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Logic Programming and Artificial Neural Networks in Pharmacological Screening of *Schinus* Essential Oils

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***Abstract*—**Some plants of genus *Schinus* have been used in the folk medicine as topical antiseptic, digestive, purgative, diuretic, analgesic or antidepressant, and also for respiratory and urinary infections. Chemical composition of essential oils of *S. molle* and *S. terebinthifolius* had been evaluated and presented high variability according with the part of the plant studied and with the geographic and climatic regions. The pharmacological properties, namely antimicrobial, anti-tumoural and anti-inflammatory activities are conditioned by chemical composition of essential oils. Taking into account the difficulty to infer the pharmacological properties of *Schinus* essential oils without hard experimental approach, this work will focus on the development of a decision support system, in terms of its knowledge representation and reasoning procedures, under a formal framework based on Logic Programming, complemented with an approach to computing centered on Artificial Neural Networks and the respective Degree-of-Confidence that one has on such an occurrence.

***Keywords*—**Artificial neuronal networks, essential oils, knowledge representation and reasoning, logic programming, *Schinus molle* L, *Schinus terebinthifolius* raddi.

I. Introduction

ESSENTIAL oils are secondary metabolites produced by flowers, leaves, stems, seeds, fruits or bark of aromatic plants. Usually, these compounds are liquid, volatile, limpid, usually with lower density than water and soluble in organic solvents. *E*ssential *O*i*ls* (*EOs*) play an important role in the protection of plants against herbivores and some insects and have also important antibacterial, antiviral, antifungal and insecticide properties [1], [2]. A large number of *EOs* and their individual components have been used as natural food flavorings, as food preservatives and as pharmaceutical agents, because of their functional properties [1], [3], [4].

Schinus L. species are trees from the *Anacardiaceae* family characterized by pungent-smell essential oils concentrated especially in fruits. The genus *Schinus* is native to South America particularly to the coast of Brazil and includes approximately 29 species [5]. *Schinus molle* L., also known as pink pepper, is naturalized in Southern Europe, including Portugal, as an ornamental plant [6].

Essential oil of *S. molle* and *S. terebinthifolius*, extracted from leaves and berries, had been characterized mainly by the high presence of monoterpens hydrocarbons, namely, myrcene, α-phellandrene, β-phellandrene and limonene [6]–[9]. The composition of these *EOs* can be different according with geographic and climatic factors and with the part of the plant (fruit or leaves) [6]–[9]. All parts of these plants have been used in traditional medicine for the treatment of several pathologies. *Schinus* plants were used in the folk medicine as topical antiseptic, digestive, purgative, diuretic, as analgesic and antidepressant and also for respiratory and urinary infections [10], [11].

Some studies about *S. molle* and *S. terebinthifolius EOs* highlight the biological properties, namely antimicrobial [6], [9], [12], antioxidant [5], [6], [8], anti-tumoural [5], [8] and anti-inflammatory activities [13], [14], and correlated them with the chemical composition.

Taking into account the geographical and seasonal variability of *Schinus EOs* chemical composition and the difficulty to infer their pharmacological properties without experimental assays for each *EO*, the present study was conducted with the objective to characterize the founding of a computational framework that uses knowledge representation and reasoning techniques to set the structure of the information and the associate inference mechanisms. We will centre on a *Logic Programming* (*LP*) based approach to *Knowledge Representation and Reasoning* (*KRR*) [15], [16], complemented with a computational framework based on *Artificial Neural Networks (ANNs*) [17].

II. Knowledge Representations and Reasoning

Many approaches to *KRR* have been proposed using *LP*, namely in the area of Model Theory [18]–[20], and Proof Theory [15], [16]. In this work it is followed the proof theoretical approach in terms of an extension to the *LP* language to *KRR*. An Extended Logic Program is a finite set of clauses in the form:

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$$p \leftarrow p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m \quad (1)$$

$$?\,(p_1, \cdots, p_n, not\ q_1, \cdots, not\ q_m)\ (n, m \geq 0) \quad (2)$$

where *?* is a domain atom denoting falsity, the p_i, q_j, and p are classical ground literals, i.e., either positive atoms or atoms preceded by the classical negation sign $\neg$ [15]. Under this emblematic formalism, every program is associated with a set of abducibles [18], [20] given here in the form of exceptions to the extensions of the predicates that make the program. Once again, *LP* emerged as an attractive formalism for knowledge representations and reasoning tasks, introducing an efficient search mechanism for problem solving.

Due to the growing need to offer user support in decision making processes some studies have been presented [21], [22] related to the qualitative models and qualitative reasoning in Database Theory and in Artificial Intelligence research. With respect to the problem of *KRR* using *LP*, a measure of the *Quality-of-Information* (*QoI*) of such programs has been object of some work with promising results [23], [24]. The *QoI* with respect to the extension of a predicate *i* will be given by a truth-value in the interval [0, 1].

It is now possible to engender the universe of discourse, according to the information given in the logic programs that endorse the information about the problem under consideration, according to productions of the type:

$$predicate_i - \cup_{1 \leq j \leq m}\, clause_j(x_1, \cdots, x_n) :: QoI_i :: DoC_i \quad (3)$$

where $\cup$ and m stand, respectively, for *set union* and the *cardinality* of the extension of $predicate_i$. On the other hand, DoC_i denotes one's confidence on the attribute's values of a particular term of the extension of $predicate_i$, whose evaluation will be illustrated below. In order to advance with a broad-spectrum, let us suppose that the *Universe of Discourse* is described by the extension of the predicates:

$$f_1(\cdots), f_2(\cdots), \cdots, f_n(\cdots)\ where\ \ (n \geq 0) \quad (4)$$

Assuming that a clause denotes a happening, a clause has as argument all the attributes that make the event. The argument values may be of the type unknown or members of a set, or may be in the scope of a given interval, or may qualify a particular observation. Taking into account the following clause where the first argument stands for itself, with a domain that ranges in the interval [0, 12], the value of the second may fit into the interval [5.5, 7] with a domain that ranges between 2.5 and 10, and the value of the third argument is unknown, being represented by the symbol $\perp$, with a domain that ranges in the interval [0, 2]. Let us consider that the case data is given by the extension of predicate f_1, given in the form:

$$f_1 : x_1, x_2, x_3 \rightarrow \{0,1\} \quad (5)$$

where "{" and "}" is one´s notation for sets, "0" and "1" denote, respectively, the truth values *false* and *true*. Therefore, one may have:

{

$\neg f_1(x_1, x_2, x_3) \longleftarrow not\ f_1(x_1, x_2, x_3)$

$f_1(\underbrace{\ 6,\ \ [5.5,7],\ \ \perp}_{attribute`s\ values\ for\ x_1,x_2,x_3}) :: 1 :: DoC$

$\underbrace{[0,12][2.5,10][0,2]}_{attribute`s\ domains\ for\ x_1,x_2,x_3}$

…

}

Once the clauses or terms of the extension of the predicate are established, the next step is to set all the arguments, of each clause, into continuous intervals. In this phase, it is essential to consider the domain of the arguments. As the third argument is unknown, its interval will cover all the possibilities of the domain. The first argument speaks for itself. Therefore, one may have:

{

$\neg f_1(x_1, x_2, x_3) \longleftarrow not\ f_1(x_1, x_2, x_3)$

$f_1(\underbrace{\ [6,6],\ \ [5.5,7], [0,2]}_{attribute`s\ values\ for\ x_1,x_2,x_3}) :: 1 :: DoC$

$\underbrace{[0,12\ ][2.5,10][0,2]}_{attribute`s\ domains\ for\ x_1,x_2,x_3}$

…

}

It is now achievable to calculate the *Degree of Confidence* for each attribute that make the term argument (e.g. with respect to the second attribute it denotes one's confidence that the attribute under consideration fits into the interval [5.5, 7]). Next, we set the boundaries of the arguments intervals to be fitted in the interval [0, 1] according to the normalization procedure given by $(Y - Y_{min})/(Y_{max} - Y_{min})$, where the Y_s stand for themselves. One may have:

{

$\neg f_1(x_1, x_2, x_3) \longleftarrow not\ f_1(x_1, x_2, x_3)$

$x_1 = \left[\frac{6-0}{12-0}, \frac{6-0}{12-0}\right]\ x_2 = \left[\frac{5.5-2.5}{10-2.5}, \frac{7-2.5}{10-2.5}\right],$
$x_3 = \left[\frac{0-0}{2-0}, \frac{2-0}{2-0}\right]$

$f_1(\underbrace{[0.5, 0.5], [0.4, 0.6], [0,1]}_{\substack{attribute`s\ values\ ranges\ for \\ x_1,x_2,x_3\ once\ normalized}}) :: 1 :: DoC$

$\underbrace{[0,1]\quad [0,1]\quad [0,1]}_{\substack{attribute`s\ domains\ for\ x_1,x_2,x_3 \\ once\ normalized}}$

…

}

The *Degree of Confidence* (*DoC*) is evaluated using the equation $DoC = \sqrt{1 - \Delta l^2}$, as it is illustrated in Fig. 1. Here Δl stands for the length of the arguments intervals, once normalized. Therefore, one may have:

$$
\begin{aligned}
&\{\\
&\quad \neg f(x_1, x_2, x_3) \longleftarrow not\ f_1(x_1, x_2, x_3)\\
&\quad f_1 \underbrace{(1, \quad 0.98, \quad 0)}_{\substack{attribute`s\ confidence\\ values\ for\ x_1,x_2,x_3}} :: 1 :: 0.66\\
&\quad \underbrace{[0.5, 0.5][0.4, 0.6][0,1]}_{\substack{attribute`s\ values\ ranges\ for\\ x_1,x_2,x_3\ once\ normalized}}\\
&\quad \underbrace{[0, 1] \quad [0, 1] \quad [0, 1]}_{\substack{attribute`s\ domains\ for\ x_1,x_2,x_3\\ once\ normalized}}\\
&\ldots\\
&\}
\end{aligned}
$$

where the *DoC's* for $f_1(1, 0.98, 0)$ is evaluated as (1+0.98+0)/3, i.e., 0.66, assuming that all the argument's attributes have the same weight.

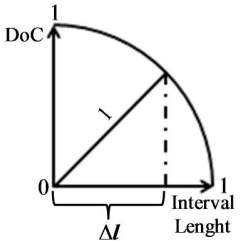

Fig. 1 Evaluation of the Degree of Confidence

III. Case Study

In order to exemplify the applicability of our problem solving methodology, we will look at a relational model, since it provides a basic framework that fits into our expectancies [25], and is understood as the genesis of the *LP* approach to *KRR* [15].

As a case study, consider a database given in terms of the extensions of the relations (or tables) depicted in Fig. 2, which stands for a situation where one has to manage information in order to predict pharmacological activity of essential oils of *Schinus* plants, namely antimicrobial, analgesic, anti-tumoral and anti-inflammatory properties.

Under this scenario some incomplete and/or unknown data is also available. For instance, in case 1, the percentage of monoterpenes hydrocarbons ranges in the interval [58, 72], while the data regarding to antioxidant tests are unknown.

The values presented in the *Hippocratic Screening* and *Antioxidant Activity* columns of *Pharmacological Activity Predict* table are the sum of the correspondent values present in *Hippocratic Screening* and *Antioxidant Activity Tests* tables, ranging between [0, 6] and [0, 12], respectively. Now, we may consider the relations given in Fig. 2, in terms of the *pharm_act* predicate, depicted in the form:

$$
\begin{aligned}
pharm_{act}: &M_{onoterpenes}H_{ydrocarbons},\ M_{onoterpenes}O_{xigenated},\\
&S_{esquiterpenes}H_{ydrocarbons},\ S_{esquiterpenes}O_{xigenated}, CL_{50},\\
&DL_{50},\ H_{ippocratic}S_{creening},\ A_{ntioxidant}A_{ctivity} \rightarrow \{0,1\}
\end{aligned}
$$

where *pharm_act* stands for the predicate *pharmacological activity, where* 0 (zero) and 1 (one) denote, respectively, the truth values *false* and *true*. It is now possible to give the extension of the predicate *pharm_act*, in the form:

$$
\begin{aligned}
&\{\\
&\quad \neg pharm\_act(MH, MO, SH, SO, CL_{50}, DL_{50}, HS, AA) \longleftarrow not\ pharm\_act(MH, MO, SH, SO, CL_{50}, DL_{50}, HS, AA)\\
&\quad pharm\_act(\underbrace{[58{,}72], [0.5{,}2], \ [2{,}4], \ [13{,}15], \ \ 48, \quad 2500, \quad 1, \quad \bot}_{attribute`s\ values}) :: 1 :: DoC\\
&\qquad \underbrace{[0{,}100]\ [0{,}100]\ [0{,}100]\ [0{,}100][25{,}3000][100{,}5000][0{,}6][0{,}12]}_{attribute`s\ domains}\\
&\ldots\\
&\}
\end{aligned}
$$

In this program, the former clause denotes the closure of predicate *pharm_act*, and the next, taken from the extension of the *pharmacological activity* relation shown in Fig. 2, presents the information regarding case 1 (one). Moving on, the next step is to transform all the argument values into continuous intervals, and then move to normalize the predicate´s arguments. One may have:

$$
\begin{aligned}
&\{\\
&\quad \neg pharm\_act(MH, MO, SH, SO, CL_{50}, DL_{50}, HS, AA) \longleftarrow not\ pharm\_act(MH, MO, SH, SO, CL_{50}, DL_{50}, HS, AA)\\
&\quad pharm\_act(\underbrace{0.990, \quad 0.999, \quad 0.999, \quad 0.999, \quad 1, \quad 1, \quad 1, \quad 0}_{attribute`s\ confidence\ values}) :: 1 :: 0.873\\
&\qquad \underbrace{[0.58{,}0.72][0.005{,}0.02][0.02{,}0.04]\ [0.13{,}0.15][0.008{,}0.008][0.49{,}0.49][0.17{,}0.17][0{,}1]}_{attribute`s\ values\ once\ normalized}\\
&\qquad \underbrace{[0{,}1] \quad [0{,}1] \quad [0{,}1] \quad [0{,}1] \quad [0{,}1] \quad [0{,}1] \quad [0{,}1] \quad [0{,}1]}_{attribute`s\ domains\ once\ normalized}\\
&\ldots\\
&\}
\end{aligned}
$$

where its terms make the training and test sets of the Artificial Neural Network given in Fig. 3.

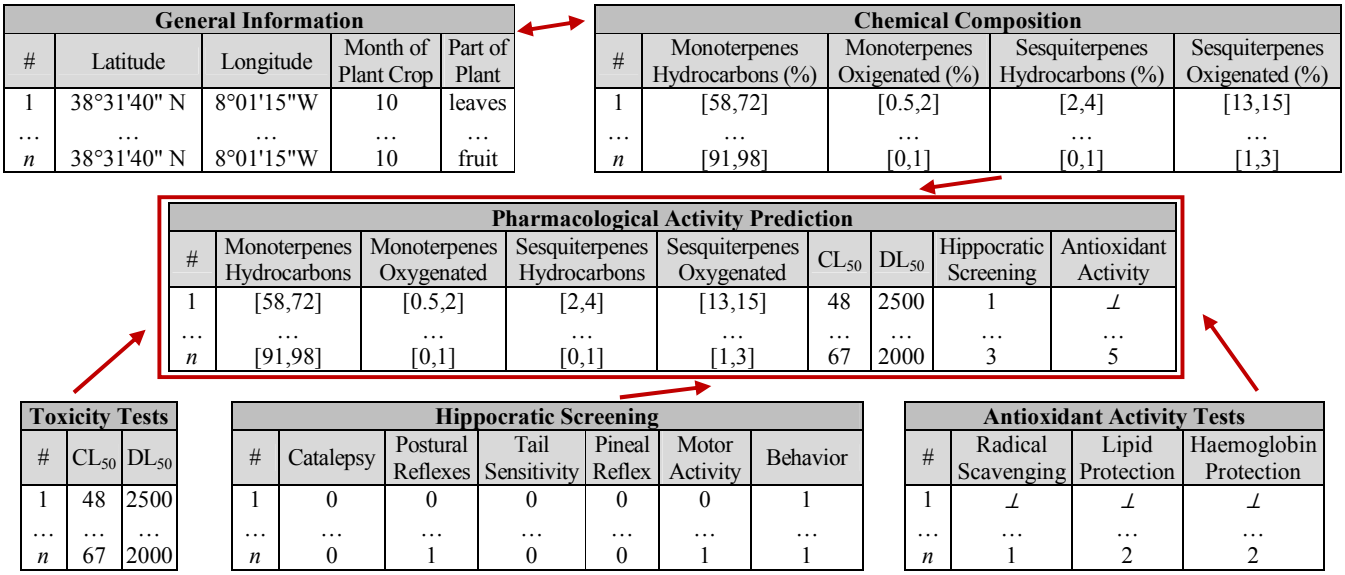

Fig. 2 An extension of the relational model. In *Hippocratic Screening* table 0 (zero) and 1 (one) denote, respectively, normal and abnormal responses. The values of *Antioxidant Activity Tests* ranges in the interval [0, 4], where 0 (zero) stands for *without antioxidant activity* and 4 (four) denotes a *very strong antioxidant activity*. The CL_{50} and DL_{50} are expressed in $mgdm^{-3}$ and $mgKg^{-1}$ (*p. o.*), respectively

IV. Artificial Neural Networks

Several studies have shown how *Artificial Neural Networks* (*ANNs*) could be successfully used to structure data and capture complex relationships between inputs and outputs [26]–[28]. *ANNs* simulate the structure of the human brain being populated by multiple layers of neurons. As an example, let us consider the first case presented in Fig. 2, where one may have a situation in which the prediction of pharmacological activity is needed. In Fig. 3 it is shown how the normalized values of the interval boundaries and their *DoC* and *QoI* values work as inputs to the *ANN*. The output translates the pharmacological activity and the confidence that one has on such a happening. In addition, it also contributes to build a database of study cases that may be used to train and test the *ANN*.

The dataset holds information about the factors considered critical in the prediction of pharmacological activity. Fifteen variables were selected allowing one to have a multivariable dataset with 32 records. Table I shows a brief description of each variable and the data type, i.e., numeric or nominal. Table II, in turns, presents a brief statistical characterization of the numeric variables.

The dataset used in the training phase it was divided in exclusive subsets through the 4-folds cross validation. In the implementation of the respective dividing procedures, ten executions were performed for each one of them. To ensure statistical significance of the attained results, 30 (thirty) experiments were applied in all tests. The back propagation algorithm was used in the learning process of the *ANN*. As the output function in the pre-processing layer it was used the identity one. In the other layers we used the sigmoid function.

A common tool to evaluate the results presented by the classification models is the coincidence matrix, a matrix of size $L \times L$, where L denotes the number of possible classes. This matrix is created by matching the predicted and target values. L was set to 2 (two) in the present case. Table III present the coincidence matrix (the values denote the average of the 30 experiments).

Table III shows that the model accuracy was 84.4% (27 instances correctly classified in 32). Thus, the predictions made by the *ANN* model are satisfactory and therefore, the generated model is able to predict pharmacological activity of *Schinus* essential oils.

TABLE I
Variables Characterization

Variable	Description	Data Type
Monoterpenes hydrocarbons	Percentage of monoterpenes hydrocarbons	Numeric
Monoterpenes oxygenated	Percentage of monoterpenes oxygenated	Numeric
Sesquiterpenes hydrocarbons	Percentage of sesquiterpenes hydrocarbons	Numeric
Sesquiterpenes oxygenated	Percentage of sesquiterpenes oxygenated	Numeric
CL_{50}	Lethal concentration 50%	Numeric
DL_{50}	Lethal dose 50%	Numeric
Catalepsy	Has muscular rigidity	Nominal
Postural reflexes	Has automatic movements that control the equilibration	Nominal
Tail sensitivity	Has tail reflex	Nominal
Pineal reflexes	Has pineal sensitivity	Nominal
Motor activity	Has motor response	Nominal
Behavior	Response of the organism to various stimuli	Nominal
Radical scavenging	Has ability to scavenging free radicals	Nominal
Lipid protection	Has ability to inhibit lipid oxidation	Nominal
Haemoglobin protection	Has ability to inhibit the Fe^{2+} oxidation	Nominal

TABLE II
STATISTICAL CHARACTERIZATION OF THE NUMERIC VARIABLES

Variable	Minimum	Maximum	Average	Standard Deviation
Monoterpenes hydrocarbons	50	80	70	5
Monoterpenes oxygenated	0	12	6	2
Sesquiterpenes hydrocarbons	2.5	25	11	4
Sesquiterpenes oxygenated	2	14	8	3
CL_{50}	44	74	50	10
DL_{50}	1000	3000	2000	300

TABLE III
THE COINCIDENCE MATRIX FOR THE ANN MODEL

Target	Predictive	
	False (0)	True (1)
False (0)	8	1
True (1)	4	19

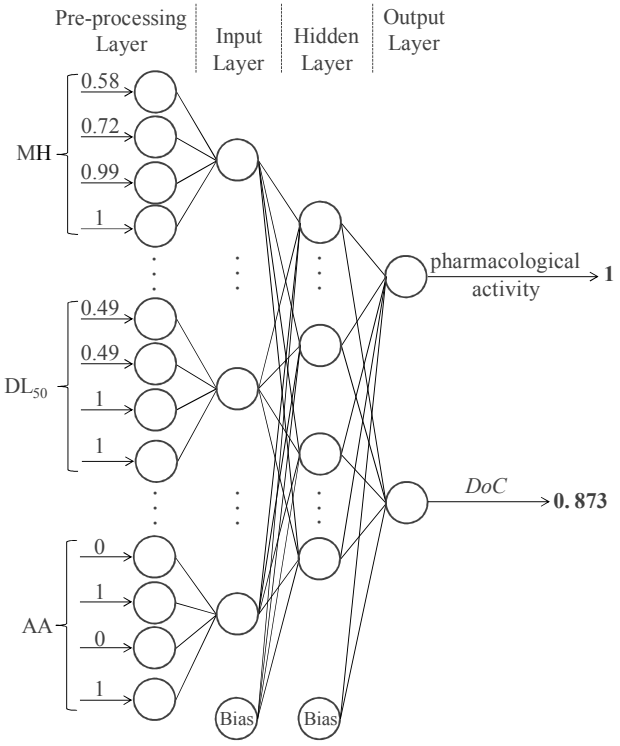

Fig. 3 The Artificial Neural Network topology

V. CONCLUSIONS AND FUTURE WORK

The proposed approach is able to give an adequate response to the need for a good method of pharmacological activity prediction. Indeed, the *Schinus* EOs chemical composition depends on geographical and seasonal features and conditioning the pharmacological properties. To go around the problem more effectively, much more variables must be studied and considered, thus fulfilling important gaps in the existent assessment methods.

Being an area filled with incomplete and unknown data it may be tackled by *Artificial Intelligence* based methodologies and techniques for problem solving. This work presents the founding of a computational framework that uses powerful *KRR* techniques to set the structure of the information and the associate inference mechanisms. Indeed, this method brings a new approach that can revolutionize prediction tools in all its variants, making it more complete than the existing methods and tools available.

The *KRR* presented above are very versatile and capable of covering every possible instance by considering incomplete, contradictory, and even unknown data. Indeed, the new paradigm for *KRR* enables the use of the normalized values of the interval boundaries and their *DoC* values, as inputs to the *ANN*. The output translates the prediction of pharmacological activities and the confidence that one has on such a happening.

Future work may recommend that the same problem must be approached using others computational frameworks like Genetic Programming [16], Case Based Reasoning [29] or Particle Swarm [30], just to name a few.

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