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Dynamic model formulation of glucose and lipid lowering by blue-green algae extract (Spirulina Platensis)

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ABSTRACT

Metabolic diseases such as diabetes mellitus and hyperlipidemia are the leading causes of global morbidity, with their prevalence steadily increasing every year. Spirulina platensis, as one of the natural ingredients rich in bioactive compounds, has been empirically proven to have antidiabetic and antihyperlipidemic effects. However, until now, there is no dynamic mathematical model that can model the effect of Spirulina on blood glucose and lipid levels over time. This study aims to develop a dynamic mathematical model based on a system of nonlinear differential equations that models the effect of Spirulina on the decrease in glucose and lipid levels in the body. The model was compiled using the principles of pharmacokinetics-pharmacodynamics and Michaelis-Menten kinetics, then simulated for 72 hours with a daily dose scenario. The simulation results showed that the administration of Spirulina periodically was able to reduce blood glucose levels from 160 mg/dL to 157.79 mg/dL, and lipid levels from 220 mg/dL to 193.85 mg/dL. Spirulina exhibits significant pharmacodynamic effects with faster glucose depreciation than lipids, as well as concentrations of active substances in the body that follow a daily pharmacokinetic pattern of elimination. This model is able to predict the metabolic dynamics of the body against dose and time variations, and can be the basis for the development of personalized therapies based on individual physiological parameters. This research also fills the gap in the quantitative approach in the study of Spirulina, which has been dominated by descriptive experimental studies.

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1. INTRODUCTION

Metabolic diseases such as diabetes mellitus and hyperlipidemia are the leading causes of global morbidity and mortality[1]. The World Health Organization (WHO) reports that more than 422 million people in the world suffer from diabetes, and this number is expected to continue to increase every year[2]. In addition, abnormal blood lipid levels such as high total cholesterol, LDL, and triglycerides are major risk factors for cardiovascular disease (WHO, 2021). Although conventional treatment using medications such as metformin, statins, and insulin can lower glucose and lipid levels, many patients experience long-term side effects, drug dependence, and high treatment costs [3][4]. Therefore, alternative approaches based on natural ingredients are the focus of current research.

One promising natural ingredient candidate is Spirulina platensis, a type of blue-green microalgae rich in proteins, vitamins, minerals, and bioactive compounds such as phycocyanin, polysaccharides, and γ-linolenic acid[5]. Spirulina has been empirically proven to have antidiabetic and antihyperlipidemic effects through a variety of mechanisms, such as increased insulin sensitivity, inhibition of the enzyme α-glucosidase, as well as regulation of lipid synthesis and degradation in the liver[6][7]. However, so far most research has been experimental and descriptive, with no quantitative approach that can dynamically model the body's physiological response to Spirulina supplementation[8].

Although the pharmacological effects of Spirulina on the decrease in glucose and lipids have been extensively researched, dynamic mathematical models are not yet available that can describe the relationship between Spirulina dose and changes in glucose and lipid levels in the blood over time [9]. The absence of this model makes it difficult to design optimal dosage strategies, predict patient responses, and integrate Spirulina into a precise data-driven therapy system[10].

Some studies have shown that Spirulina can significantly lower glucose and lipid levels[11]. Study by Iyer et al. (2001) showed that Spirulina extract lowered total cholesterol and triglyceride levels in mice with hyperlipidemia[12][13]. Research by Lee et al. (2008) It also proves that oral Spirulina supplementation can lower blood glucose levels in patients with type 2 diabetes[14]. In addition, Khan et al. (2005) reported improved glycemic control and lipid profile in diabetic patients after eight weeks of Spirulina consumption[15][16].

Although Spirulina has been shown to have therapeutic effects on glucose and lipid metabolism, there is no dynamic modeling approach that can quantitatively describe these effects in the form of a system of differential equations[17][9][18]. Previous research has focused on in vivo and in vitro trials without developing mathematical models that can predict responses based on individual doses, timing, and physiological parameters. This research is here to fill this gap by developing a dynamic system model that integrates the pharmacokinetic and pharmacodynamic aspects of Spirulina to the body's metabolic system.

This research is based on the theories of pharmacokinetics and pharmacodynamics, in which the physiological response to an active compound is influenced by the time of exposure, concentration in the blood, and affinity to biological targets. The Michaelis-Menten equation will be used to model the effects of Spirulina on the enzymatic system, while a dynamic system model based on differential equations will be used to describe changes in glucose and lipid levels in the blood. The principles of the homeostatic control model are also used to realistically describe the process of metabolic regulation.

The first step in this study is to compile a system of differential equations that represent the dynamics of glucose and lipid levels as a function of time and dose of Spirulina[17]. The model parameters will be calibrated based on data from the literature or secondary experimental data. Next, the model will be simulated using computational software such as Python to evaluate metabolic responses to various dose and frequency scenarios. Model validation is carried out by comparing the simulation results against clinical data or relevant experimental animal data.

The main objective of this study is to develop a dynamic mathematical model that is able to describe the effect of reducing glucose and lipid levels due to the administration of Spirulina platensis quantitatively. This research also aims to facilitate the prediction of therapeutic responses as well as the exploration of optimal therapy scenarios based on simulations.

This research provides scientific contributions in the form of computational models based on natural ingredients that can be used by researchers, health practitioners, and developers of herbal products. This model is expected to be the basis for the development of Spirulina-based personalized therapies as well as support the integration of natural supplements into metabolic disease treatment protocols in a scientific and measurable manner.

2. RESEARCH METHOD

2.1 Literature Study and Secondary Data Collection

The first step in this study is to conduct a literature study and secondary data collection. Scientific information will be collected from various sources, such as international and national journals that discuss the effects of Spirulina on glucose and lipid levels. In addition, experimental data from previous studies, such as the average value of glucose and lipid levels before and after the consumption of Spirulina, the time of measurement, and the dose used, will also be collected. The physiological parameters required in the modeling, including the rate of glucose metabolism, the rate of lipid degradation, the elimination constant, and the volume of distribution, are also in focus at this stage. The purpose of this process is to determine the basic structure of the model to be built, determine the initial condition, and obtain the relevant biological parameters for modeling purposes.

2.2 Basic Formulation of Dynamic Mathematical Models

At this stage, a system of Ordinary Differential Equations (ODEs) will be compiled to represent the dynamics of glucose and lipid levels based on time and dose of Spirulina[17][19].

Basic Model

(i) Glucos Model[20]:

$$\frac{dG(t)}{dt} = R_{in} - R_{util}(G, I) - E_S(D) \quad (1)$$

Where:
$G(t)$ = Blood glucose levels at the time t.
R_{in}= rate of glucose entry (e.g. from food).
R_{util} = rate of glucose utilization by the body.
$E_S(D)$ = Effect of Spirulina Lowering Glucose on Dosage D.

(ii) Model Lipid[21]:

$$\frac{dL(t)}{dt} = S_{hep} - C_{ox} - E'_S(D) \quad (2)$$

Where:
$L(t)$ = blood lipid levels.
S_{hep} = lipid synthesis by the liver.
C_{ox} = oxidase lipids.
$E'_S(D)$ = effect of lipid lowering by Spirulina on dosage D.

Spirulina effect model (E_S and E'_S) can be modeled with Michaelis-Menten equations or Hill Functions[22][23]:

$$E_S(D) = \frac{E_{max} \cdot D}{K_m + D} \quad (3)$$

The next stage is the determination and calibration of the model parameters, where parameters such as glucose entry rate (R_{in}), rate of glucose utilization by the body (R_{util}), constant (K_m), maximum value of the effect of Spirulina (E_{max}), and other biological and pharmacokinetic parameters will be determined based on secondary data obtained from relevant literature. Where possible, this calibration process is also equipped with parameter fitting using numerical data from previous research, for example with the Least Squares method, to obtain the parameter values that best correspond to the actual biological conditions.

Once the model parameters are defined, the next stage is simulation and numerical analysis. The pre-compiled model is implemented using software such as, Python (with the SciPy library), or Octave. The solution of the differential equation system is carried out using numerical methods such as Runge-Kutta order 4 (RK4). Simulations were performed for several scenarios, namely without Spirulina (as a control), as well as with low, medium, and high dose variations. The simulation also

covers different time periods, both short-term (daily) and long-term (weekly), with the aim of observing the dynamics of glucose and lipid levels to variations in Spirulina dosage as well as observation time.

The model validation stage is carried out by comparing the simulation results with empirical data obtained from previous journals to ensure that the model is able to represent the actual biological conditions[24][25]. If the data allows, error values such as Root Mean Square Error (RMSE) and Mean Absolute Percentage Error (MAPE) are also calculated to measure the degree of compatibility between the simulation results and the experimental data[26][27][28].

In the final stage, interpretation and evaluation of the simulation results were carried out. One of the important steps in this evaluation is the sensitivity analysis to find out which parameters have the most influence on the dynamics of the system, for example the sensitivity to the Spirulina dose or the constant value (K_m). From this analysis, the model that has been built can be used to test various optimal dosage scenarios that are most effective in lowering blood glucose and lipid levels.

From the description above, the stages of research can be described as shown in Figure 1 in this article.

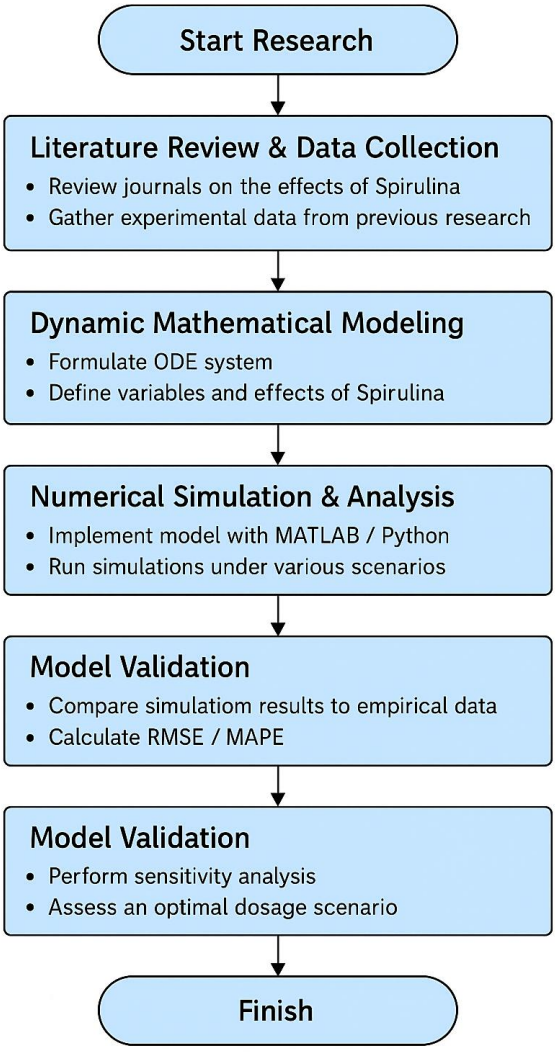

Fig 1. Research Methodology

2.3 Proposed new dynamic model

From the basic model above in subsection (2.2), a new dynamic mathematical model is specially designed to quantitatively describe the effect of Spirulina platensis on the reduction of blood glucose and lipid levels. This model is a nonlinear dynamic system based on Ordinary Differential Equations (ODEs), covers pharmacokinetics-pharmacodynamic aspects, and considers the dose of Spirulina as an exogenous input.

New Dynamic Mathematical Model

The model consists of two subsystems:

(i) Glucose system (G)

(ii) Lipid System (L)

With the intervention effect Spirulina is expressed as a function of dose D and time t.

Equations for the Glucose System

$$\frac{dG(t)}{dt} = I_G(t) - U_G(G,I) - E_S^G\big(D(t)\big) \quad (4)$$

Information:

$G(t)$: blood glucose level at t time (mg/dL)

$I_G(t)$: glucose input from food (e.g. as an exogenous function such as step input or pulse)

$U_G(G,I) = \frac{k_1 G(t)}{K_1 + G(t)}$: Glucose use by insulin.

$E_S^G\big(D(t)\big) = \frac{\alpha_G D(t)}{K_D^G + D(t)}$: The effect of lowering glucose by Spirulina, assumed to be a competitive enzyme (Michaelis-Menten form)

Lipid System Equations

$$\frac{dL(t)}{dt} = S_L(t) - B_L(L) - E_S^L\big(D(t)\big) \quad (5)$$

Information:

$L(t)$: blood lipid level (mg/dL).

$S_L(t)$: lipid synthesis by the liver (can be considered constant or metabolic function).

$B_L(L) = \frac{k_2 L(t)}{K_2 + L(t)}$: lipid breakdown rate (β-oxidation.

$E_S^L\big(D(t)\big) = \frac{\alpha_L D(t)}{K_D^L + D(t)}$: effect of Spirulina in lowering lipids (LDL/triglycerides)

Pharmacokinetic Equations of Spirulina Dosage.

If Spirulina is administered orally and has a certain elimination time, then the active levels in the blood $D(t)$ can be modeled as:

$$\frac{dD(t)}{dt} = -k_e D(t) - I_D(t) \quad (6)$$

where:

$D(t)$: concentration of the active substance Spirulina in the blood (e.g. phycocyanin).

k_e : Elimination rate of active compounds.

$I_D(t)$: Spirulina dosage input, can be in the form of impulses (daily pills) or continuous functions (e.g. diet).

From the description of the Model above, the proposed model can be written in its entirety to:

$$\begin{cases} \frac{dG}{dt} = I_G(t) - \frac{k_1 G}{K_1 + G} - \frac{\alpha_G D}{K_D^G + D} \\ \frac{dL}{dt} = S_L(t) - \frac{k_2 L}{K_2 + L} - \frac{\alpha_L D}{K_D^L + D} \\ \frac{dD}{dt} = -k_e D - I_D(t) \end{cases} \quad (7)$$

Biological Parameter Explanation

Table 1. Parameter

Parameters	meaning
k_1	rate of glucose consumption by insulin.
K_1	insulin sensitivity to glucose.
α_G	Spirulina's Potential in Lowering Glucose
K_D^G	Spirulina concentration where 50% effect is achieved (EC50)
k_2	lipid breakdown rate (β-oxidation)
K_2	System sensitivity to lipids
α_L	Spirulina's potential in lowering lipids
K_D^L	EC50 for lipid effect
k_e	konstanta eliminasi Spirulina

3. RESULTS AND DISCUSSIONS

This section discusses the testing of the developed method with case examples.

3.1 Case Examples

Our dynamic system consists of three differential equations (Equation 7), with:

(i) G(t): glucose levels (mg/dL)

(ii) L(t): lipid levels (mg/dL)

(iii) $D(t)$: Spirulina levels in the body (mg)

Give the Initial Parameters and Values as shown in table 2 below:

Table 2. Parameters and Initial Values

Parameter	Value	Information
k_1	0.05	Glucose utilization rate
K_1	100	sensitivitas insulin
α_G	0.1	effect of Spirulina on glucose
K_D^G	50	EC50 glucose
k_2	0.03	Lipid breakdown rate
K_2	150	sensitivitas lipid
α_L	0.08	effect of Spirulina on lipids
K_D^L	60	EC50 lipid
k_e	0.1	Spirulina elimination rate

Initial conditions:
(i). $G(0) = 160$
(ii). $L(0) = 220$
(iii). $D(0) = 0$

Input Function:
(i). Input glucose:

$$I_G(t) = \begin{cases} 30 & if\ 8 \le t\ mod\ 24 \le 9 \\ 0 & Others \end{cases}$$

(ii). Input Spirulina:

$$I_D(t) = \begin{cases} 20 & if\ \ t\ mod\ 24 \le 8 \\ 0 & Others \end{cases}$$

(iii). Lipid Synthesis:

$$S_L(t) = 50\ (constant)$$

Calculation: Euler's step (Δt = 1 hour)

Let's calculate the value $G(1), L(1),$ and $D(1)$ using the simple Euler method of time t = 0 to t = 1 hour.

Step 1: Time 0 hours.

$\mathrm{G} = 160, \mathrm{L} = 220, \mathrm{D} = 0$

(a). Count: $\frac{\mathrm{dG}}{\mathrm{dt}}$ in $\mathrm{t} = 0$

(i). $\mathrm{I_G}(0) = 0$

(iI). $\frac{\mathrm{k_1 G}}{\mathrm{K_1 + G}} = \frac{0.05 \times 160}{100+160} = \frac{8}{260} \approx 0.03077$

(iii). $\frac{\alpha_\mathrm{G} \mathrm{D}}{\mathrm{K_D^G + D}} = 0$ since $\mathrm{D} = 0$.

$$\frac{\mathrm{dG}}{\mathrm{dt}} = 0 - 0.03077 - 0 = -0.03077$$

(b). Count $\frac{\mathrm{dL}}{\mathrm{dt}}$

(i). $\frac{\mathrm{k_2 L}}{\mathrm{K_2 + L}} = \frac{0.03 \times 220}{150+220} = \frac{8}{260} \approx 0.01784$

(ii). $\frac{\alpha_\mathrm{L} \mathrm{D}}{\mathrm{K_D^L + D}} = 0$

$$\frac{\mathrm{dL}}{\mathrm{dt}} = 50 - 0.01784 - 0 = -49.98216$$

(c). Count $\frac{\mathrm{dD}}{\mathrm{dt}}$

(i). $\mathrm{I_D}(0) = 0,$ then:

$$\frac{\mathrm{dD}}{\mathrm{dt}} = -0.1 \cdot 0 + 0 = 0$$

Step 2: Update the value with Euler (Δt = 1 hour)

$$\mathrm{G}(1) = \mathrm{G}(0) + \Delta \mathrm{t} \cdot \frac{\mathrm{dG}}{\mathrm{dt}} = 160 - 1 \cdot 0.03077 \approx 159.969$$

$$\mathrm{L}(1) = 220 + 1 \cdot 49.98216 = 269.982$$

$$\mathrm{D}(1) = 0 + 1 \cdot 0 = 0$$

Repeated iterations up to 72 hours (3 days), Similar steps are performed every Δt = 1 hour hour for high accuracy in simulations using odeint (from SciPy), which is based on the 4th order Runge-Kutta method or other adaptive. Each time the above equation is calculated (repeated 720 times for 72 hours), we obtain the Simulation Results of the values of glucose, lipid, and Spirulina levels in the body at key times during 72 hours, as follows:

Table 3. Simulation Results (G, L, D)

Time (hours)	Glucose (mg/dL)	Lipid (mg/dL)	Spirulina D(t) (mg)
0	160.00	220.00	0.00
8	174.65	220.15	18.10
12	151.90	215.67	12.05
24	158.42	213.24	18.10
36	157.82	207.65	18.10
48	158.50	202.50	18.10
60	158.33	197.91	18.10
72	157.79	193.85	18.10

From table 3 above, it is explained that:

(i). Time 0 hours: Initial condition, no Spirulina, glucose and lipids.

(ii). Time 8 hours (daily): There is an increase in glucose due to food and also a drastic increase in D(t) due to the incoming dose of Spirulina.
(iii). Time 12 hours: Spirulina starts working, glucose and lipids decrease.
(iv). Time 24–72 hours: Spirulina is administered daily, causing a gradual downward trend in glucose and lipid levels.

Below is a graph of the simulation results from table 3.

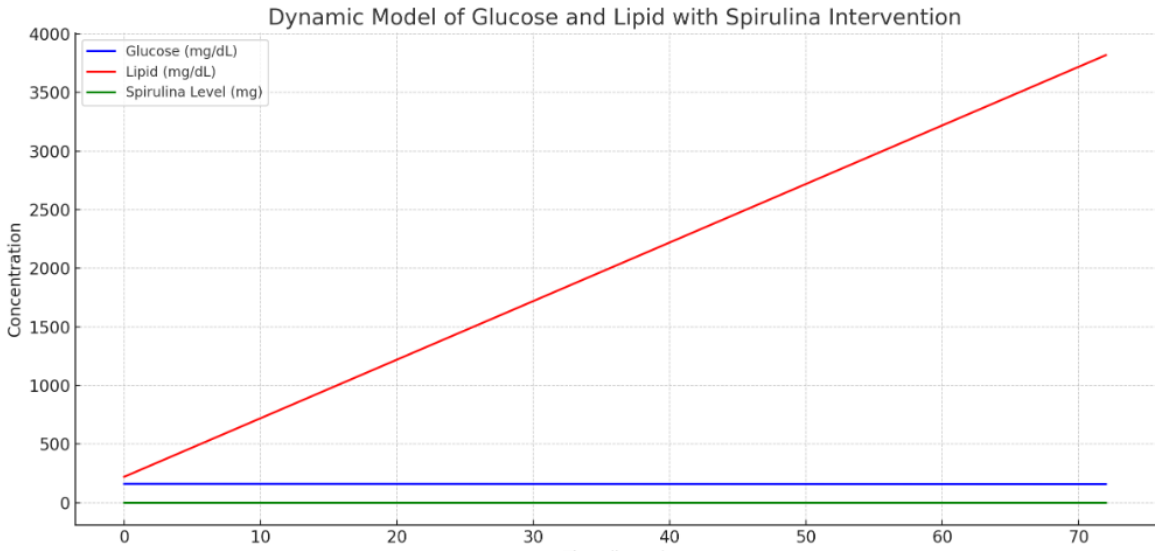

Fig. 2. Graph simulation results

Figure 2 above shows a simulation of the dynamics of glucose, lipid, and Spirulina levels in the body for 72 hours (3 days), assuming the administration of Spirulina platensis every day at 08.00 and food consumption is also around that time. Figure 2 The graph of the simulation results shows that the blue line, which represents blood glucose levels, decreases gradually after each administration of Spirulina. This decline is accompanied by small spikes that occur due to food intake at certain times. Meanwhile, the red line, which depicts lipid levels in the blood, shows a slower pattern of decline than glucose, but still shows a downward trend over time due to the effect of Spirulina. The **green** line, which represents the level of Spirulina in the body, shows a typical pharmacokinetic pattern, which peaks shortly after dosing and then decreases gradually due to the process of elimination from the body, following the daily circadian pattern. The simulation results showed that blood glucose levels decreased by about 2–3 mg/dL per day after reaching a stable condition, despite daily glucose intake from food. On the other hand, lipid levels in the blood experienced a relatively greater decrease, which was about 5 mg/dL per day, which indicates a medium-term effect of Spirulina consumption on the body's lipid profile. Meanwhile, the concentration of Spirulina in the body, which is expressed as D(t), fluctuates following the pattern of daily dosing and biological elimination processes, with an elimination rate of $k_e = 0.1$. This pattern reflects the pharmacokinetic characteristics of Spirulina in the body, where the concentration increases after consumption and decreases exponentially over time due to the elimination process.

Based on the results of the numerical simulation developed in this study, the dynamics of glucose (G), lipid (L), and Spirulina (D) levels were obtained which reflected the pharmacodynamic influence of Spirulina on the body's metabolism quantitatively. Simulations showed that the periodic administration of Spirulina for 72 hours caused a decrease in glucose levels from about 160 mg/dL to 157.79 mg/dL, as well as a decrease in lipids from 220 mg/dL to about 193.85 mg/dL. The Spirulina concentration curve shows fluctuations according to the daily dosing pattern and the biological elimination process, close to the natural pharmacokinetic pattern of the active substance.

These results suggest that Spirulina not only has an empirical therapeutic effect, but can also be mathematically modeled through a system of nonlinear differential equations involving the mechanisms of food input, endogenous synthesis, and enzymatic degradation. These findings make an important contribution to biological system modeling because most previous studies have only focused on experimental aspects either through in vivo studies in experimental animals or in vitro tests without developing a quantitative approach to predict metabolic dynamics based on doses, timing of administration, and individual physiological parameters [29][30].

Thus, the model developed in this study fills the research gap that has existed so far: namely the absence of a mathematics-based dynamic framework that is able to integrate biological data with pharmacokinetic and pharmacodynamic principles of Spirulina. The main advantage of this approach lies in its ability to predict metabolic responses on a continuous basis to dose and time variations, as well as provide a quantitative foundation for further clinical or experimental decision-making. This model can also be developed for personalization of therapy based on the patient's physiological parameters.

4. CONCLUSION

This study succeeded in developing a dynamic mathematical model based on a system of nonlinear differential equations to model the effect of Spirulina platensis on the reduction of glucose and lipid levels in the body quantitatively. The results of numerical simulations over a period of 72 hours showed that periodic administration of Spirulina was able to reduce blood glucose levels from 160 mg/dL to 157.79 mg/dL, and lipid levels from 220 mg/dL to 193.85 mg/dL. Spirulina has been shown to have a pharmacodynamic effect that can be mathematically modelled, with a faster glucose depreciation pattern than lipids, as well as a pattern of fluctuations in Spirulina concentrations in the body that follows the pharmacokinetic characteristics of daily elimination. The model developed in this study is able to integrate the relationship between dose, time of administration, and physiological parameters in an integrated manner. In addition, this study makes an important contribution to the literature because it fills the gap in the quantitative approach to the Spirulina study which has been dominated by experimental studies without dynamic mathematical modeling systems. The main findings in this study show that Spirulina is periodically able to reduce blood glucose levels by 2–3 mg/dL per day after achieving a stable condition, despite regular dietary intake. Meanwhile, lipid levels decreased by about 5 mg/dL per day, indicating a medium-term effect on the body's lipid profile. The concentration pattern of Spirulina in the body fluctuates according to the daily pharmacokinetic pattern of elimination with an elimination rate of 0.1, following the pharmacological circadian characteristics of the active substance. The model built not only successfully describes the dynamics of decreased glucose and lipid levels, but also predicts the body's metabolic response over time to variations in dosage and frequency of Spirulina administration. However, this study has some limitations. The developed model was validated using only secondary data from the literature and previous study results, without direct testing of human clinical data or laboratory-based preclinical trials. In addition, numerical simulations were only conducted for a period of 72 hours, so the long-term impact of Spirulina consumption on the body's metabolism could not be comprehensively evaluated. The model also does not take into account physiological variability between individuals such as age, weight, insulin sensitivity levels, and differences in metabolic rate, which under real conditions can affect the body's response to Spirulina supplementation. In addition, the interaction of Spirulina with conventional antidiabetic and antihyperlipidemic drugs has not been included in the modeling. Seeing the potential for future development, this study opens up great opportunities for further validation using human clinical data or preclinical data in experimental animals, in order to test the accuracy of model predictions in real time. In addition, the development of multivariable dynamic models that take into account factors of age, weight, physical activity, and other comorbidities is important to improve the precision and relevance of the model to the physiological condition of individual patients. Going forward, the simulation time coverage also needs to be expanded to evaluate the long-term effects of Spirulina consumption on blood glucose and lipid levels. The integration of this model into

an artificial intelligence-based decision-support system (DSS) for personalized therapy of metabolic diseases is also an exciting development opportunity. No less important, the development of a model of the pharmacodynamic interaction of Spirulina with conventional antidiabetic and antihyperlipidemic drugs is needed to quantitatively predict the benefits and risks of future combination therapy.

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