





Estimation of aloin concentration in *Aloe vera* L. (*Aloe barbadensis* Mill.) by mathematical modeling

Estimación de la concentración de aloína en *Aloe vera* L. (*Aloe barbadensis* Mill.) mediante modelización matemática

Estimativa da concentraçãõ de aloína em *Aloe vera* L. (*Aloe barbadensis* Mill.) por modelagem matemática

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Abstract

Aloin is one of the secondary metabolites that gives plants of the genus *Aloe* spp. their healing properties. The concentration of aloin is related to the fresh mass and, its industrial purification involves laboratory processes that add extra costs to its commercialization. The objective of this research was to mathematically modelize the estimation of the aloin concentration in *A. vera* L. from the fresh mass. The theory of discrete perfect least squares approximations was used, considering linear and exponential approximation functions. For the tabulation of the data, the option of class mark and the average of the values were used. The analyses of the approximations indicate that the exponential curves approximate the data better (with $R^2 = 75\%$ and 82% for the two options, respectively) than the straight lines (with $R^2 = 65\%$ and 70% for the two options, respectively). The use of these approximations is recommended to estimate the concentration of aloin in *A. vera* plants based on their fresh mass, facilitating the measurement of this secondary metabolite, and minimizing costs in the industrialization process.

Resumen

La aloína es uno de los metabolitos secundarios que le otorga a las plantas del género *Aloe* spp., sus propiedades curativas. La concentración de aloína está relacionada con la masa fresca y su purificación industrial requiere procesos de laboratorio que agrega costos extras a la comercialización. El objetivo de este trabajo fue modelizar matemáticamente la estimación de la concentración de aloína en *A. vera* L., a partir de la masa fresca. Se usó la teoría de aproximaciones de mínimos cuadrados perfectos discretos, considerando la función de aproximación lineal y exponencial. Para la tabulación de los datos se usaron las opciones de marca de clase y el promedio de los valores. Los análisis de las aproximaciones indican que las curvas exponenciales aproximan mejor los datos (con un $R^2 = 75\%$ y 82% para las dos opciones, respectivamente) que las líneas rectas (con un $R^2 = 65\%$ y 70% para las dos opciones, respectivamente). El uso de estas aproximaciones se recomienda para la estimación de la concentración de aloína en *A. vera* en función a su masa fresca, facilitando la medición de este metabolito secundario y minimizando gastos en el proceso de industrialización.

Palabras clave: aloína; concentración; estimación; modelización matemática.

Resumo

Aloin é um dos metabólitos secundários que dá às plantas do gênero *Aloe* spp., suas propriedades curativas. A concentração de aloin está relacionada à massa fresca e sua purificação industrial requer processos laboratoriais que agregam custos extras à comercialização. O objetivo deste trabalho foi modelar matematicamente a estimativa da concentração de aloína em *A. vera* L. a partir da massa fresca. Foi utilizada a teoria das aproximações de mínimos quadrados perfeitos discretos, considerando a função de aproximação linear e exponencial. Para a tabulação dos dados, foram utilizadas as opções de marcação da classe e a média dos valores. As análises das aproximações indicam que as curvas exponenciais aproximam melhor os dados (com $R^2 = 75\%$ e 82% para as duas opções, respectivamente) do que as retas (com $R^2 = 65\%$ e 70% para as duas opções, respectivamente). O uso dessas aproximações é recomendado para estimar a concentração de aloína em *A. vera* com base em sua massa fresca, facilitando a mensuração desse metabólito secundário e minimizando custos no processo de industrialização.

Palabras-chave: aloin; concentração; estimativa; modelagem matemática.

Introduction

Aloe vera L (= *Aloe barbadensis* M.= sábila or aloe) is cultivated all over the world for agricultural, medicinal, cosmetic and decorative purposes, being its place of origin the northern limits of the Arabian Peninsula, located in southern Africa (Klopper & Smith, 2013; Pandey & Singh, 2016). Aloes have been named since ancient times because in the Bible it is said that they were employed as perfumes and in the funerary arts. Numerous studies show that the genus *Aloe* was subjected to strong environmental processes diversifying by speciation, giving rise to the extraordinary diversity of species known today (Klopper & Smith, 2013; Deng-Feng *et al.*, 2019).

The therapeutic and medicinal properties of *A. vera* as a pain reliever, analgesic, bactericide, moisturizer, emollient, anti-inflammatory, antitumor, among others, is well documented, thanks to the metabolites that are synthesized by secondary routes (Mahor & Ali, 2016). One of them is aloin, considered the active compound of these plants, which is found in their exudates with a defensive function and is the taxonomic marker of the genus *Aloe* spp, it also has a laxative action in humans, so the consumption of supplements based on this compound can have toxic effects if ingested in large quantities (Minjares & Femenia, 2019).

This compound is found especially in the acíbar or juice of the leaves and when extracted from this yellow liquid and after a drying process, it appears as a yellow powder of bitter taste, product of its chemical structure, characterized by being a glycoside formed from an anthraquinone (genin) linked with a sugar. Aloin can be presented in two different isomeric forms, aloin-A (barbaloin) and aloin-B (isobarbaloin), in such a way that some of them can produce one of the two types or present a mixture of them. Likewise, their concentration may vary according to the species, age of the plants, region and time of collection (Kaparakou *et al.*, 2020).

Depending on the *Aloe* spp. product to be offered on the market (medicines, cosmetics, beverages, food, etc.), it is necessary to determine the aloin concentration and ensure that it complies with international requirements. In this sense, the European Union established that, in the case of foods and medicines, the maximum limit of aloin must be 0.1 mg.kg^{-1} (EEC 88/388) (Official Journal of the European Communities, 1988). The same regulation was established by the International Aloe Science Council for the United States. In the cosmetic industry, there is no direct consumption of any part of the plant, therefore, the use of both acíbar and gel, either concentrated or powdered, is accepted (Pedroza *et al.*, 2009). The aloin concentration is more accurately measured by chromatographic methods; however, these methods of analysis are laborious and expensive to apply at the industrial level, in which large volumes of plant material are handled. Therefore, it is convenient to establish an alternative that allows estimating the aloin concentration in *A. vera* L., considering other variables that are easy to handle for both the producer and the industry, for example, fresh and dry mass of the plant, which allows knowing the aloin content without the need of resorting to laborious laboratory protocols.

Mathematical modeling allows to test the consequence of changes in a system due to it describes phenomena using the language of mathematics. When using a mathematical model, the first step is to identify the significant variables in the system, which will be included in the model. The second step is related to the determination of the equations that govern the system that allow predictions to be made. Although mathematics offers the facility of proving general results, these critically depend on the formulation of the equations used. Small changes in the structure of the equations can involve enormous changes in the mathematical methods.

The use of simulation and prediction models has become popular in agriculture and has become a tool both for research, as well as for producers, technical consultants and industrialists, who can now mathematically define the best crop management practice in certain situations (FAUBA, 2018). In addition, modeling has been used to improve the effects of industrialization processes of agricultural products. In this regard, Martinez *et al.* (2017) optimized the protocol for removing aloin from *A. vera* gel by employing three input variables: temperature, agitation time, and activated carbon concentration. The

results showed that the latter two variables exerted a significant action on the removal of aloin from *A. vera* gel.

Due to the mathematical modeling is an important tool for the calculation of the yields of crops of interest, the objective of the present research was to apply the mathematical modeling to estimate the aloin concentration in *A. vera* L. starting from the fresh mass values of the plant.

Materials and methods

Plant material

Ten plants of *A. vera* were randomly collected in seven commercial farms located in the western region of Venezuela, three in the central zone of Falcon state (farm 1: 11°03'13"N69°45'07"W, farm 2: 11°29'16"N 69°21'08"W and farm 3: 11°14'26"N 70°06'08"W), another located in northern Falcon state (farm 4: 11°52'22"N 69°59'18"W) and three in northern Zulia state (farm 5: 10°51'34"N 71°45'44"W, farm 6: 10°54'56"N 71°49'38"W and farm 7: 10°40'14"N 71°31'36"W). The collection was carried out between the months of January to March, which corresponds to the dry season in the country.

According to Ewel and Madriz (1976), the climates of these sites correspond to a thorny-tropical forest and very dry tropical forest, with altitudes of 0-200 mamsl, with temperatures above 25 °C and rainfall between 250 and 800 mm per year, with high solar radiation.

Plants in good health and with at least 10 leaves and approximately 35 cm in height were selected. Subsequently, they were taken to the nursery of the Facultad de Humanidades de la Universidad Del Zulia, and they were sown in plastic containers with equal proportions of sand and organic fertilizer, to achieve vegetative reproduction.

Approximately 10 months after sowing, three sprouts from each mother plant, for a total of 210 plants evaluated. Later, they were transplanted into new plastic containers and were irrigated once a week.

Determination of fresh mass and aloin concentration

When the sprouts were six (6) months old, fresh mass (PF) and aloin concentration (CA) were determined by high performance liquid chromatography (HPLC). For this purpose, each one was sanitized and subsequently weighed on a commercial balance. Then, they were homogenized in a blender and this content was stored in hermetically sealed bags in a -18°C freezer. This material was freeze-dried in a LABCONCO LYLH-LOCK 6 equipment for 72 hours until it reached complete dehydration. The powder was sent to the chromatography laboratory of the Facultad de Agronomía de la Universidad Del Zulia, (Venezuela) to measure CA according to the protocol previously established by Molero *et al.* (2016). The CA value corresponds to the amount of grams per 100 g of fresh plant mass.

Data tabulation

It was planned to use the theory of approximations, to find the function that best fit the collected data. However, it was observed that there were data with the same abscissa, which clearly indicates that they did not represent a function. For the development of the approximation theory, it is assumed that it starts with a function (Epperson, 2021; Chapra & Canales, 2015; Burden & Faires, 2011) which is desired to be approximate or, in its defect, a set of data (which represent a function) to which is required to approximate by means of an approximation function. In view of this, it was proceeded to tabulate the data in classes. The procedure used to tabulate the data was the following: per each plant analyzed of *Aloe vera*, PF value was

corresponded to the CA. To describe the classes, the Herbert Sturges' Rule was used (González, 2017; Sturges, 1926).

$$k = 1 + 3.322 \log(n),$$

where

k is the number of intervals to be formed and n is the total number of data collected or, in other words, the total number of samples taken. To define the classes it is necessary to know the range that each class should have. The range is defined, using the number k from the Herbert Sturges' Rule (González, 2017; Sturges, 1926), as follows:

$$\text{Range} = (\text{Max}\{\text{Fresh mass}\} - \text{Min}\{\text{Fresh mass}\})/k,$$

where

$\text{Max}\{\text{Fresh mass}\}$ is the maximum value and $\text{Min}\{\text{Fresh mass}\}$ is the minimum value of the set of all the values and data collected from the PF. The Sturges' rule is a criterion that helps to formally determine the number of classes needed to represent a data set (González, 2017; Sturges, 1926).

Once the classes were defined, it was proceeded to determine the best representative of each class, discriminating between the class mark and the average of all the fresh masses measured that fall into each class. We proceeded, then, to work with the two possibilities as options for the tabulation of the PF, denoted by x_i , to then make comparisons and see which of the two options produces a better approximation.

These two options were used for the approximation functions proposed in the following paragraphs.

Approximation theory

The theory of discrete least squares approximations was used to find the functions that best fit the tabulated data. This theory was used because it allows finding the function that "best" fits a given data set (Epperson, 2021; Chapra & Canales, 2015; Burden & Faires, 2011). The two options, described in the previous section, were considered for both a linear approximation function and an exponential approximation function.

For the case of the linear function, the objective is to find the line that best approximates the tabulated data, with which a function of the form should be found (Burden & Faires, 2011):

$$y = a \cdot x + b,$$

where

$$a = \frac{m \sum_{i=1}^m x_i y_i - (\sum_{i=1}^m x_i)(\sum_{i=1}^m y_i)}{m \sum_{i=1}^m x_i^2 - (\sum_{i=1}^m x_i)^2},$$

represents the slope of the linear function, and,

$$b = \frac{(\sum_{i=1}^m x_i^2)(\sum_{i=1}^m y_i) - (\sum_{i=1}^m x_i y_i)(\sum_{i=1}^m x_i)}{m \sum_{i=1}^m x_i^2 - (\sum_{i=1}^m x_i)^2},$$

represents the intercept of this function with the y-axis. Also, it is considered that x_i and y_i correspond to the fresh mass and the aloin concentration, respectively, for each i -th class, and m is the number of classes corresponding to k in the previous section.

In the second case, it was intended to find the exponential curve that best approximates the tabulated data, with which a function of the form should be found (Burden & Faires, 2011):

$$y = be^{ax}$$

where

$$a = \frac{m \sum_{i=1}^m x_i \ln(y_i) - (\sum_{i=1}^m x_i)(\sum_{i=1}^m y_i)}{\sum_{i=1}^m x_i^2 - (\sum_{i=1}^m x_i)^2}$$

represents the coefficient of the argument of the exponential function, and

$$\ln(b) = \frac{(\sum_{i=1}^m x_i^2)(\sum_{i=1}^m \ln(y_i)) - (\sum_{i=1}^m x_i \ln(y_i))(\sum_{i=1}^m x_i)}{m \sum_{i=1}^m x_i^2 - (\sum_{i=1}^m x_i)^2}$$

where b represents the degree of the slope of the exponential curve, considering that x_i and y_i correspond to the fresh mass and the aloin concentration, respectively, for each i - th class, and m is the number of classes that correspond to k in the previous section.

To calculate the linear and exponential approximations of the data, the Excel spreadsheet for Windows environment was used (Charte 2016) and they were corroborated with InfoStat statistical package (Di Rienzo *et al.*, 2011). The comparisons between the four approximations were carried out using the coefficient of determination (R^2).

Results and discussion

As it was mentioned in materials and methods, the number of the data collected was $n = 210$ for each characteristic studied, therefore, from the Herbert Sturges Rule it is deduced that $k \approx 9$. From the collected numbers, the maximum and minimum PF values were 523 g and 100 g respectively, and the average of all the PF data was 252.2 g. In this sense, the range is approximately equal to 47, which defines PF.

Once the classes were defined, the CA data were classified into each class. The maximum and minimum CA values were 0.03 g and 6.771g.100⁻¹ g of PF, respectively, with an CA average value of 1.242g.

Table 1 shows the two options proposed in the methodology for PF; the first option, calculating the class mark in each class, and the second option, calculating the fresh mass average of each class using all the collected values corresponding to each particular class. The aloin concentration average for each class is also included.

Table 1. Distribution of aloin concentration with respect to fresh mass (PF) classes in *Aloe vera* L.

	PF Classes	x1-PF marks	x2-Prom. PF Class	y-Prom. CA.
1	100-147	123.5	117.3	0.93
2	147-194	170.5	174.9	0.93
3	194-241	217.5	215.2	1.34
4	241-288	264.5	259.6	1.54
5	288-335	311.5	310.0	1.60
6	335-382	358.5	357.3	1.82
7	382-429	405.5	400.4	2.93
8	429-476	452.5	446.8	2.75
9	476-523	499.5	520.0	6.77
	Total Sum:	2803.5	2801.6	-

The results of the linear and exponential approximations for the two options are presented below.

Results for the approximations by linear function

For this case it was obtained:

$$y=0.011443x-1.2754,$$

for the first option (class mark) and,

$$y = 0.011509x-1.2935,$$

for the second option (averages of the CA values in each class).

Figure 1 shows the linear approximations of the aloin concentration. The validation of these results with the InfoStat software showed that: $a = 0.01$ and $b = -1.28$, which are clearly rounded values of those calculated for the first linear approximation ($a = 0.011443$ and $b = -1.2754$).

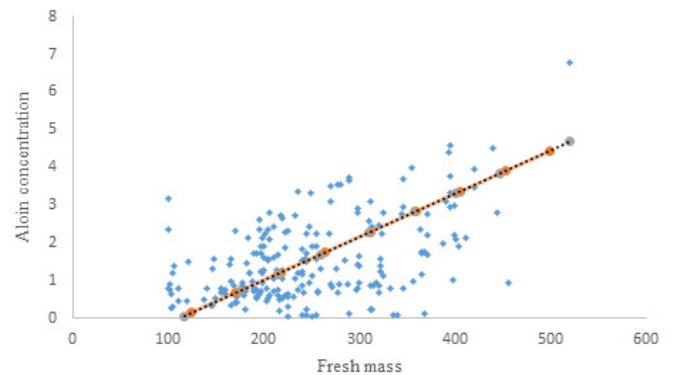


Figure 1. Linear approximations of aloin concentration

The red solid line represents the first of the linear approximation equations found, and the black dotted line corresponds to the second one. It can be seen that practically both lines overlap.

Results for the approximations by exponential function

For this case of approximation by exponential function, the following results were obtained.

$$y = 0.44886 e^{0.00458x},$$

for the first option (class marks) and,

$$y = 0.45896 e^{0.00452x},$$

for the second option (averages of the CA values in each class).

Figure 2 shows the two corresponding curves to the calculations performed for the approximations of aloin concentration by exponential functions.

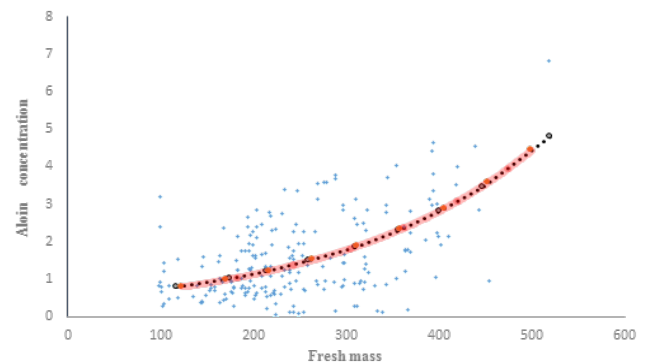


Figure 2. Exponential approximations of aloin concentration.

The red solid curve represents the first of the exponential approximation equations found and corresponds to the first option (class marks). The black dotted curve corresponds to the second option (CA averages). It can be seen that practically both exponential curves are overlapping.

The concentration of aloin depends on several factors and for the industrialization of commercial aloe vera-based products, it is necessary to quantify the CA data and other plant components in order to meet the demands and specifications required by international standards.

When observing the graphs of the mathematical models obtained, both linear (figure 1) and exponential (figure 2), there is no noticeable difference between the two straight lines or between the two exponential curves, which correspond to the two tabulation options. What is observed is that both straight lines overlap, and both exponential curves overlap. In view of this, the coefficient of determination, (R^2), was calculated for each of the models to analyze their behavior with respect to the data. The coefficient of determination is a statistic that determines the quality of the model to replicate the results, and the proportion of variation in the results that can be explained by the model (Steel & Torrie, 1960). It is used in the context of a statistical model whose main purpose is to predict future results or to test a hypothesis. But first, we proceeded to validate the models using ANOVA; that is, to test the three assumptions (Martinez *et al.*, 2021). The first assumption requires that the residuals approximate a normal distribution. In figure 3 (a and b), it is observed that they do not have exactly a normal distribution. However, since in this research the size of the groups is equal to each other, ANOVA is robust with respect to non-normality (Glass & Hopkins, 1996; Blanca *et al.*, 2017).

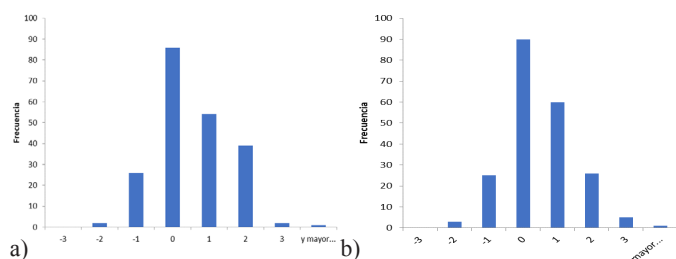


Figure 3. Histograms of aloin concentration residuals.

The second case requires that the aloin concentration residuals do not show a tendency (completely dispersed) with respect to the fresh mass (figure 4).

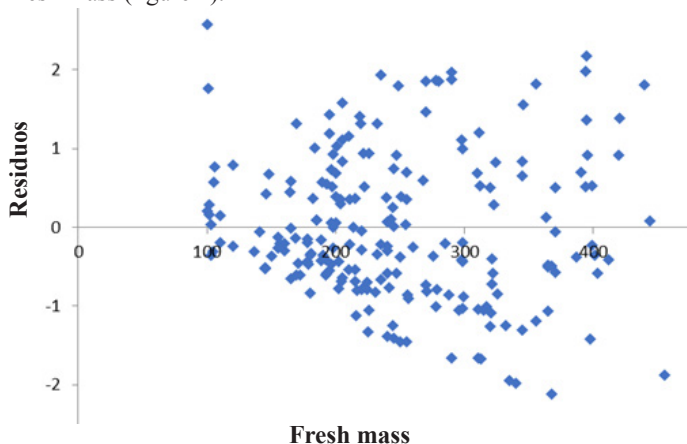


Figure 4. Dispersion of the residual concentration of aloin regarding to the fresh mass.

For this purpose, the Durbin-Watson (DW) statistic was calculated for each model. For linear model 1, $DW=1.493$; for linear model 2, $DW=1.490$; for exponential model 1, $DW=1.726$; and for exponential model 2, $DW=1.793$.

The third assumption requires that homoscedasticity be respected. Similar to normality, when the size of the groups is equal, ANOVA is robust to heteroscedasticity (Statistics Solutions, 2013). The p value for the linear approximation model 1 (i.e., the model worked with the data classified with the class marks), is 0.551 and for the linear model 2 (i.e., the model worked with the data classified with the averages of the CA values in each class) is 0.563. For the exponential approximation model 1 (the data classified with the class marks), the p-value found is 0.929 while for the exponential model 2 (with the averages of the CA values in each class) it is 0.857. The models can be considered robust because they predict with acceptable accuracy the aloin concentration with the following coefficients of determination, R^2 ; for the linear approximation models, with the data classified with the class marks (linear model 1), $R^2 = 0.6540$ ($\approx 65\%$) and with the data classified with the averages of the CA values in each class (linear model 2), $R^2 = 0.6990$ ($\approx 70\%$). For the exponential approximation models, with the data classified with the class marks (exponential model 1), $R^2 = 0.8055$ ($\approx 81\%$) and with the data classified with the averages of the CA values in each class (exponential model 2), $R^2 = 0.8712$ ($\approx 87\%$).

Based on the previous analysis, the use of the exponential approximation mathematical model 2 is recommended to estimate or infer aloin concentration as a function of fresh mass only. This model is given by the equation of exponential approximation found:

$$y = 0.44886 e^{0.00458x},$$

where x represents the fresh mass (PF) of the plant and y represents the aloin concentration.

In this research, the mathematical model did not discriminate the plants by their origin, but they were considered as belonging to a region that conglomerates all the populations into one.

The use of mathematical modeling to analyze the drying of *A. vera* leaves has been widely employed (Moradi *et al.*, 2019; Sabat *et al.*, 2018), as well as for the study of mass transfer during the gel rehydration phenomenon (Vega-Galv3ez *et al.*, 2009) and in the determination of optimal conditions for the removal of aloin from the gel (Mart3nez *et al.*, 2017; Jawade & Chavan, 2013), but no research is recorded on the application of these models to estimate the concentration of aloin, or any other secondary metabolite in *Aloe* spp. using only the fresh mass of the plant, so comparative studies of these results with those obtained in other works cannot be made. However, the robustness of the model was verified.

Conclusions

In this research, based on the mathematical modeling to estimate the concentration of aloin in *A. vera* L., from the values of the fresh mass, it is concluded that the exponential curves found, approximate the data better than the calculated straight lines. Therefore, this model is recommended for the estimation of the aloin concentration in naturally propagated plants from their fresh mass and it can be used to carry out future investigations about the concentration of metabolites and other chemical compounds in plants of the *Aloe* genus by means of least squares approximations considering nonlinear polynomial functions. In the same way, this model is useful for the agricultural producer or interested person since it will be able to estimate the value of CA starting from an easy-to-measure parameter, such as the fresh mass of the plant, without

having to resort to laborious and expensive laboratory protocols and techniques, minimizing expenses and production stages.

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