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Application of Mathematical Modeling in Production of Solvent Extraction of a Medicinal Plant

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Abstract: This paper is intended to provide a mathematical model about mass transfer of natural medicinal components in production process of andrographolide as a medical plant. An inverse problem that included a partial differential equation in conjunction with initial and boundary conditions is introduced to estimate diffusivity of andrographolide during production of solvent extraction. To solve the inverse diffusion problem at the beginning a numerical-probabilistic algorithm is employed based on Monte Carlo simulation then effective diffusivity and solute concentration of leaf particles are determined. A numerical test is performed in order to show the efficiency and accuracy of the present work.

Key words: Medicinal plant · Andrographolide · Mathematical modeling · Diffusion coefficient · Monte Carlo simulation

INTRODUCTION

Andrographis paniculata is a herbaceous plant in the family Acanthaceae, native to India and Sri Lanka. It is widely cultivated in southern Asia, where it is used for treatment of infections and some other diseases. Before the creation of antibiotics, it was often used. Mostly the leaves and roots were used for medicinal purposes. Andrographis paniculata is an erect annual herb extremely bitter in taste in all parts of the plant body. The plant is known in north-eastern India as Maha-tita, literally means *king of bitters* and known by various vernacular names. In Iran, it is known as Naine-havandi. As an Ayurveda herb it is known as Kalmegh or Kalamegha, which means *dark cloud*. In Malaysia, it is known as Hempedu Bumi which literally means *bile of earth*, since it is one of the most bitter plants that are used in traditional medicine. The genus Andrographis consists of 28 species of small annual hrubs essentially distributed in tropical Asia. Only a few species are medicinal among which Andrographis paniculata is the most popular one. Andrographis paniculata grows widely in the tropical areas of Asia and it belongs to the acanthaceae family. It has an annual growth of 30-70 cm height. Although it grows erect to a height of 30-110 cm in moist, shady places. The slender stem is dark green, squared in cross-section form with longitudinal furrows and wings along the angles. The lance-shaped leaves have hairless blades measuring up to 8 centimeters long by 2.5 wide. The small flowers are born in spreading raceme. The fruit is a capsule around 2 centimeters long and a few millimeters wide, see Figure 1. It contains lots of yellow-brown seeds [1-5].

Phytochemistry of Andrographolide: Andrographolide is the major constituent extracted from the leaves of the plant Andrographis paniculata which is a bicyclic diterpenoid lactone. Other activities under various experimental conditions of treatment with galactosamine, paracetamol etc., are also attributed to Andrographolide. The hepatoprotective action of andrographolide is related to the activity of certain metabolic enzymes. Systematic studies on chemistry of Andrographolide paniculata have been carried out by Chao *et al*., [6]. Some known constituents are:

Fig. 1: Andrographis paniculata

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Table 1: Identifiers of Andrographolide.

CAS number	*Pub Chem*	*Chem Spider*	*UNII*
5508-58-7	5318517	16735664	410105*JHGR*

Table 2: Properties of Andrographolide.

Molecular formula	*Molar mass*	*Exact mass*
*C*20*H*30*O*5	350.45 g=mol	350.209324
Density	*Melting point*	*Solubility in water*
1.2317 g=cm3	230-231 *C*	sparingly soluble

1) 14-Deoxy-11-dehydroandrographolide, Plant.
2) 14-Deoxy-11-oxoandrographolide, Plant.
3) 5-Hydroxy-7,8,2',3'-Tetramethoxyflavone, Plant.
5) Andrographine, Root.
4) 5-Hydroxy-7,8,2'-Trimethoxy-flavone, Tissue Culture.
6) Andrographolide, Plant.
7) Neoandrographolide, Plant.
8) Panicoline, Root.
9) Paniculide-A, Plant.
10) Paniculide-B, Plant.
11) Paniculide-C, Plant.

In fact Andrographolide is a labdane diterpenoid that is the main bioactive component of the Andrographis paniculata which is a medicinal plant. Andrographolide is an extremely bitter substance extracted from the stem and leaves of the andrographis paniculata, which is grown for medicinal purposes in China and India. IUPAC name is:

3-[2-[decahydro-6-hydroxy-5- (hydroxymethyl)-5,8a- dimethyl-2-methylene-1- napthalenyl]ethylidene] dihydro- 4-hydroxy-2(3H)-furanone.

Some identifiers of Andrographolide are introduced in Table 1. Furthermore, some well known properties of Andrographolide are listed in the Table 2.

Solvent Extraction of Andrographolide: Andrographolide is a natural medicinal component which has been extensively used as a traditional medicine for fever, dysentery, diarrhea, inflammation and sore throat. Researchers have recently found that andrographolide is promising for the treatment of AIDS and numerous symptoms associated with immune disorders. Like other natural medicinal components, the most common method to obtain andrographolide is solid–liquid extraction. Wongkittipong *et al*., [7] performed an experimental study on the solvent extraction of andrographolide from leaves and stems of Andrographis paniculata. Solvent extraction of andrographolide from plant particles is composed of mass transfer of the solute from small pores to the surface of particles and from the surface to the solvent. The effective diffusivity, interfacial equilibrium

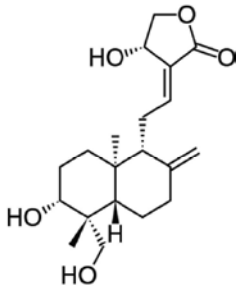

Fig. 2: Andrographolide

concentration between particle surface and solvent attached to the particle and mass transfer resistance of the solvent attached to the particles have strong effects on mass flux of the solute. When all free solute of the particles has been dissolved in the solvent, diffusional mass transfer dominates and consequently interfacial mass transfer is significantly affected by interfacial equilibrium concentration that is determined by partition coefficient. Furthermore, the size and the geometry of particles as well as the mass fraction of different particle geometries in a mixture of plant materials have significant effects on mass flux during the solvent extraction of andrographolide [7-9]. Literature review show that Izadifar and Baik in [7] have been investigated a coupled genetic algorithm and numerical model (GA-NM) as an inverse simulation for estimated four key parameters key variables including effective diffusivity, partition coefficient, average particle size and mass fraction of two geometries of particles for the extraction of andrographolide in plant materials for different temperatures and solvent concentrations of extraction process. The objective of this study is to approximate diffusion coefficient as a function of time via an inverse problem. The inverse problem is the mathematical model for solute concentration in leaf particles when we assume that the shape of leaf particles is close to plate. In fact this paper represents the numerical estimations of couple solute concentration in leaf particles and diffusion coefficient in a one-dimensional parabolic partial differential equation using a numerical-probabilistic algorithm based on Monte Carlo method. Effective diffusivity of andrographolide is determined for a fixed temperature and the fixed specific area of the solid particle. At the end of introduction we mentioned that:

To the best of our knowledge the mathematical model that related to production process of solvent extraction of medicinal plant with unknown time dependent diffusion coefficient has not been studied. All previous works in the field of production of solid-liquid extraction of

medicinal plant, specially extraction of andrographolide, have been considered as an inverse problem with availability prior information for unknown parameters such as diffusion coefficient. But in the present work it is assumed that no prior information is available on the functional form of the unknown diffusion coefficient and thus, it is classified as the function estimation in inverse calculation. Furthermore, according to the latest information from the previous works it is believed that the solution of inverse problem that obtained during production of solvent extraction for estimated unknown parameters, specially solute concentration of leave particle, based on numerical-probabilistic algorithm included the Monte Carlo method has been investigated for the first time in the present study.

Mathematical Modeling: In this section we will consider an inverse problem of determining two unknown functions $U(x,t)$ and $a(t)$ in a one-dimensional linear parabolic equation. The problem is that one needs to find the solute concentration of leaf particles $U(x,t)$ and diffusion coefficient $D_{eff} = a(t)$ that satisfies initial boundary value problem

$$U_t = a(t)U_{xx}, \quad 0 < x < l, \quad t>0, \tag{1}$$

$$U(x, 0)= u_0, \quad 0 < x < l, \tag{2}$$

$$\frac{\partial U}{\partial x}(0,t) = 0, \quad t > 0, \tag{3}$$

$$\frac{\partial U}{\partial x}(1,t) = \psi(t), \quad t > 0, \tag{4}$$

In addition, an overspecified condition is also considered available. To estimate the unknown coefficient $a(t)$, the additional information of measurements on the boundary $x = x_1$, $0 < x_1 < l$, is required. Let the measurements of solute concentration of leaf particles taken at $x = x_1$, over the time period $(0, t_f)$ be denoted by

$$U(x_1, t) = h(t), \quad 0 < t < t_f \tag{5}$$

Where t_f is the final time for measurements. The additional condition is performed based on simulating numerically the diffusion process of Andrographolide. It is evident that for an unknown function $a(t)$, the problem (1)-(4) is under-determined and we are forced to impose additional information (5) to provide a unique solution pair $(U(x,t),a(t))$ to the inverse problem (1)-(5). It is worth noting that the function $\psi(t)$ in condition (4) is considered as a known continuous function and the unknown function $a(t)$ is positive [6].

Numerical Algorithm: The numerical algorithm that applied in this study is discussed in the following steps:

Step 1. Finite Difference Method for Discretizing: At the beginning of the numerical algorithm, finite-difference method is employed to discretize the problem domain. The fully implicit finite difference approximation is used [10-11] for discretizing problem (1)-(5). Therefore, the equation (1) is approximated at the point $(p; q)$ by the difference equation

$$F_{p,q}(u) = \frac{u_{p,q+1} - u_{p,q}}{\upsilon} - \frac{u_{p-1,q+1} - 2u_{p,q+1} + u_{p+1,q+1}}{\mu} = 0, \tag{6}$$

Where $a_{q+1} = a(q\upsilon+\upsilon)$, $xp\mu$, $t = q\upsilon$, $n\mu = 1$, $p = 1(1)n = 1$ and $r = \frac{\upsilon}{\mu^2}$. Therefore the discretized form of problem (1)-(5) may be written in the following matrix form

$$AU = b \tag{7}$$

Step2. Monte Carlo method: At first, Jacobi overrelaxation iterative method is used to convert the system (7) into an equivalent system of the following form

$$U = LU + f \tag{8}$$

Where $L = I - DA$, $f = Db$ and $D = diag(\frac{\gamma}{A_{11}},...,\frac{\gamma}{A_{nn}})$ is a diagonal matrix. Therefor, the sequence of approximate solution vectors of system (8) is generated by applying recursive equation

$$U^{(k)} = LU^{(k-1)} + f, k = 1,2,..., .$$

Now, we consider a Markov chain with transition matrix $P = \{p_{ij}\}$, $i, j = 1,...,N$. The random variable $\Gamma_k[H] = \frac{H_{x_0}}{p_{x_0}} \sum_{m=0}^{k} W_m c_{x_m}$, is defined where $W_m = W_{m-1}\frac{l_{x_{m-1,m}}}{p_{x_{m-1,m}}}$, $m = 1,2,....$ and $W_0 = 1$. We also consider the problem of finding the inner product .

$$\langle H, U \rangle = h_1 u_{1,q+1} + ... + h_N u_{n,q+1},$$

Where $H^t = (u_{1,q+1},...,u_{n,q+1})$ is a given vector and $U^t = (u_{1,q+1},...,u_{n,q+1})$ is the numerical solution of the linear system (8). It is worth noting that the mathematical expectation value of the random variable $\Gamma_k[H]$ is equal to

the inner product $\left\langle H,U^{(k)}\right\rangle$, i.e., $E(\Gamma_k[H])=\left\langle H,U^{(k)}\right\rangle$, [12]. To estimate $\left\langle H,U^{(k)}\right\rangle=h_1u^{(k)}_{1,q+1}+...+h_1u^{(k)}_{n,q+1}$, we simulate N random paths

$$x_0^{(s)}\to x_1^{(s)}\to x_2^{(s)}\to ...\to x_k^{(s)},\quad s=1,...,N,$$

each with the length of k and evaluate the sample mean

$$\Omega_k[H]=\frac{1}{N}\sum_{s=1}^{N}\Gamma_k^{(s)}[H]\approx E(\Gamma_k[H])=\left\langle H,U^{(k)}\right\rangle.$$

In fact, from Theorem 3 we conclude that $\Gamma_k[H]$ is an unbiased estimator of the inner product $\left\langle H,U^{(k)}\right\rangle$. It is readily seen that by setting

$$H^t=(\underbrace{0,...,0}_{j},1,0,...,0)$$

We obtain

$$\left\langle H,U^{(k)}\right\rangle=u^{(k)}_{j,q+1},\ j=1,...,n$$

Hence $\Gamma_k[H]$ is an unbiased estimator of the $u^{(k)}_{j,q+1}$.

Step3. Monte Carlo Optimization Technique: In this work the polynomial form is proposed for the unknown function $a(t)$ before performing the inverse calculation. Therefore $a(t)$ can be approximated as

$$\hat{a}(t)=c_0+c_1t+...+c_mt^m$$

Where $\{c_0,c_1,...,c_m\}$ are constants which remain to be determined simultaneously. The unknown coefficients $\{c_0,c_1,...,c_m\}$ can be determined in such a way that the following functional is minimized:

$$J(c_0,c_1,...,c_m)=\sum_{t=0}^{T_f}\left|U^{cal}(x_1,\eta:c_0,c_1,...,c_m)-h(t)\right|^2.$$

Here, $U(x_1,\eta,\ c_0,c_1,...,c_m)$ are the calculated partial pressures. These quantities are determined from the solution of the direct problem given previously by using an approximated $\hat{a}(t)$ for the exact $a(t)$. The estimated values of c_j, $j=1,...,m$ are determined until the value of $j(c_0,c_1,...,c_m)$ is minimum. Therefore for estimating unknown coefficients c_j we consider the following deterministic optimization problem.

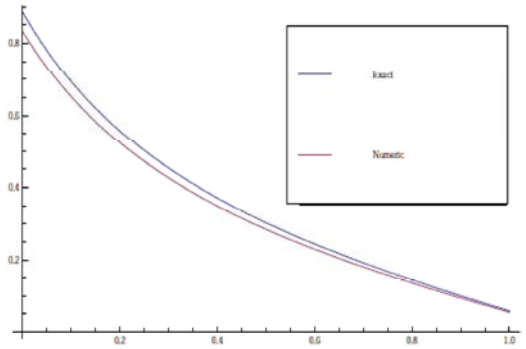

Fig. 3: Numerical result for diffusion coefficient $a(t)$.

Table 3: Results for $U(x,t)$ with $\gamma=0.101$, $\mu=0.005$ and $\upsilon=0.005$, $k=10$ and $N=1000$

t	Error (p=1)	Error (p=2)	Error (p=3)	Error (p=4)	Error (p=5)
0.01	0:00309	0:01093	0:00963	0:002174	0:00316
0.1	0:00410	0:00351	0:00230	0:009107	0:00029
0.5	0:00276	0:00138	0:00070	0:003718	0:00170
0.8	0:00104	0:02003	0:00303	0:000906	0:00490
1.00	0:00382	0:00570	0:00429	0:005060	0:000161

$$\min_{C\in D\subset R^{m+1}}J(C)=J(C^*)=J^*,\qquad (9)$$

Where $J(C)$is real-valued bounded function defined on a closed bounded domain $D\subset R^{m+1}$ and $C=(c_0,c_1,....,c_m)$.

Experimental Results: To give a clear overview of the present algorithm, the following examples are considered and the results are obtained.

Example 1. Consider (1)-(5) with

$$U(x,0)=0,\quad 0<x<1,$$

$$\frac{\partial U}{\partial x}(1,t)=\psi(t)=\frac{-\pi}{2}\sin(t+2),\quad t>0,$$
$$U(\frac{2}{3},t)=h(t)=\frac{1}{2}\sin(t+2),\quad t>0,$$

for which the exact solution is

$$U(x,t)=\cos(\frac{\pi}{2}x)\sin(t+2),$$

and

$$a(t)=\frac{-4}{\pi^2}\tan(t+2)>0.$$

The results obtained for $U(x,t)$ with $\gamma=0.101$, $\mu=0.005$ and $\upsilon=0.005$, $k=10$ and $N=1000$ are presented in Table 3. Furthermore, result for diffusion coefficient $a(t)$ is presented via Figure 3.

CONCLUSION

The present study successfully applied the numerical algorithm involving the finite differences method in conjunction with Monte Carlo method to solve a diffusion problem related to production process of solvent extraction of a well-known medicinal plant. From the numerical experiment, it can be seen that the proposed numerical method is efficient and accurate to estimate the solute concentration of leaf particles $U(x,t)$ in a one-dimensional linear parabolic partial differential equation.

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