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Dynamic Model of Andrographolide Therapy for COVID-19 †

Panittavee Yarnvitayalert and Teerapol Saleewong *

Department of Mathematics, Faculty of Science, King Mongkut's University of Technology Thonburi, Bangkok 10140, Thailand; panittavee.n@mail.kmutt.ac.th

* Correspondence: teerapol.sal@kmutt.ac.th

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Abstract: *Andrographis paniculate* extract (APE) has been used as a Thailand traditional medicine owing to andrographolide which is effective for the viral clearance and prevention of disease progression. Several viral infections have been treated with APE, including SARS-CoV-2. The recommended dosage is 180 mg three times a day. We constructed a mathematical viral dynamic model of the SARS-CoV-2 model with andrographolide therapy by different doses. The pharmacokinetic/pharmacodynamic (PK/PD) model reduces the duration of viral clearance with a dose of 60 mg per day. Moreover, APE improved the therapeutic efficacy of COVID-19 therapy.

Keywords: andrographolide; COVID-19; PK/PD model; viral dynamic model

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1. Introduction

Andrographolide is the major active component in Andrographis paniculate extract (APE) and has been used for the treatment of viral diseases such as COVID-19 due to its inhibited production of SARS-CoV-2 infectious virions [1]. Many researchers reported the clinical use of andrographolide for relieving symptoms of common colds and upper respiratory tract infections. In 2003, Kulichenko et al. tried the treatment of influenza with 30 mg and 45 mg of APE per day and decreased the duration of viral disease [2]. Saxena et al. found that 60 mg of APE per day relieved symptoms of uncomplicated upper respiratory tract infections (URTI) [3]. Thamlikitkul et al. researched the efficacy of APE (180–360 mg per day) for pharyngotonsillitis and observed the relief of fever and sore throat. Further, patients were satisfied with a higher dose of APE [4]. In 2021, Kulthanit et al. proposed COVID-19 treatment with 180 mg of APE per day for 5 days [5]. Nevertheless, there are limitations in the clinical use of APE. Thus, we investigated the potential mechanism and effect of andrographolide on the life cycle of SARS-CoV-2.

The pharmacokinetics (PK) of andrographolide on the life cycle of SARS-CoV-2 were explored in terms of in vivo mechanism that cannot be quantified without a blood test or reverse transcription-polymerase chain reaction (RT-PCR) tests to report the quantity of andrographolide in plasma and viral cells. Mathematical modeling is effective for the quantitative and qualitative study of COVID-19 because the model illustrates the amount of andrographolide, viral cell growth, and target cell infection. Goncalves et al. reported a viral dynamic model by using a standard target cell limit model with the eclipse phase to describe SARS-CoV-2 infection and determined viral growth parameters to predict the effects of antiviral treatments [6]. Dodds et al. discussed the potential drugs that influenced the SARS-CoV-2 viral cell cycle to reduce viral load and host cell infection [7].

For andrographolide treatment, we constructed a viral dynamics model which was a two-compartment model using pharmacokinetics and pharmacodynamics (PK/PD) in this study and investigated the efficacy of andrographolide on the SARS-CoV-2 infection. Andrographolide was measured in the plasma and tissue of subjects who took APE and its inhibitory potential was evaluated on viral production. The viral dynamic model

was refined with an effective andrographolide dose considering the behavior of target cell infection, virus-cell spread, and virus shedding duration. It was also explored if andrographolide dose affected the relief of symptoms such as fever, cough, and sore throat.

2. Mathematical Model

To investigate the effect of andrographolide dose on the viral life cycle, daily dosages of 30, 45, 60, 180, and 360 mg were given to the subjects, and PK/PD characteristics of andrographolide were explored [8]. PK was defined in in vivo distribution [8], whereas PK was determined to see if the drug's effect was related to its concentration. The relationship between PK and PD was investigated in the experiment, as seen in Figure 1.

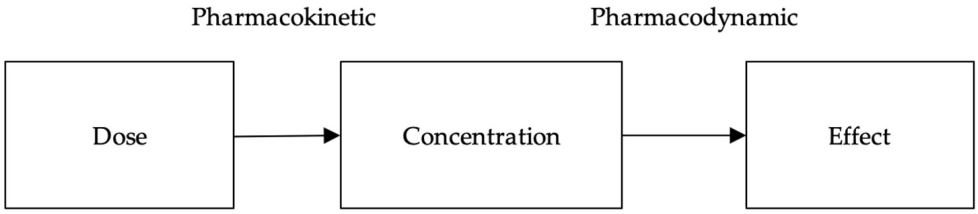

Figure 1. Relationship between pharmacokinetic and pharmacodynamic of PC.

2.1. PK Model

After patients took APE, andrographolide existed in plasma and tissue in the human body. Andrographolide was uptaken into plasma (C_p) at a certain rate of *Dose* and removed by a rate of k_{10}. Then, andrographolide was uptaken in peripheral tissue (C_t) at a rate of k_{12}, and transferred to plasma at a rate of k_{21}. PK of andrographolide is shown in Figure 2, which explains the concentration of andrographolide in the human body using the two-compartment model. The mathematical equation corresponding to the PK of andrographolide is expressed as

$$\begin{aligned} dC_p/dt &= Dose - (k_{10} + k_{12})C_p + k_{21}C_t, \\ dC_t/dt &= k_{12}C_p - k_{21}C_t, \end{aligned} \quad (1)$$

where C_p is the concentration of andrographolide in plasma, C_t is the concentration of andrographolide in peripheral tissue, and k_{10}, k_{12}, and k_{21} are rates.

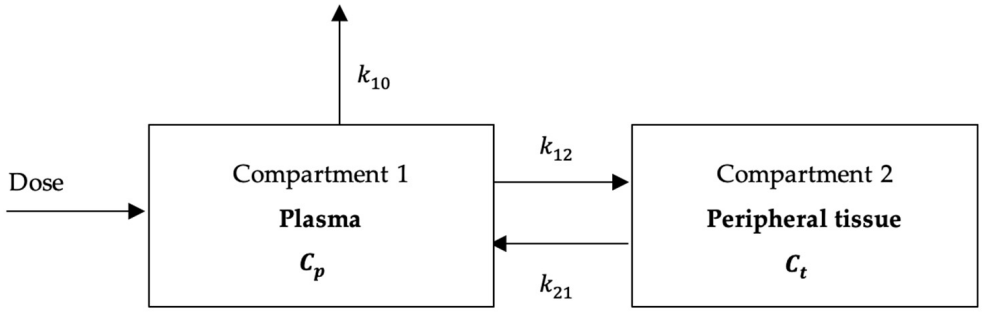

Figure 2. Pharmacokinetic of andrographolide.

2.2. PK/PD Model

The drug's effect is related to its concentration in plasma. Thus, the efficacy of andrographolide was assessed with the following equations.

$$\varepsilon(t) = C_p(t)/[C_p(t) + IC_{50}], \quad (2)$$

where IC_{50} is the half-maximal inhibitory concentration.

The average efficacy of andrographolide during the first 5 days of treatment was quantified as

$$\varepsilon_{mean} = 1/5 \int_0^5 [\, C_p(t)/(C_p(t) + IC_{50})]\, dt \quad (3)$$

As andrographolide inhibited the production of SARS-CoV-2 infectious virions, the inhibitory impact of andrographolide was adjusted in the proposed viral dynamic model.

2.3. Viral Dynamic Model

The coronavirus interacts with epithelial cells through the membrane by being bound between the receptor and the protein spike. Then, the uninfected target cell (T) is infected at a certain in the eclipse phase, β, and survives during the incubation period to productively infect cells at a rate of k. New viruses are RNA replicated at a productive rate of p. This process duplicates RNA to reproduce new viruses. The infected cell dies at a rate of δ. New viruses interact with and infect other epithelial cells. Virus cells die at a rate of c (Figure 3).

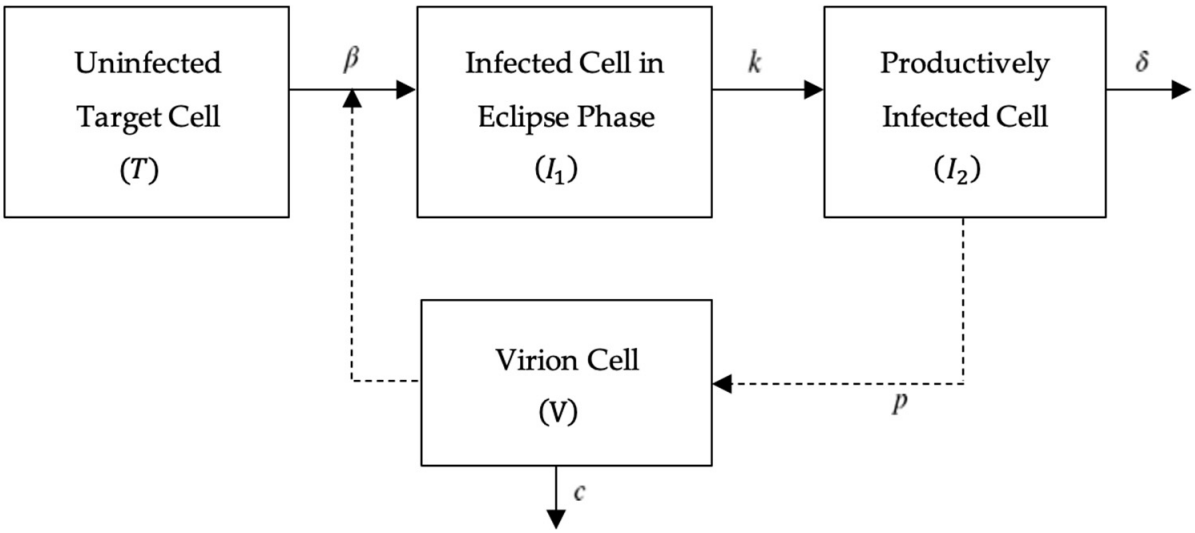

Figure 3. Viral dynamic model of SAR-CoV-2 in eclipse phase.

The mathematical equation corresponding to the viral dynamic model for SARS-CoV-2 treated with andrographolide is as follows.

$$\begin{aligned} dT/dt &= -\beta VT \\ dI_1/dt &= \beta VT - kI_1 \\ dI_2/dt &= kI_1 - \delta I_2 \\ dV/dt &= pI_2 - cV - \beta VT \end{aligned} \quad (4)$$

where T is target cells, I_1 is infected cells in the eclipse phase, I_2 is productively infected cells, V is virus cells, and β, k, δ, p, and c are constants.

2.4. Ordinary Differential Equation

Andrographolide inhibited RNA replication in the life cycle of viruses. RNA was replicated at a rate of p. Thus, the viral dynamic model was adjusted by the PK/PD of andrographolide, as shown in Figure 4.

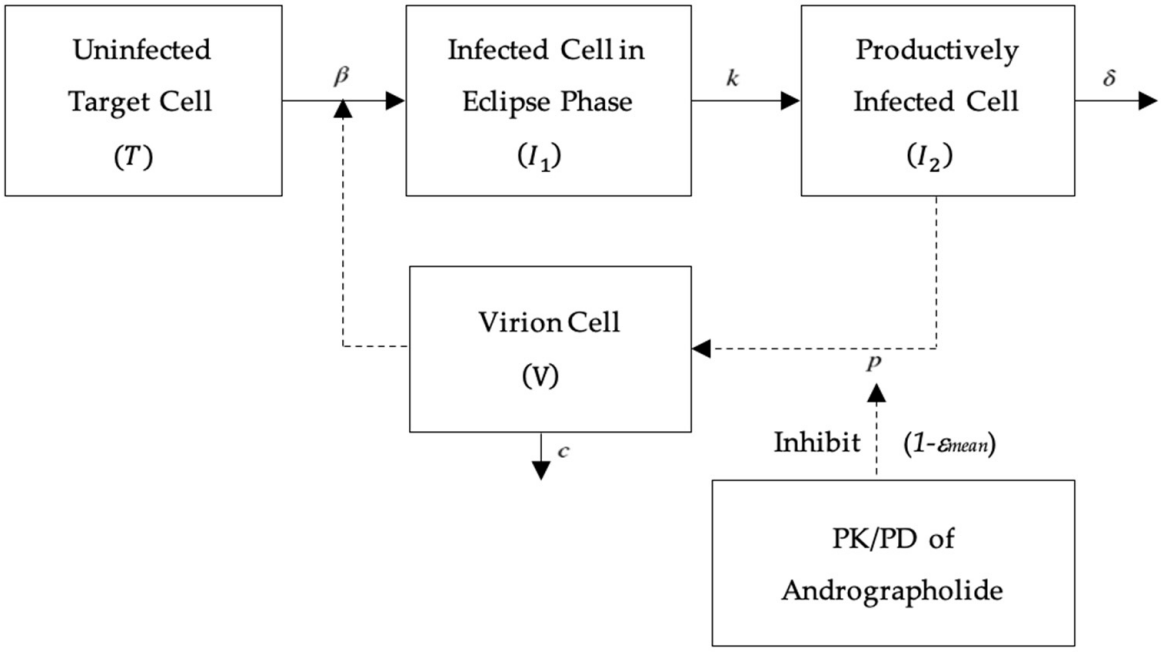

Figure 4. Viral dynamic model of SAR-CoV-2 treated with andrographolide.

Therefore, Equation (4) was rewritten as follows.

$$\begin{aligned} dC_p/dt &= Dose - (k_{10} + k_{12})C_p + k_{21}C_t, \\ dC_t/dt &= k_{12}C_p - k_{21}C_t, \\ dT/dt &= -\beta VT, \\ dI_1/dt &= \beta VT - kI_1, \\ dI_2/dt &= kI_1 - \delta I_2, \\ dV/dt &= (1 - \varepsilon_{mean})\, pI_2 - cV - \beta VT, \end{aligned} \tag{5}$$

where the efficacy is defined as $\varepsilon(t) = C_p(t)/[C_p(t) + IC_{50}]$, and the mean effectiveness of andrographolide in the first 5 days is given by $\varepsilon_{mean} = 1/5\,{}_0\int^5[C_p(t)/(C_p(t) + IC_{50})]$. The half-maximal inhibitory concentration, IC_{50}, was 9.54 μg/mL [5]. The variable of system equation as show in Table 1.

Table 1. Summary of variables of viral dynamics model.

	Variable	Unit
C_p	Andrographolide in plasma	ng/mL
C_t	Andrographolide in tissue	ng/mL
T	Target cells	cell/mL
I_1	Infected cells in eclipse phase	cell/mL
I_2	Productively infected cells	cell/mL
V	SARs-CoV-2	cell/mL

3. Results

We used the mathematical model based on Equation (5) to determine the viral load in the andrographolide therapy. Firstly, we chose the initial value $C_p(0)$ = Dose (ng/mL), $C_t(0)$ = 0 ng/mL, $T(0) = 1.33 \times 10^5$ cell/mL, $I_1(0)$ = 0 cell/mL, $I_2(0)$ = 0 cell/mL, $V(0) = 10^2$ cell/mL [6] and fixed the parameters as shown in Table 2. The rates k_{10}, k_{12}, and k_{21} were calculated by fitting the plasma concentration [9]. The chosen dosages for andrographolide were 30, 45, 60, 180, and 360 mg per day. The numerical simulation was

carried out with MATLAB to illustrate how andrographolide diffusion in human plasma and tissue impacted the dynamic behavior of viruses (Figure 5). The plasma concentration of andrographolide increased substantially and remained steady for 10 h after beginning the experiment. The mean efficacy of andrographolide, ε_{mean}, is presented in Table 3. It was found that the behavior of target and viral cells was similar. The infection occurred on Day 5 and ended on Days 25−30.

Table 2. Related parameters of viral dynamics model.

Parameter	Values	Dimension	References
Dose	[30, 45, 60, 180, 360]	mg/day	-
k_{10}	3.6228	h^{-1}	[9]
k_{12}	4.2259	h^{-1}	[9]
k_{21}	1.4233	h^{-1}	[9]
β	2.21×10^{-5}	mL/cells/day	[6]
k	3.00	day^{-1}	[6]
δ	0.60	day^{-1}	[6]
p	22.71	day^{-1}	[6]
c	10.00	day^{-1}	[6]

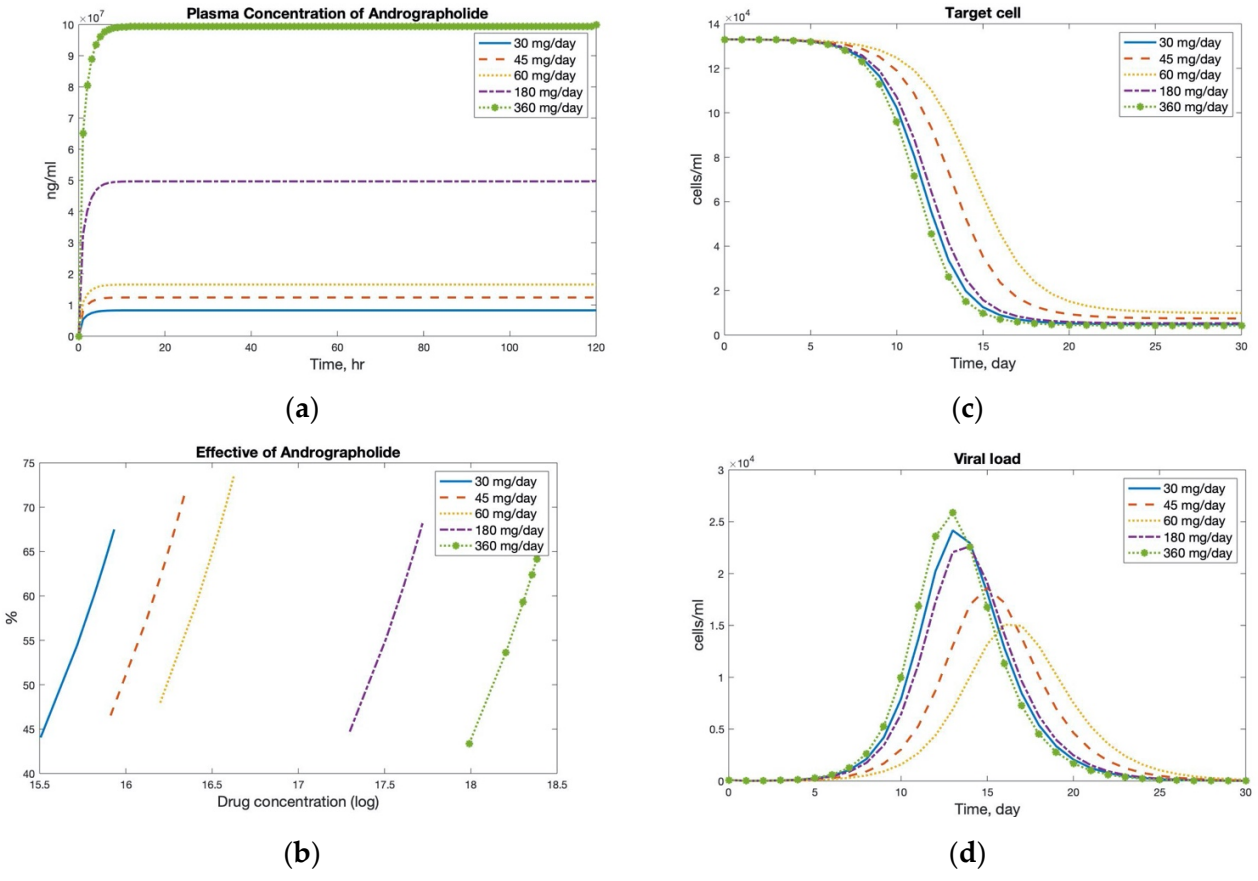

Figure 5. Numerical solution of PK/PD model and viral dynamic model of COVID-19 with andrographolide treatment in (**a**) the plasma concentration of drug dosage, (**b**) the effective of drug dosage, (**c**) the quantitative of target cell, and (**d**) the quantitative of viral cell.

In Thailand, the therapeutic dosage of andrographolide is 3 × 180 mg per day. The solution of the PK/PD model and the viral dynamics model with andrographolide treatment of the dosage is shown in Figure 6. In terms of PK, the concentration of andrographolide in plasma and tissues increased and remained steady for 10 h after beginning the dosage.

Considering the latent time of 3 days, target cell infection occurred on Day 5, and the virus load peaked on Day 15. The viral clearance occurred on Day 25.

Table 3. Mean efficacy of andrographolide to treat COVID-19.

Dose (mg/mL)	Mean Efficacy (ε_{mean})
30	66.30
45	69.90
60	72.11
180	67.13
360	65.34

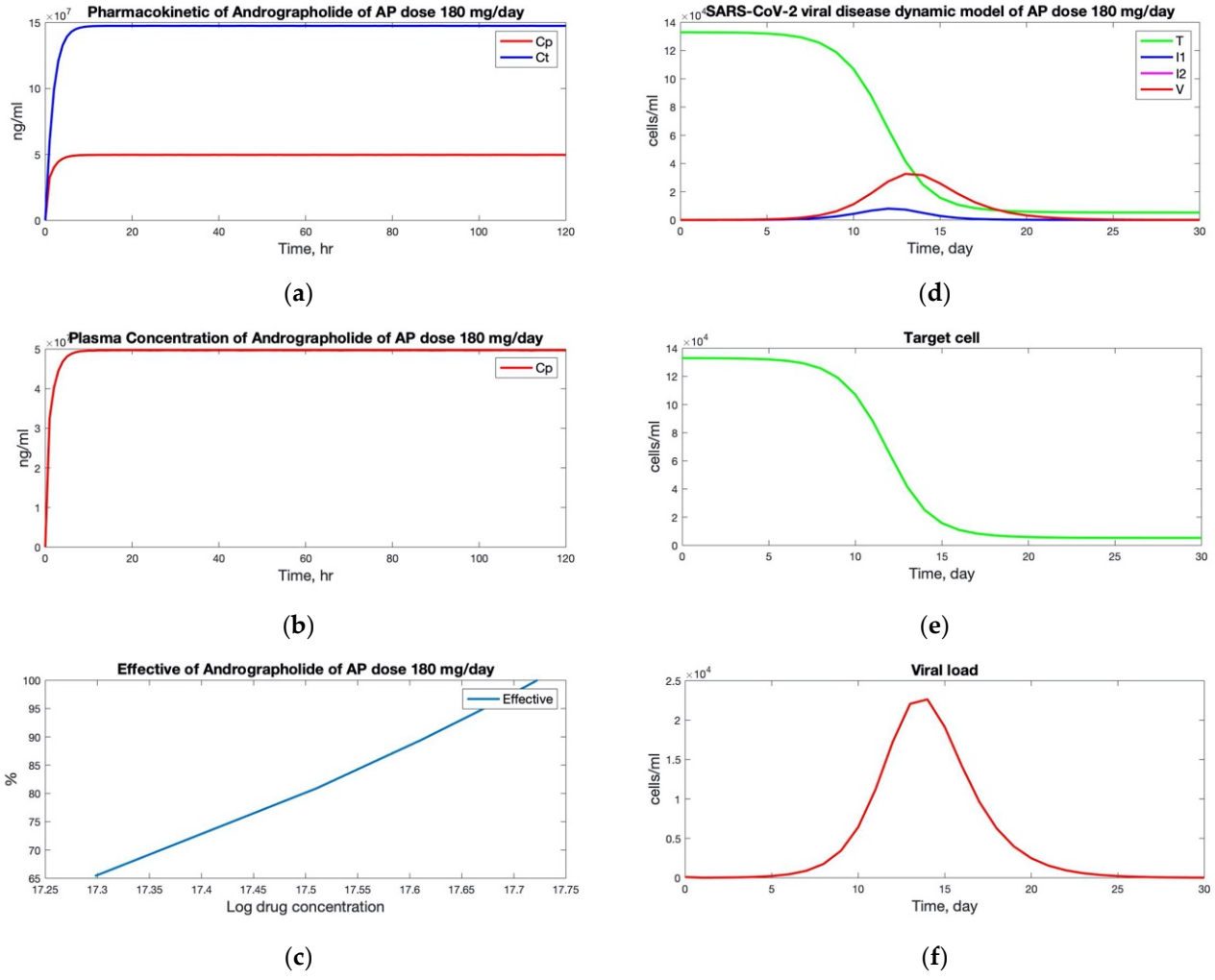

Figure 6. Numerical solution of PK/PD model and viral dynamic model of COVID-19 with a dose of 180 mg per day of andrographolide: (**a**) pharmacokinetics of daily dose of 180, (**b**) plasma concentration of andrographolide, (**c**) efficacy of andrographolide at IC_{50}, (**d**) number of COVID-19 cells, (**e**) number of uninfected target cell, and (**f**) viral load of viral dynamics model.

4. Conclusions

The PK/PD model and the viral dynamic model of andrographolide dose on COVID-19 were explored in this study. Andrographolide effectively reduced viral load and target cell infection, showing its efficacy. A dose of 60 mg per day of andrographolide dairy was the most efficient in preventing infection. Andrographolide can be used for the therapy of COVID-19. Due to possible toxicity, side effects, misuse, allergy symptoms, and interactions of APE with other medications, the use of andrographolide must be decided by physicians

or pharmacists. As there is an increasing demand for APE with its benefits, the quality of APE in terms of safety and efficacy must be supervised and controlled to use it as medicine.

Author Contributions: Conceptualization, P.Y. and T.S.; methodology, P.Y. and T.S.; software, P.Y.; validation, P.Y. and T.S.; formal analysis, P.Y. and T.S.; investigation, P.Y. and T.S.; resources, P.Y.; data curation, P.Y. and T.S.; writing—original draft preparation, P.Y.; writing—review and editing, P.Y. and T.S.; visualization, P.Y. and T.S.; supervision, T.S. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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