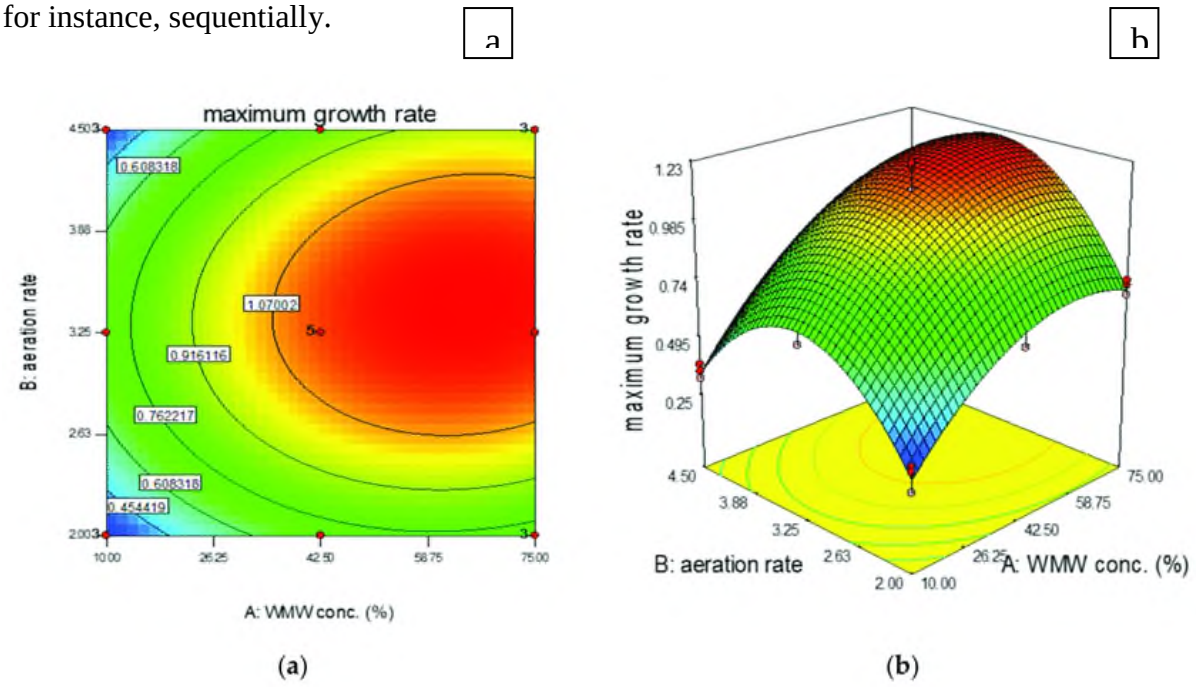


Figure 9. (a) 2D contour plot, and (b) 3D response surface plot

1.3. Steps for RSM application

Here are some stages in the use of RSM as an optimization method:

1.3.1. Screening of variable

Numerous variables may affect the response of the system studied, and it is practically impossible to identify and control the small contributions from each one. Therefore, it is necessary to select those variables with major effects. Screening designs should be carried out to determine which of the several experimental variables and their interactions present more significant effects. They are applied in the context of optimizing separation techniques during screening and in robustness testing, and in the context of optimizing formulations, products, or processes. Most often, two-level screening designs, such as fractional factorial or Plackett–Burman designs are the most widely used in the step of selection of factors because they are economic and efficient **(Bezerra et al., 2008; Dejaegher and Vander Heyden, 2011; Hibbert, 2012; Vera Candioti et al., 2014).**

1.3.2. Choice of the experimental designe

The most ideal operating conditions are reached by using more sophisticated experimental designs, such as central composite designs (CCD), Box-Behnken designs (BBD), or

Doehlertmatrices (DM), after the significant factors have been identified **(Ferreira et al. 2007a)** In contemporary, commercial statistical computer tools, the researcher is given with a variety of designs to choose from. These designs vary from one another in terms of the amount of runs, blocks, and experimental points they choose. **(Baş and Boyacı, 2007).** Two of the most common design generally used in response surface modeling of extractions are central composite and Box–Behnken design

- **Centralcomposite design**

A central composite design (CCD) contains a two-level full factorial design (2f experiments), a star design (2f experiments) and a centre point, requiring N = 2f + 2f + 1 experiments to examine f factors. Thus for two factors, 9 experiments are needed, while for three factors, 15 are needed (Figure 13 and Table 3). The points of the full factorial design are situated at the factor levels −1 and +1, those of the star design at the factor levels 0, −α and +α, and the centre point at the factor levels 0. Depending on the α value, two CCD's exist, i.e. a face-centred CCD (FCCD) with |α|= 1 examining the factors at three levels, and a circumscribed CCD (CCCD) with |α|> 1 examining the factors at five levels. For a so-called rotatable CCCD, the α level should be |α| = (2f) 1/4, i.e. 1.41 and 1.68 for 2 and 3 factors, respectively (RS2). The CCD requires minimal experiments while producing results that are comparable to those of the full factorial, three-level design, making it a better choice. **(Hibbert, 2012)**

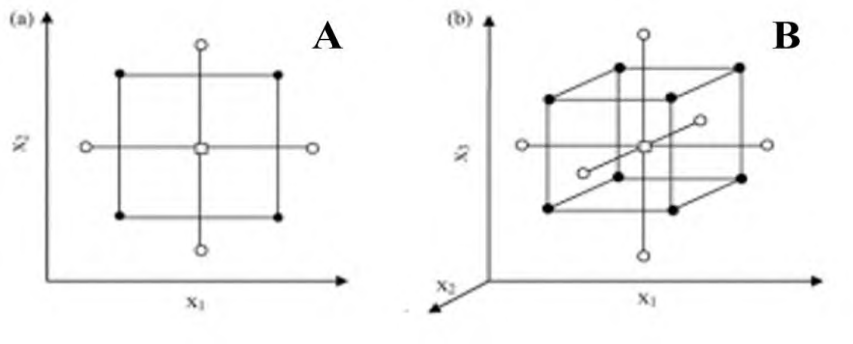


Figure 10: Central composite designs for the optimization of: (A) two variables (α= 1.41) and (B) three variables (α = 1.68). (○) Points of factorial design, (●) axial points and (□) central point **(Bezerra et al. 2008).**

Table III. Central composite design for 3 factors. Etc. refers to possible replicates of the center point.

EXPERIMENTS	**FACTORS**		
	A	**B**	**C**
1	-1	-1	-1
2	1	-1	-1
3	-1	1	-1
4	1	1	-1
5	-1	-1	1
6	1	-1	1
7	-1	1	1
8	1	1	1
9	-α	0	0
10	+α	0	0
11	0	-α	0
12	0	+α	0
13	0	0	-α
14	0	0	-α
15, etc.	0	0	0

- **Box-Behnkendesign**

A Box–Behnken design contains N = (2f (f−1)) + 1 experiments, of which one centre point. For two factors, no design is described. For three factors, 13 experiments are described to be performed **(Figure. 14 and Table IV)**. This experimental approach has been used to optimize a number of physical and chemical processes, although its use in analytical chemistry is still far less common than that of central composite design **(Ferreira et al. 2007a).**

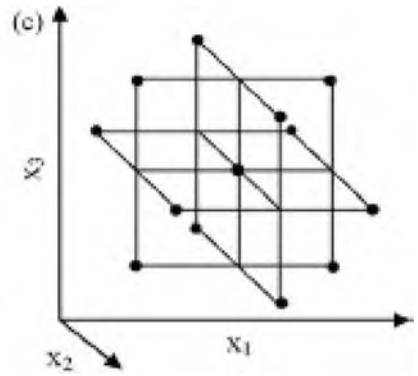


Figure 11. Box–Behnkendesign to examine three factors in 13 experiments **(Bezerra et al. 2008)**

Table IV. Box–Behnken design for 3 factors. Etc. refers to possible replicates of the center point **(Ferreira et al. 2007b).**

EXPERIMENTS	**FACTORS**		
	A	**B**	**C**
1	1	1	0
2	1	-1	0
3	-1	1	0
4	-1	-1	0
5	1	0	1
6	1	0	-1
7	-1	0	1
8	-1	0	-1
9	0	1	1
10	0	1	-1
11	0	-1	1
12	0	-1	-1
13, etc.	0	0	0

1.3.3. Determination of the model equation

The simplest model which can be used in RSM is based on a linear function. For its application, it is necessary that the responses obtained are well fitted to the following equation: $y = \beta 0 \sum k\ i=1 \beta iXi + \varepsilon$ (1) where k is the number of variables, β0 is the constant term, βi represents the coefficients of the linear parameters, xi represents the variables, and ε is the residual associated to the experiments.

As a result, there shouldn't be any curvature in the replies. A second-order model must be applied in order to assess curvature. When extra effects, such as second-order effects, are significant, two-level factorial designs—which are used to estimate first-order effects—fail. In two-level factorial designs, curvature can therefore be assessed at a central point. There should be more terms in the polynomial model's subsequent level that describe how the various experimental variables interact with one another. This way, a model for a second-order interaction presents the following terms:

$y=\sum \beta iXi + \sum 1 \leq i \leq j \beta ijXiXj + \varepsilon$ (2)

Where βij represents the coefficients of the interaction parameters.

In order to determine a critical point (maximum, minimum, or saddle), it is necessary for the polynomial function to contain quadratic terms according to the equation presented below:

$y = \beta 0 + \sum \beta iXi \sum k\ i=1\ \beta iiXi\ 2 + \sum k\ 1 \leq i \leq j\ \beta ijXiXj + \varepsilon$ (3)

Where βii represents the coefficients of the quadratic parameter.

To estimate the parameters in Eq. (3), the experimental design must ensure that all variables are applied to at least three factor levels. **(Bezerra et al. 2008).**

1.3.4. Model fitting evaluation

Sometimes the experimental domain under study cannot be adequately described by the mathematical model developed after fitting the function to the data. The use of analysis of variance (ANOVA). is the more trustworthy method to assess how well the model was fitted

The main goal of an analysis of variance (ANOVA) is to contrast the variation resulting from the treatment (a change in the combination of variable levels) with the variation resulting from random mistakes that are a natural part of the measuring process for the generated responses. This comparison allows one to assess the relevance of the regression used to

predict answers while taking into account the sources of experimental variance. **(Bezerra et al. 2008).**

Another approach to judge the model is if it fails the fit test. It describes how the data vary around the fitted model. If a model reveals both a significant regression and a non-significant lack of fit, it will be well matched to the experimental data. In other words, the regression equation must adequately capture the majority of the observed variation, and the residuals will definitely account for the remaining variation. The majority of residual variance is caused by pure error (random variation in measurements) rather than a lack of fit, which is directly connected to the quality of the model. **(Bezerra et al. 2008).**

1.3.5. Determination of the optimal conditions

The surfaces produced by linear models can be used to show the original design's displacement in order to achieve the ideal conditions. The best operational state must be found inside the examined experimental condition by visual inspection, however, if the experimental region cannot be moved for practical or technical reasons. The residual, for a particular set of conditions, is the variation between the calculated and experimental result. A successful mathematical model must have low residuals value when fitting experimental data. **(Bezerra et al. 2008)**

Section 2: Artificial Neural network

2.1. History

In the 1940s, scientists working to replicate how the human brain works created basic hardware (and later software) models of biological neurons and the systems that control their interactions. The first comprehensive analysis of the artificial neural network was published by McCulloch and Pitts. The same authors investigated single layer perceptron-based network paradigms for pattern recognition four years later. These biological and psychological discoveries were combined by a group of researchers in the 1950s and 1960s to create the first artificial neural network (ANN)**(Zilouchian, 2001)**

2.2. Similarities between Biological neural networks (BNN) and artificial neural networks (ANN)

2.2.1. Biological neuron

The human nervous system consists of billions of neurons of various types and lengths relevant to their location in the body. Every neuron shares many characteristics with other cells of the human body but it has particular and special properties to receive process and transmit an electric signal through all the interconnections of the brain communication system. Some neurons are connected with receivers or effectors and others are connected to transmit and process information. The area of connection is called a synapse and binds the axon of a neuron with dendrites of the adjacent as shown in **Figure 15**. The information is transmitted from one neuron to another. This information is transmitted in the form of impulses through the dendrites. Impulses tend to excite the cell. When the excitation accumulated exceeds a threshold value, the neurons send a signal through the axon to other neurons. The majority of the ANN models present the basic operation of the neuron (**Funes, E et el,. 2015)**

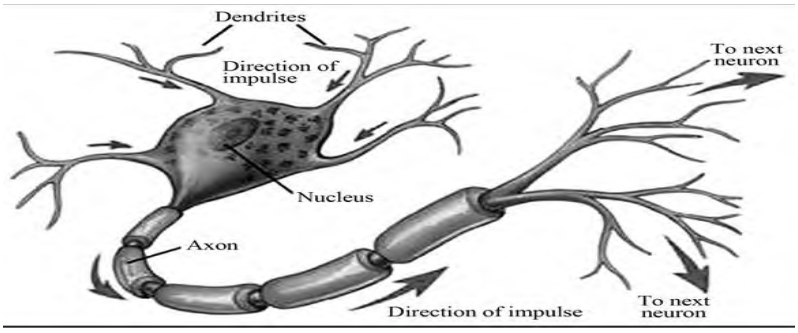


Figure 12. Structure of a biological neuron. To can compare the performance of artificial neural it must know the structure of a biological neuron (**Funes, E et el,. 2015)**

2.2.2. Artificial neuron

Models called artificial neurons make an effort to imitate the actions of biological neurons. Each neuron is represented by a processing unit that is a component of the neural network, a bigger entity. Generally speaking, each neuron communicates with other neurons via its axon, and the axon receives information via potential differences or power waves, depending on the potential of the neuron. Its synapses add all excitatory impacts to the input signals before simulating it with positive weights and inhibiting it with negative weights. The neuron delivers a signal to neighboring neurons via its output synapse if positive excitatory effects are predominate. As seen in **Figure 16**, these entries Xi make up this process unit (artificial neuron).

They receive information in the form of stimulation at (x1, x2,...xn), which are equivalent to the dendrites. The weights that are present in synapses are equivalent to transmitting mechanisms in real neurons. The chemical impulses that occur at synapses and cause neurons to modify their behavior are equaled by these values (Xi and Wi). These numbers serve as the entry point for the network weighting algorithm, which transforms them into potential. (**Funes, E et el,. 2015)**

This potential is equal to the total amount of signals received by a biological neuron through its dendrites. The synaptic weights and input weights are added together to create the weighting function. The activation function turns this value into another form so that the output neurons can work, and here is where the weighting function gets its output. The activation function that results in the output of this neuron's signal to a neighboring neuron evaluates the output network. The ability to provide results in a variety of ways will provide the activation function **(Table 1)**. In conclusion, the synthetic neuron mimics the behavior of a real neuron in a very simplified manner. (**Funes, E et el,. 2015)**

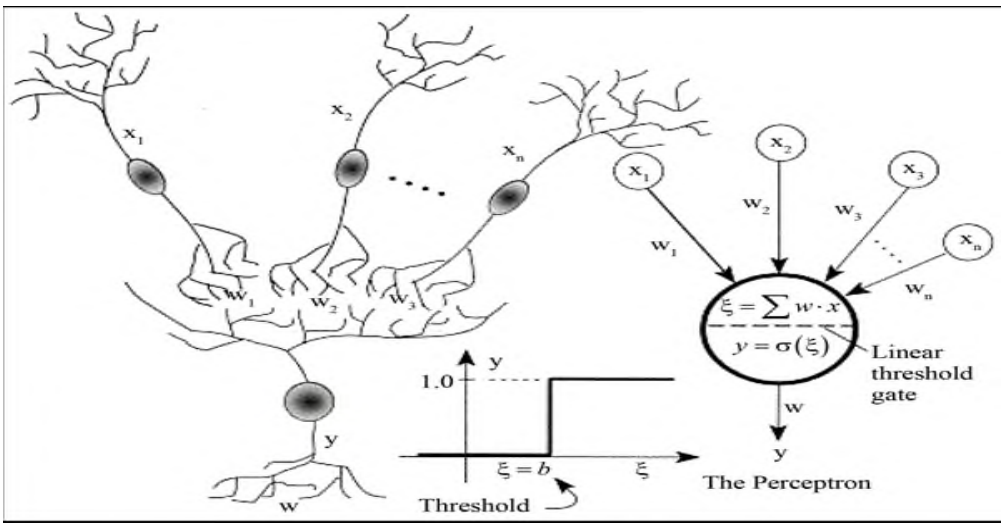
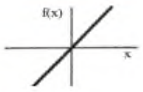
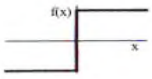
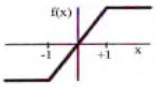
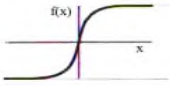
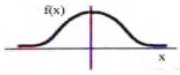
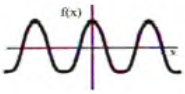


Figure 13. Similarity among a biological neuron and an artificial neuron. In this figure it can observe the difference and similarly between both neuron (**Funes, E et el,. 2015)**

Table V. Roles of activation of an artificial neural network. These roles are necessary can activate an ANN. According the use of which network the role will be different (**Funes, E et el,. 2015)**

Name	Formula	Range	Graphical
Identity	$y = x$	$[-\infty, +\infty]$	
Unit step	$y = sign(x)$ $y = H(x)$	$\{-1, +1\}$ $\{0, +1\}$	
Piecewise linear	$y = \begin{cases} -1, \text{si } x < -l \\ x, \text{ si } +l \le x \le -l \\ +1, \text{si } x > +l \end{cases}$	$[-1, +1]$	
Sigmoid	$y = 1/(1 + e\,\hat{}\,(-x))$ $y = tgh(x)$	$[0, +1]$ $[-1, +1]$	
Gaussian	$y = Ae^{-Bx^2}$	$[0, +1]$	
Sinusoidal	$y = A\sin(\omega x + \varphi)$	$[-1, +1]$	

2.3. Deep neural network

Deep neural networks (DNN) include the input and output layer, multiple hidden layers. DNNs can deal with linear or non-linear problems by computing the probability of each output layer by layer through appropriate activation function. DNNs are usually applied

in image understanding and speech recognition, and so on. DNNs essentially are full-connected neural networks. Deep neural network is sometimes called multi-layer perceptron (MLP). The input feature vectors transformed by the hidden layer, then reach to the output layer, finally get the classification result. It was a linear classification model of two categories, mainly used for linear classification and its classification ability was limited. The early discrete transfer functions have some shackles for multiplayer perceptron, so we can use some continuous functions to avoid this problem, e.g. tanh function or sigmoid function. DNNs can be constructed through adding the number of neurons and hidden layers**(Mu and Zeng, 2019)**

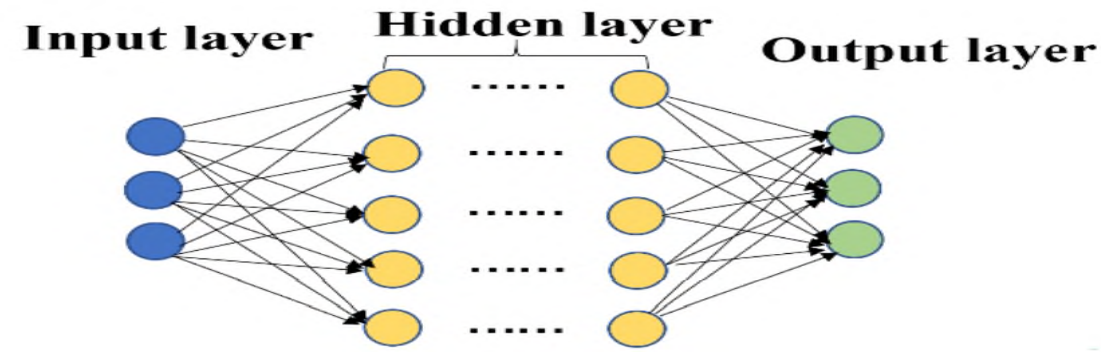


Figure 14. Deep neural network structure**(Mu and Zeng, 2019)**

- **Input layer:** A layer of neurons that receives information from external sources, and passes this information to the network for processing. These may be either sensory inputs or signals from other systems outside the one being modeled.
- **Hidden layer:** A layer of neurons that receives information from the input layer and processes them in a hidden way. It has no direct connections to the outside world (inputs or outputs). All connections from the hidden layer are to other layers within the system.
- **Output layer:** A layer of neurons that receives processed information and sends output signals out of the system. Bias: Acts on a neuron like an offset. The function of the bias is to provide a threshold for the activation of neurons. The bias input is connected to each of the hidden and output neurons in a network.**(Zilouchian, 2001)**

2.4. Process of learning

Learning ANN consists in determining precise values of weights for all connections, all trained for the efficient resolution of a problem. During the training session, the weights

converge gradually to the values that make each entry to produce the desired output vector. The end of the learning period can be determined:

• using a number fixed cycles,

• When the error falls below a preset amount,

• When the modification of the weights is irrelevant.

Depending on the scheme of learning and the problem to be solved, three types of learning schemes can be distinguished:

- **Supervised learning:** In the supervised knowledge the training is controlled by an external agent (supervisor, teacher), which watches the answer that the network is supposed to generate from a determined entrance. The supervisor compares the output of the network with the expected one and determines the amount of the modification to be made in the weight. The objective is to decrease the difference between the answer of the network and the desired values. For example the ANN that uses this type of learning is Adeline, MPL, BP, and Associative Memory Bi-directional.
- **Unsupervised learning:** The ANNs with unsupervised learning (also known as self-supervised) do not require any external element to adjust the weight of the communication links to their neurons. The main problem in the unsupervised classification is to divide the space where the objects are in groups or categories. The ANN that use this type of learning are Hopfield, Machines Boltzmann and Cauchy, networks with competitive learning, such as SOM and ART.**(Funes et al., 2015)**

2.5. Applications of neural networks

The ANNs are an emerging computer technology that can be used in a large number and variety of applications such as, control, monitoring and modeling, recognition, detection an research for patterns, predicts on-line, image processing, optimization and signal processing. This applications can use in several fields as production of manufacturing, agriculture…, business, marketing, medicine, transports, energy, trade the greater, etc… In this paper, we can see some examples, what use has artificial neural network in different food industry.**(Funes et al., 2015)**

CHAPTER III: Materials and methods

1. Plant material

The fruit samples of almond (*Prunusamygdalus*) were collected by hands in the area of El Kseur (Bejaia. Algeria) in July 2021. The almonds fruits were immersed in hot water in order to easily remove the skin. After, this later was dried for about 1 day in a stove at 40 ± 1 C°. Dried by-product was ground with an electrical grinder (IKA model-A11, Staufen, Baden Württemberg, Germany). The powder obtained was passed through 125µm sieve. The moisture of the samples of almond's skin was measured after maintaining samples in a stove at 103 ± 2 °C until it reached constant weight. The result is average of three samples.

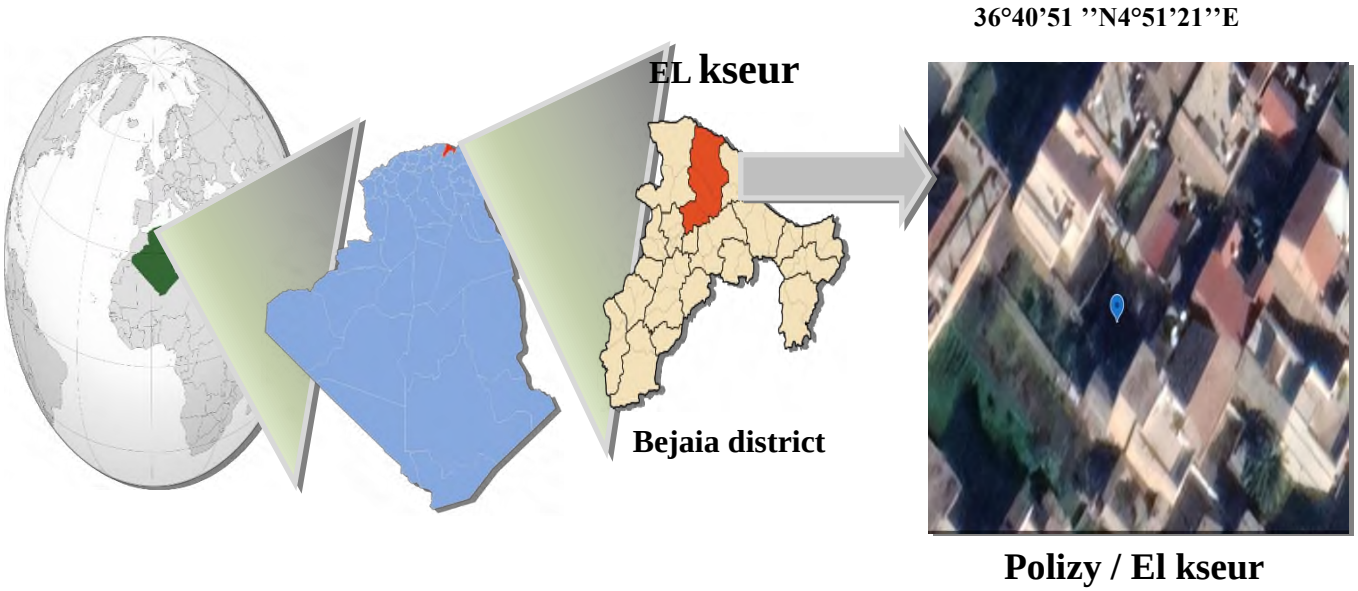


Figure 15. Sample collection area (Polizy / El kseur)(The geographical position is according to Google maps)

2. Extraction procedure

A domestic microwave oven (NN-S674MF, Samsung, Malaysia) with cavity dimensions of 22.5 cm × 37.5 cm × 38.6 cm and 2.45 GHz working frequency was used. The apparatus was equipped with a digital control system for irradiation time and microwave power (the latter linearly adjustable from 100 to 900 W). The oven was modified in order to condensate into the sample the vapors generated during extraction giving a constant sample

volume. For the extraction, 0.5 g of the sample was placed in a round-bottom flask with 30 ml of solvent. The flask was placed in a microwave oven and connected to condenser. Then, the extract was filtered hrough a Whatman No. 1 filter paper the supernatant was collected in a volumetric flask. The extract was stored at 4 °C until further use.

3. Determination of TPC content

TPC content was determined by the Folin–Ciocalteu method reported by **(Dahmoune et al., 2013**). One milliliter of Folin–Ciocalteu reagent (diluted ten times by water) was mixed with 200 µL of the extract. After 5 min, 1 mL of aqueous solution of sodium carbonate (6%) was added. The mixture was kept for 30 min at room temperature. Absorbance was measured at 750 nm using a UV–Vis spectrophotometer (Model: SpectroScan 50, Nicosia, Cyprus)..The absorbance of the extract was compared with a gallic acid standard curve for estimating concentration of TPC in the sample. The TPC was expressed as mg of gallic acid equivalents (GAE) per gram of powder on dry weight (DW) basis.

4. Determination of antioxidant activity

4.1. Total antioxidant activity

The total antioxidant capacities of the samples were evaluated by the method reported by Sethiya et al. (2014) . An aliquot of 200 µL of the sample solution (three replicates) was mixed with 2 mL of the reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate and 4 mM ammonium molybdate). The mixture was stirred and incubated in water bath at 90°C for 90 mn. For the blank, ethanol was used instead the sample. The absorbance of the sample was measured at 695 nm

4.2. DPPH radical scavenging activity

The antioxidant activity (AA) of the extracts was estimated by the DPPH method, according to the procedure described by**(Haddadi-Guemghar et al., 2014).** An aliquot of 0.5 mL of sample solution was mixed with 1.5 mL of ethanolic solution of DPPH (0.2 mM). The reaction mixture was incubated for 30 min in the dark at room temperature. The absorbance of the resulting solution was measured at 515 nm using a UV–Vis spectrophotometer. Ethanol instead of sample solution was used as a control. The AA of the tested samples was measured as a decrease in the absorbance and was calculated using the equation Eq. (1).

$$\text{TAA (\%)} = \frac{Ac - As}{Ac} \times 100 \quad \text{(Eq1).}$$

Where A_c and A_s are the absorbance at 515 nm of the control and sample, respectively.

4.3. Ability of chelating ferrous ions

The Fe2+-chelating ability of the extracts were measured by the ferrous iron–ferrozine complex method **(Decker and Welch, 1990)**. The extracts were dissolved with methanol to prepare various sample solutions at 10, 8, 6, 4, and 2 mg/mL. The reaction mixture containing 2mM FeCl2 (0.05 mL) and 5mM ferrozine (0.2mL) and the extract solution (0.8 mL) at various concentrations was mixed and then incubated for 10 min at 25°C. The absorbance of the reaction was recorded at 562 nm. The absorbance of the control was determined by replacing the sample with methanol. Ascorbic acid and α-tocopherol were used as positive control. The ability of the extract to chelate ferrous ion was calculated using the equation

(%) = [(A562 of control_A562 of sample)/A562 of control]x100

4.4. Hydroxyl radicals scavenging activity

The hydroxyl radicals scavenging activity were determined by an improved Fenton-type reaction **(Yin et al., 2018)**. 1 mL sample of different concentrations mixed with 1 mL FeSO4 (9 mM), 1 mL salicylic acid-ethanol (9 mM) and 1 mL H2O2 (9 mM), respectively. Then the mixtures incubated at 37 °C for 30 min. Finally, the absorbance of mixture was measured at 510 nm. The radical scavenging capacity of HO• was calculated using the following equation:

$$\text{Hydroxyl radicals scavenging rate\%} = \frac{A_0\left(A_i - A_j\right)}{A_0} \times 100$$

Where Ai is the absorbance of the sample, and Aj is the absorbance of the control (distilled water instead of the H2O2). A0 is the absorbance of the blank (distilled water instead of the sample)**.**

5. Antidiabetic activity

A total of 500 µL of extract (0.6-1.4mg/mL) was placed in a test tube and 500µL of 0.02 M sodium phosphate buffer (pH 6.9) containing α-amylase solution was added. This solution was pre-incubated at 25°C for 10 min, after which 500µL of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added at timed intervals and then incubated at 25 °C for 10 min. The reaction was terminated by adding 1000 µL of dinitrosalicylic acid (DNS) reagent. The tubes were then incubated in boiling water for 5 min and cooled to room temperature. The reaction mixture was diluted with 10 mL distilled water and the absorbance was measured at 540 nm using a spectrophotometer (Biowave II, Biochrom, UK). The control was prepared using the same procedure replacing the extract with distilled water while activity of the standard was tested by replacing the extract with acarbose (0.6–1.4mg/mL)**(Kazeem and Ashafa, 2015)**. The a-amylase inhibitory activity was calculated as percentage inhibition, thus;34

$$\text{Antidiabetic activity (\%)} = \frac{\text{As} - \text{Ac}}{\text{Ac}} \times 100$$

Concentrations of extracts resulting in 50% inhibition of enzyme activity (IC50) were determined graphically.

2. Experimental design and statistical analysis

2.1. Response surface methodology

A central composite design (CCD) which contains a two-level full factorial design (2f experiments), a star design (2f experiments) and center points was used in this study in order to optimize microwave assisted extraction of total phenolic compounds from almond's skin. Three factors which affect extraction yield were arranged at three levels, with six replicates at thecentral point (20 runs). The coded variables were used instead the real variables to normalize extraction parameters. The table 1 shows experimental design built by JMP software. The optimization model which can describe the relation between extraction parameters (microwave power *A*, extraction time *B* and ethanol concentration *C*) and the yield of TPC extraction by microwaves was fitted to quadratic polynomial equation (Eq. 1)

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_{11} A^2 + \beta_{22} B^2 + \beta_{33} C^2 + \beta_{12} AB + \beta_{13} AC + \beta_{23} BC \quad \text{Eq.1}$$

where *Y* is the predicted response of TPC, $\beta_0$is the intercept coefficient, β_1, β_2 and β_3 are the linear coefficient, β_{11}, β_{22} and β_{33} are the quadratic coefficient, β_{12}, β_{13} and β_{23} are the interaction coefficient, and X_1, $X_2$and X_3 are coded independent variables.

Analysis of variance (ANOVA) was used to statistically test the results, with a significance threshold of 0.05. According to the calculated coefficient of multiple determination (R^2), coefficient of variance (CV), and *p-values* for the model and lack of fit testing, the model's suitability was determined.

2.2. Artificial Neural Network

Artificial neural networks (ANNs) are mathematical representations of the biological nervous system's operation that were developed in the field of artificial intelligence. ANNs have shown to be an effective modeling method for complex and nonlinear problems. Effectively, Due to their structure and underlying principles, artificial neural networks have many characteristics with the brain, including their capacity to learn from experience.

The response output of TPC yield was predicted using the JMP software utilizing the same data used for RSM modeling. Two thirds of this data set were used to training the ANN while the remainder of the data was employed to validate the model.

ANN model was developed by a back-propagation learning algorithm; this learning algorithm consists of three steps: computing output values and estimating weights and biases; correcting calculation errors on return trips to the network that act in the direction of the negative gradient; and updating the weights (ref).

For assessing the statistical significance of the created ANNs models, the determination coefficient (R2), the root mean square error (RMSE), the Log likelihood test, Mean Absolute Deviation (MAD), and Sum of Squar Error (SSE) of the function were used.

CHAPTER IV: Results and discussion

1. Optimization of MAE procedure by RSM

1.1. Fitting the model

In RSM, natural variables are transformed into coded variables that have been defined as dimensionless with a mean zero and the same spread or standard deviation **(Liyana-Pathirana and Shahidi, 2005)**. There are many factors that affect extraction efficiency of MAE **(Hayat et al., 2010)**. It was necessary to investigate the extraction variables in order to determine the best combination of variables for the best extraction yield. In this study, three independen variables; microwave power, irradiation time and solvent concentration, that affect MAE of antioxidants from almonds by-products were optimized using CCD. The extraction efficiency of the microwave process was estimated by measuring TPC yield of almond's skin extract. Following the experimental design by CCD, twenty runs of the extraction including six replicates of the center points were conducted **(Table V1)**

Table V1: Three-level, three-variable experimental design applied for MAE and experimentally observed values of investigated response TPC

Microwave power (W)	Extraction time (s)	Ethanol concentration (%)	Experimental (mg GAE/100g DW)
300	30	0	41.04
600	120	40	485.65
900	30	80	373.46
900	210	0	109.78
600	120	40	452.63
300	210	80	388.56
600	120	40	499.66
300	30	80	262.65
300	210	0	20.52
900	210	80	246.24
600	120	40	451.44
900	30	0	150.82
600	120	80	415.53
300	120	40	423.73
600	120	0	141.57
600	30	40	486.23
600	210	40	435.56
600	120	40	480.71
900	120	40	460.67
600	120	40	419.63

During the optimization of the process from 0.5 g of almond's skin with 30 mL. of solvent, the TPC obtained were between 20.52 to 499.56 mg GAE/100g DW.

Table VI. Experimental design with the observed responses of total phenolic compounds (TPC) viekd from almond's skin extracts using microwave-assisted extraction (MAE).

The ANOVA results for the quadratic model based on TPC, are summarized in **Table VII.** The fitness of the model was evaluated by the lack of fit test ($p > 0.05$). Statistical analysis

indicated that the proposed model was adequate, possessing no significant lack of fit ($P > 0.05$) and with satisfactory values of the R^2.

The adjusted coefficient of determination ($adj.R^2$) indicates that the model accurately represents the relationship between the chosen parameters (Hayate Haddadi-Guemghar et al., 2014; Jing Wang et al., 2008). The $adj.R^2$ of TPC 0.96 (Table 2), which indicate that the accuracy and general availability of the polynomial models are adequate. Predicted R-squared ($Pred.R^2$) is a measure of how good the model predicts a response value. The $Adj.R^2$ and Pred. R^2 should be within approximately 0.20. If they are not, there may be a problem with either the data or the model. The Pred. R^2 (0.78) is in reasonable agreement with the $Adj.R^2$ Adequate precision measures the signal to noise ratio. A ratio greater than 4 is desirable, thus, a ratio of 20.24 indicated an adequate signal model

Coefficient of variation (CV) describes the extent to which the data were dispersed. In general, a small value of CV gives a better reproducibility, and a high CV value indicates that variation in the mean value is high and does not satisfactorily develop an adequate response model (Liyana-Pathirana and Shahidi, 2005). The CV value was within the acceptable range

1.2. Mathematical model and influence of extraction parameters

The quadratic model calculated for TPC yield after neglecting the statistically insignificant terms ($p > 0.05$) was:

$$Y = +477.33 + 1222.27C - 32.21AB - 28.82AC - 43.70A^2 - 207.35C^2$$

Where Y is the TPC yield and A, B, and C are the coded values of microwave power, irradiation time and ethanol concentration, respectively

The significance of each coefficient was determined using the F-test and *p*-value and it is shown in **Table VII**. The corresponding variables would be more significant if the absolute F-value becomes greater and the *p*-value is smaller **(Gan and Latiff, 2011)**.The *p*-value less than 0.05 indicates that model terms are significant. In this case, ethanol concentration (C) and its quadratic term (C^2) was the major factor affecting the extraction of TPC followed by interaction terms of microwave power with irradiation time (AB) and microwave power with ethanol concentration (A). It can be seen that irradiation time(A) did not influence the extraction yield but its quadratic term did it.

Table VII. Estimated regression coefficients for the quadratic polynomial model and the analysis of variance (ANOVA) for the experimental results of TPC using a quadratic response surface model

Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**Prob > F**	
Model	4,91E+05	9	54567,79	52,2	< 0.0001	significant
A-Microwave power	4180,8	1	4180,8	4	0,0734	
B-Extraction time	1289,13	1	1289,13	1,23	0,2928	
C-Ethanol concentration	1,50E+05	1	1,50E+05	143,02	< 0.0001	
AB	9360,54	1	9360,54	8,95	0,0135	
AC	6644,16	1	6644,16	6,36	0,0303	
BC	453,76	1	453,76	0,43	0,5249	
A^2	5251,76	1	5251,76	5,02	0,0489	
B^2	1719,5	1	1719,5	1,64	0,2286	
C^2	1,18E+05	1	1,18E+05	113,11	< 0.0001	
Residual	10453,05	10	1045,31			
Lack of Fit	8475,73	5	1695,15	4,29	0,0681	not significant
Pure Error	1977,32	5	395,46			
Cor Total	5,02E+05	19				
R^2	0.97					
Adj R^2	0,96					
Pred R^2	0,78					
Adeq precision	20,24					
CV (%)	9,53					

1.3. Response surface analysis

The best way to visualize the influence of the independent variables on the dependent one is to draw response surface plots of the model **(Wei et al., 2009)**. Response surface methodology plays a key role in identifying the optimum values of the independent variables efficiently, under which dependent variable could reach the maximum **(Sun et al., 2010).**

The 3D response surface plots are the graphical representations of regression equation. They provide a method to visualize the relationship between response and experimental levels of each variable and the type of interactions between two variables. RSM design with 20 experiments was employed to optimize three variables including; microwave power, irradiation time and solvent concentration, aiming at obtaining the highest The effects of microwave power (A) and irradiation time (B) on the TPC of the almond's skin extracts are reflected in **Figure 19.** The independent variables A and B had a significant effect ($p < 0.05$) on the TPC. As A and B increase, the TPC sharply increased, achieving saturated value when the extraction was performed for 210 s at 800 W. The experimental results demonstrate that an increase in the microwave power from 400 to 800 W over a period of 210 s improves TPC yield up to 35.15%. High microwave power can bring up the temperature of the system and result in the increase of the extraction yield until it becomes insignificant or declines. It is known that the temperature is controlled by incident microwave power that controls the amount of energy provided to the matrix, which is converted to heat energy in the dielectric material. At high temperatures the solvent power increases because of a drop in viscosity and surface tension, facilitating the solvent to solubilize solutes, and improving matrix wetting and penetration **(Veggi et al., 2013)**. Also, rapid rupture of the cell wall takes place at a higher temperature when using higher power

The total phenol content increased with increasing time **(Şahin et al., 2013)**, at higher long time heating might make phenolics dissolve and diffuse quickly and thoroughly**(Wang et al., 2013)**.

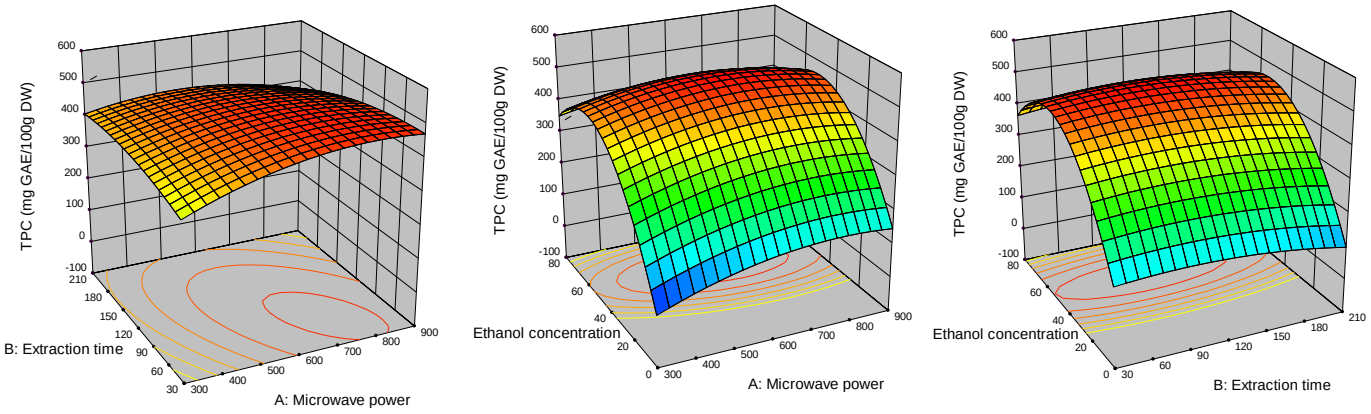


Figure 16. Response surface analysis for the total phenolic yield from almond skin with microwave assisted extraction method with respect to microwave power; extraction time and ethanol concentration, according to the RSM model.

1.4. Optimal extraction conditions

Using a quadratic model to describe the experiment, three experimental variables for maximum extraction of phenolic compounds from almond skin were optimized. Optimization using the desirability function **(Figure 17)** indicated that the optimal conditions for extraction of phenolic compounds with a desirability of 0.89 were as follows:

Microwave power: 661W.

Extraction time: 91.42mn

Ethanol concentration: 50.99%

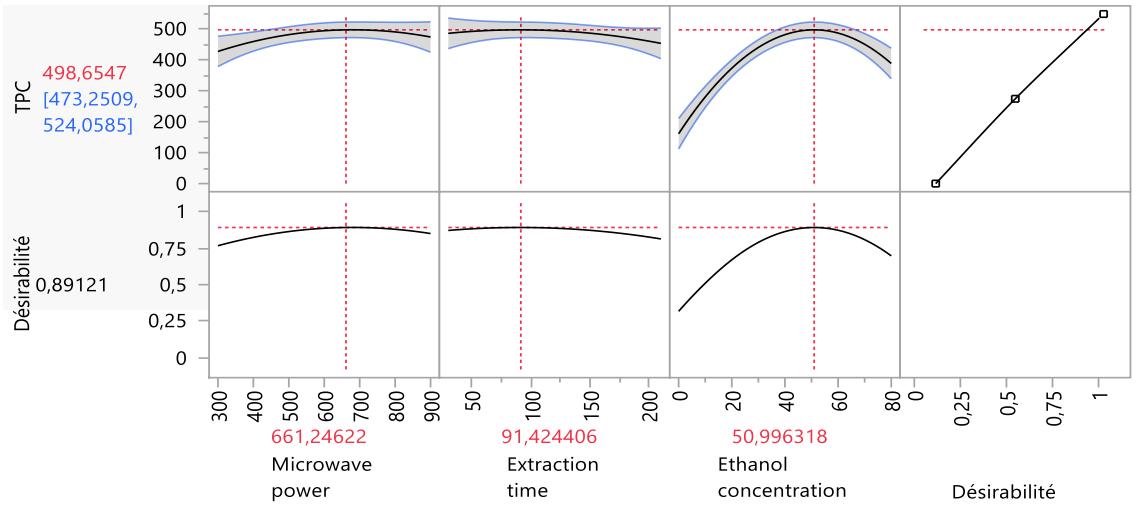


Figure 17. Profiler of prediction value and desirability function by response surface methodology

2. Optimization of MAE procedure by ANN

2.1. Development of the ANN model

The right network size should be chosen carefully while using ANN modeling. The network's performance won't be satisfactory if it has a very small network size (a few neurons in the hidden layer). In contrast, if the hidden layer contains an excessive number of neurons, the training will take a very lengthy time and could be hampered by local minima or over-fitting **(Ghoreishi and Heidari, 2013)**.

The performance of an artificial neural network (ANN) model (MLP: multi-layer perceptron) was improved by adjusting the neurons number of hidden layer and activation functions to best fit the training data and experimental results.

Three inputs (MAE process parameters) and one output (Total phenolic compounds yield) were used to generate the ANN model with one hidden layer. The hidden layer's neuron count was adjusted from one to ten, and each network was repeated five times with initial biases and weights that were chosen at random. A hidden layer with six neurons and gaussian activation function **(figure 21)** were choose as the best neuron network architecture giving the satisfactory statistical parameters between predicted and experimental points in both training and validation test **(table VIII)**

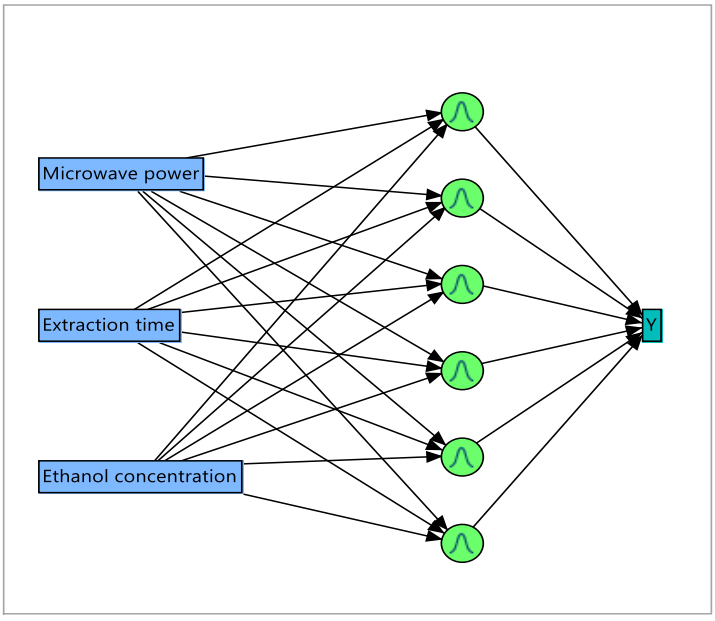


Figure 18. A schematic diagram of the neural network structure for ultrasound assisted extraction of TPC.

Table VIII. The effectiveness of the ANN training and ANN validation models

Statistical parameters	Training	Validation
R^2	0.99	0.98
RMSE	10.11	21.46
MAD	7.40	19.30
-Log Likelihood test	48.51	31.39
Sum of frequence	13	7

RMSE, root mean square error; MAD, Mean absolute deviation;

2.2. ANN surface plots

The relative impact of each extraction variable may be seen using a surface plot created in JMP by providing the ANN model with matrice of extraction condition parameters. In order to create the surface plots, the third variable for each plot was fixed at its middle value (120s, 40%, and 600W), and the outcomes of this study can be seen in **figure 19**. This investigation was conducted using the same methodology as with the RSM model. It is plain to see from **Fig. 19A** that increasing microwave power from 300W 1) to 900W improves the recovery of phenolic content, which increases internal mass transfer and, in turn, increases the recovery of TPC extraction. In **figure 19B** we could see a negative interaction effect between microwave power and irradiation time, which means that the couple microwave power and extraction time are inversely related. **Figure 19C** shows that increasing the ethanol concentration to 50% increases, significantly the extraction yield to 560mg/100gDW. This value decreases rapidly as the ethanol concentration decreases.

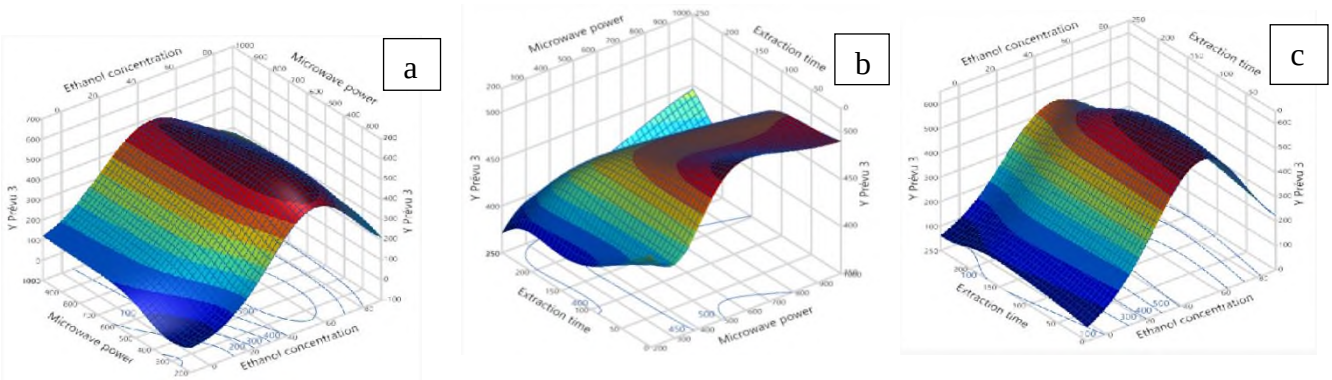


Figure 19. Graph of observed values versus predicted values of almond skin TPC for ANN model

2.3. Optimal extraction conditions

Using ANN model to describe the experiment, three experimental variables for maximum extraction of phenolic compounds from almond skin were optimized. Optimization using the desirability function **(Figure 20)** indicated that the optimal conditions for extraction of phenolic compounds with a desirability of 0.99 were as follows:

Microwave power: 562.54W

Extraction time: 30mn

Ethanol concentration: 52.92%

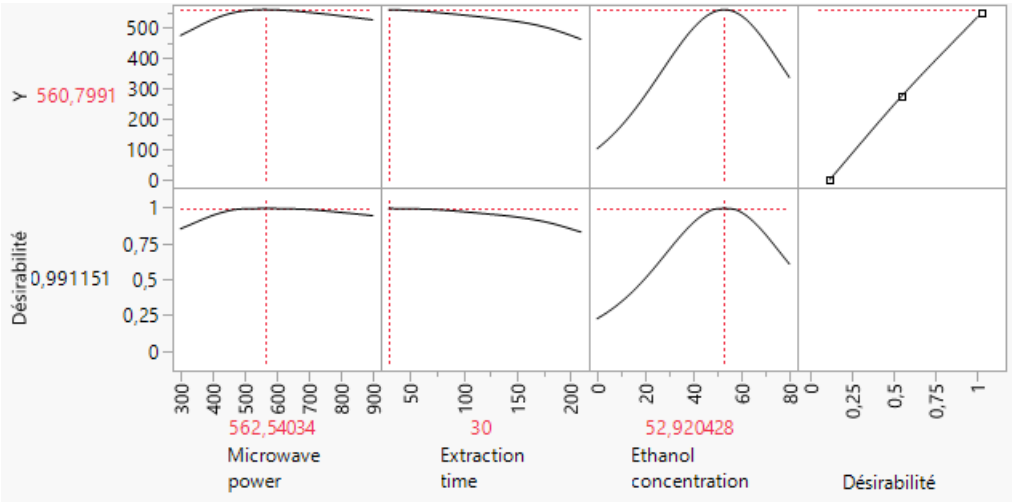


Figure 20. Profiler of prediction value and desirability function by ANN model

3. Comparison between RSM and ANN optimization

The recovery of TPC as predicted by RSM and ANN are compared to the experimentally obtained value in **table IX**. The residuals obtained by subtracting the predicted value from the experimental value show that the values predicted by the ANN are closer to the experimental values. The adequacy and precision of ANN compared to RSM to predict responses is confirmed by regression analysis displayed in **figure 24.** This correlation is quantified by coefficient of determination R^2. The determination coefficient (R^2) in RSM and ANN were given 0.98 and 0.99, respectively. Thus the calculated R^2 demonstrates a superior accuracy of ANN in contrast with the traditional optimization tool (RSM)

Table IX. The experimental design and corresponding responses for central composite design (CCD) based on response surface methodology (RSM) and artificial neural network (ANN) and predicted values for yield of total phenolic compounds from almond skin (TPC) using microwave assisted extraction (MAE).GAE,gallic acid equivalents; referred to dry weight(wd

			TPC yield (mg GAE/100DW)				
Microwave power	Extraction time	Ethanol concentration	Experimental	Predicted ANN	Predicted RSM	Residual ANN	Residual RSM
300	30	0	41.04	42.86	32.64	-1.82	8.40
600	120	40	485.65	475.83	486.57	9.82	-0.92
900	30	80	373.46	369.28	371.42	4.18	2.04
900	210	0	109.78	112.29	93.40	-2.51	16.38
600	120	40	452.63	475.83	486.57	-23.20	-33.94
300	210	80	388.56	392.32	380.52	-3.76	8.04
600	120	40	499.66	475.83	449.94	23.83	49.72
300	30	80	262.65	256.86	283.12	5.79	-20.47
300	210	0	20.52	54.03	26.65	-33.51	-6.13
900	210	80	246.24	249.80	258.73	-3.56	-12.49
600	120	40	451.44	475.83	449.94	-24.39	1.50
900	30	0	150.82	152.47	162.95	-1.65	-12.13
600	120	80	415.53	389.69	392.64	25.84	22.89
300	120	40	423.73	425.83	413.57	-2.10	10.16
600	120	0	141.57	138.13	148.09	3.44	-6.52
600	30	40	486.23	499.71	464.06	-13.48	22.17
600	210	40	435.56	424.70	441.36	10.86	-5.80
600	120	40	480.71	475.83	474.72	4.88	5.99
900	120	40	460.67	477.20	454.46	-16.53	6.21
600	120	40	419.63	475.83	474.72	-56.20	-55.09

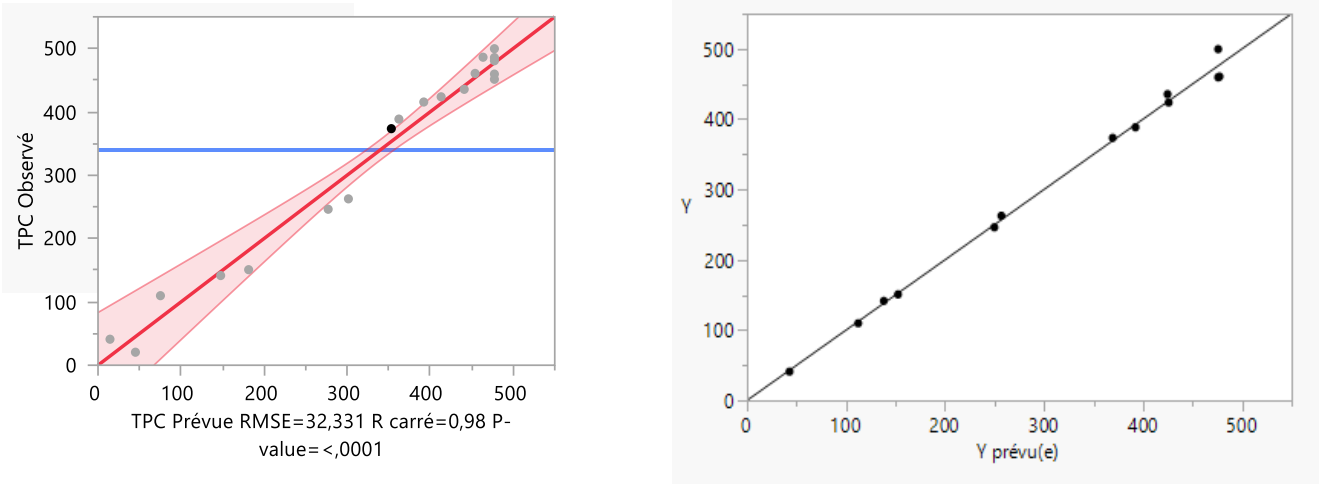


Figure 21. Response surface analysis for the total phenolic yield from almond skin with microwave assisted extraction method with respect to microwave power; extraction time and ethanol concentration, according to the ANN model

4. Antioxidant activity

Several studies have reported an interesting composition in polyphenols of almond skins. The chemical characterization of these compounds allowed to observe a predominance of flavonoids, which directed the research towards the characterization of the biological activities of almond skins **(Bolling, 2017; Bolling et al., 2009; Wijeratne et al., 2006)**. The antioxidant activity of almond skin extract obtained at optimal extraction conditions has been assessed by DPPH and hydroxyl scavenging activity, phosphomolybdate essay and ferrous chelation test

Globally, the *in vitro* measurement of free radical scavenging activity uses the DPPH method **(Jagtap et al., 2010)**. Studying the scavenging impact on proton radicals is the process used to test antioxidant activity by this method. The ability of the sample compounds to scavenge stable organic free radicals with a deep violet color, which gave the absorbance maximum within 515-528 nm range, was used in the current study to evaluate antioxidant capacity. The DPPH radical scavenging effects of almond skin extract and Trolox hydrosoluble analogue of vitamin E were presented in figure **25a**. The results show an increase of scavenging activity of the almond skin extract and standard with increasing of concentration.

Theresults ranged from 30 to 75% for almond skin extract, and 60 to 98% for Trolox, which confirms that almond skin extract exhibit DPPH radicals scavenging activity with a manner of concentration-dependent.

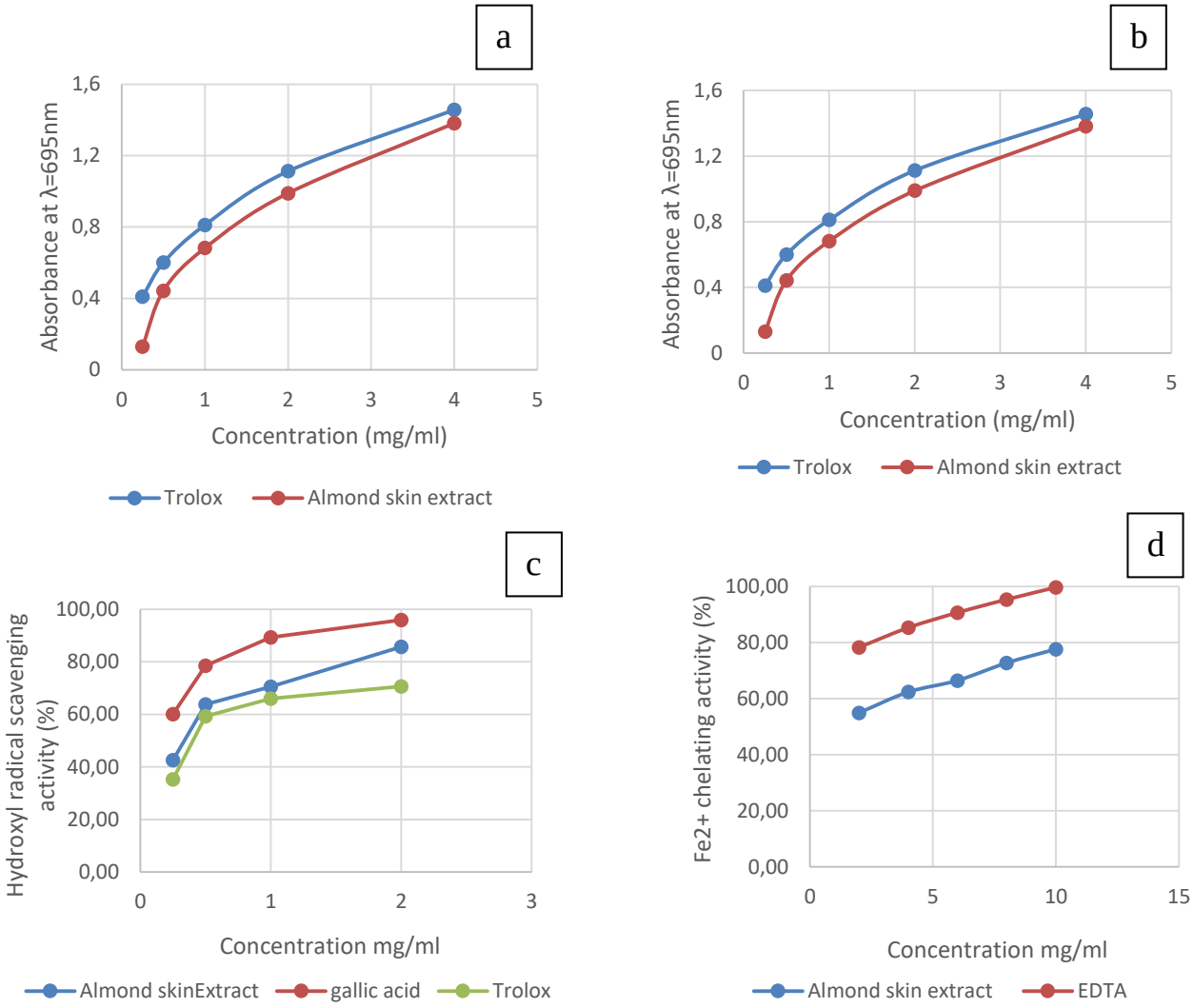


Figure 22. Antioxidant activity of almond skin a: DPPH radicals scavenging activity; b: total antioxidant activity; c: hydroxyl radicals scavenging activity; d: ferrous chelating activity

5. Antidiabetic activity

Antihyperglycemic effect was tested by inhibiting the activity of α-amylase, enzyme of carbohydrate metabolism. The α-amylase is a digestive enzyme, produced by the salivary glands and the pancreatic glands, also synthesized in the fruits of plants during their maturation. This enzyme is main for the absorption and digestion of starch and carbohydrate integrated in food, this may be a target for the treatment of diabetes **(Moura et al., 2018).**

Acarbose is a well-known drug used as an inhibitor of the enzyme α-amylase. It delays carbohydrate digestion and decreases postprandial plasma glucose levels. However, it has adverse effects such as diarrhea, hernias, ulceration. Inhibitors of α-amylase of natural origin such as flavonoids and phenolic compounds of plants are suggested as phenolic compounds are suggested as an alternative approach for the prevention and treatment of treatment of diabetic disease with little or no risk of side effects.

The graph in **figure 23** shows that almond skin extract exhibit inhibition of α-amylase. Theresults ranged from 30 to 60% for almond skin extract, and 40 to 68% for acarbose, which confirms that almond skin extract can modulate enzymatic activity. Studies reveal that phenolic compounds, such as flavonoids and tannins, can inhibit digestive enzymes. However, the inhibitory capacity is linked with their chemical structure, intermolecular interactions, and the method used **(Fidelis et al., 2020)**

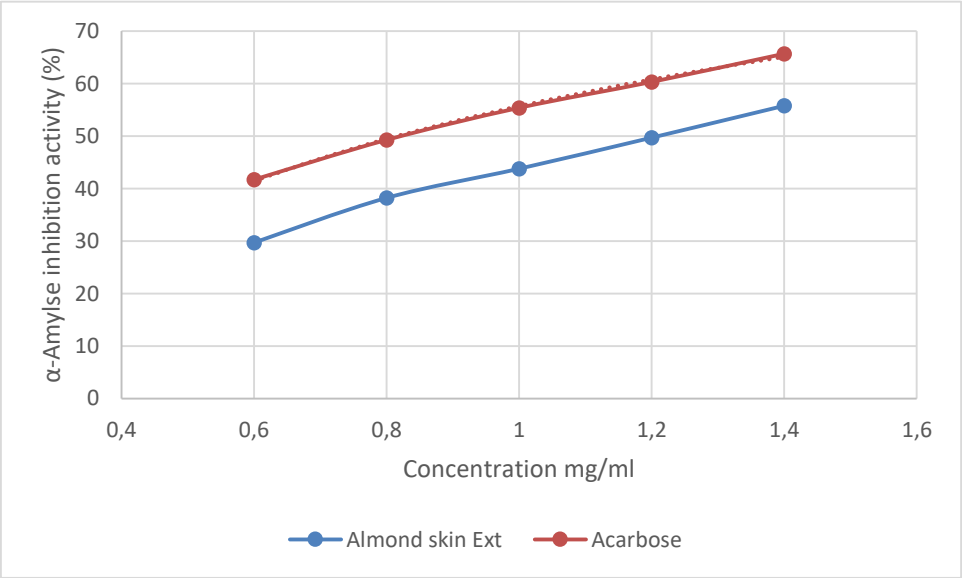


Figure 23.α-amylase inhibition of almond skin extract with acarbose

Conclusion

Conclusion

Microwave assisted extraction technique of phenolic compounds from almond skin has been optimized using RSM and ANN approach.

In this research, RSM and ANN combined with experimental data, were employed to optimize the extraction of phenolic compounds from almond skin with the influence of the microwave power, extraction time and solvent concentration levels.The optimal conditions for phenolic extraction from almond skin with RSM were 661 W, 91s, 50% ethanol and with ANN were 562 W, 30s, 52% ethanol.

The optimized extract revealed heigh antioxidant activity, determined by four tests: DPPH radical scavenging activity, Ability of chelating ferrous ions, Hydroxyl radicals scavenging activity and phosphomolybdate ammonium essay.

Antidiabetic activity test revealed that skin extract exhibit inhibition of α-amylase ranged from 30 to 60% while acarboseexhibit inhibition ranged from 40 to 68%.

The results of ANN and RSM models based on validation data showed that RSM (R^2 = 0.98) and ANN (R^2 = 0.99) are useful and perfect methods to predict TPC by applying MAE process, however, ANN has a higher accuracy

The research findings for MAE optimization with RSM and ANN models will provide effective guidelines and the results would be a good database to the Food-industry applications for use in health-care food

In perspective, we could deepen this work by characterizing the phenolic profile of almond skin and by optimizing other extraction methods such as ultrasound assisted extraction method.

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Appendix

Figure 1. Generation of almond by-products (left) and proportion of constituents of almond fruits (right).**(Barral-Martinez et al., 2021)**

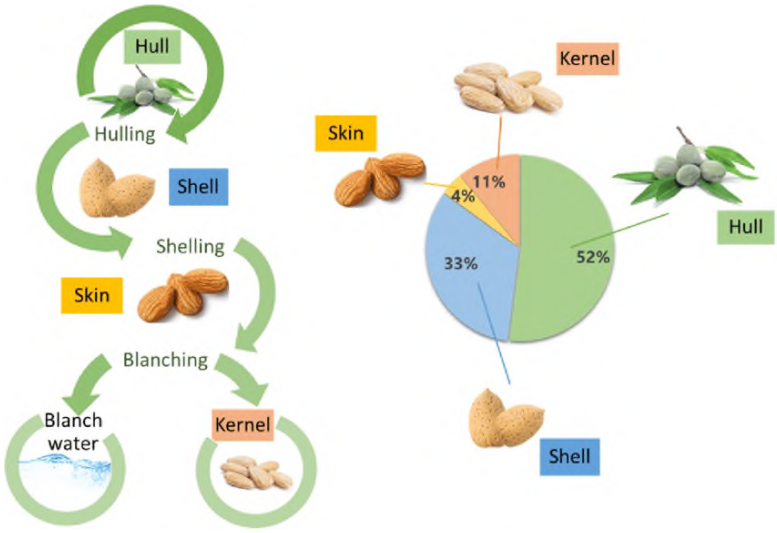
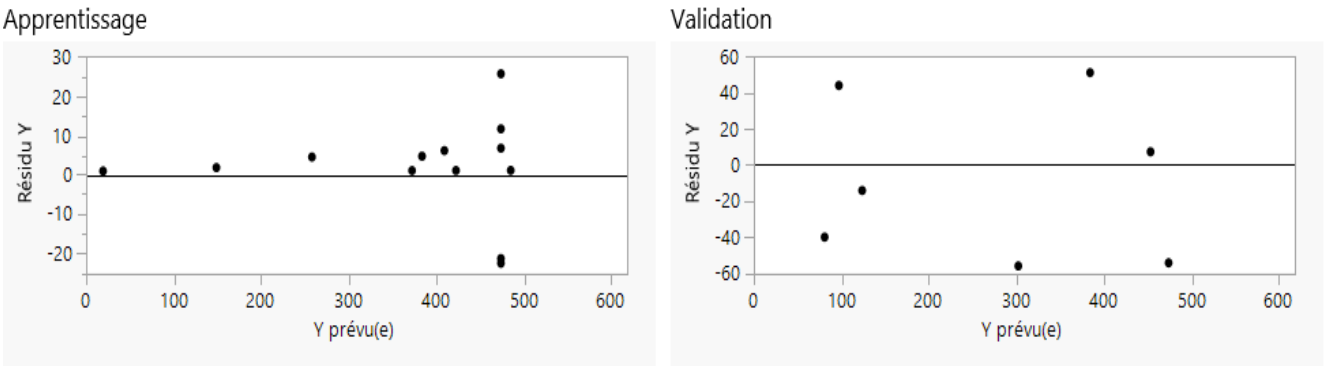


Table 1. Almond production by top 7 almond-producing countries.

Country	2014	2015	2016	2017	2018	2019
United States	1,545,500	1,302,998	1,376,337	1,476,539	1,872,500	1,936,840
Spain	195,704	211,084	199,167	255,503	339,033	340,420
Australia	55,978	63,331	72,902	75,373	69,880	146,410
Morocco	101,026	97,723	112,681	116,923	117,270	102,185
Iran	136,338	146,000	111,845	129,566	139,029	177,015
Italy	74,016	70,399	74,584	79,599	79,801	77,300
Turkey	73,230	80,000	85,000	90,000	100,000	150,000

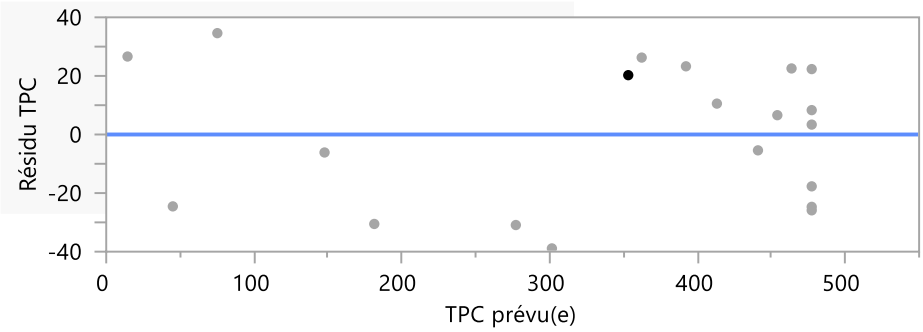
Data are expressed in tonnes.

Figure 2. Plot of residuals against predicted values with ANN



Appendix

Figure 3. Plot of residuals against expected values with RSM



Abstract

Optimization with response surface methodology (RSM) and artificial neural networks (ANNs) were efficaciously applied for the study ofthe operating parameters of microwave assisted extraction (MAE) in the recovery of phenolic compounds from almond skin. These models were used to evaluate the effects of process variables and their interaction toward the attainment of their optimum conditions. Under the optimal conditions (91s extraction time, 661w microwave power and 50% ethanol concentration), for RSM and for ANN (30s extraction time, 562w microwave power and 52% ethanol concentration). A comparison between the model results and experimental data gave high correlation coefficients (R2 ANN = 0.99, R2 RSM = 0.98), and showed that the two models were able to predict a total phenolic compounds (TPC) by microwave assisted extraction. The results of ANN were found to be more consistent than RSM since better statistical parameters were obtained. The extract obtained from optimal conditions was tested for its antioxidant and antidiabetic activity.

KEYWORDS: Microwave-assisted extraction, Phenolic compounds, Almond skin, response surface methodology, artificial neural networks

Résumé

L'optimisation avec la méthodologie de surface de réponse (RSM) et les réseaux de neurones artificiels (ANN) ont été appliqués de manière efficace pour l'étude des paramètres de fonctionnement de l'extraction assistée par micro-ondes (MAE) dans la récupération des composés phénoliques de la peau d'amande. Ces modèles ont été utilisés pour évaluer les effets des variables du processus et leur interaction en vue d'atteindre les conditions optimales. Dans les conditions optimales (91s de temps d'extraction, 661w de puissance de micro-ondes et 50% de concentration d'éthanol), pour RSM et pour ANN (30s de temps d'extraction, 562w de puissance de micro-ondes et 52% de concentration d'éthanol). Une comparaison entre les résultats du modèle et les données expérimentales a donné des coefficients de corrélation élevés (R^2 ANN = 0,99, R^2 RSM = 0,98), et a montré que les deux modèles étaient capables de prédire un total de composés phénoliques (TPC) par extraction assistée par micro-ondes. Les résultats du modèle ANN se sont avérés plus cohérents que ceux du modèle RSM puisque de meilleurs paramètres statistiques ont été obtenus. Les activités antioxydante et antidiabétique ont été testées sur l'extrait de la peau d'amande obtenu dans les conditions optimales

MOTS CLÉS : Extraction assistée par micro-ondes, composés phénoliques, peau d'amande, méthodologie de surface de réponse, réseaux de neurones artificiels.