

Impact of imperatorin and isoimperatorin on the pharmacokinetics of abemaciclib both in vivo and in vitro

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Abstract

Abemaciclib is used for the treatment of breast cancer (BC) in clinics. The combination of abemaciclib and imperatorin or isoimperatorin has been studied *in vitro* and *in vivo* to explore the pharmacokinetics of Chinese herbs and anti-cancer medicines. Eighteen male SD rats were randomly allocated to three groups: control, isoimperatorin (50 mg/kg) and imperatorin (50 mg/kg). The concentration level of abemaciclib in the plasma was determined using the UPLC-MS/MS technique on rats. Molecular simulation docking with AutoDock 4.2 software and rat liver microsome incubation were utilized to analyze the inhibitory mechanisms. In this study, we found that co-administration of imperatorin and isoimperatorin resulted in higher $AUC_{(0-\infty)}$ and C_{max} values and lower CL_Z/F values ($p < 0.05$). In addition, both imperatorin and isoimperatorin showed moderate inhibition for abemaciclib with IC₅₀ values of 6.79 μ M and 6.56 μ M, respectively. Intriguingly, we found that imperatorin, isoimperatorin and abemaciclib exhibit similar binding capacities with CYP3A4. Moreover, the results indicated that imperatorin and isoimperatorin significantly impaired the pharmacokinetics of abemaciclib *in vivo*. Therefore, our research suggests that the combination of abemaciclib and imperatorin or isoimperatorin should be considered more in clinical practice.

1 Introduction

Abemaciclib was approved for the treatment of advanced or metastatic breast cancer (BC) patients with hormone receptor-positive and human epidermal growth factor 2-negative cells [1, 2]. Abemaciclib was approved by the FDA on September 28, 2017 for the treatment of advanced or metastatic BC in patients with hormone receptor-positive and EGF receptor-2 (HER2) negative cells [3]. Abemaciclib is administered twice daily for four weeks [4]. Abemaciclib penetrates the blood-brain barrier and alleviates tumor progression in preclinical orthotopic models [5].

Abemaciclib is primarily metabolized by cytochrome P450 3A4 enzymes. CYP3A4 forms three active metabolites of abemaciclib including N-desethylabemaciclib (M2), hydroxyabemaciclib (M20) and hydroxyl-N-desethylabemaciclib (M18). Abemaciclib exposure was assessed in two clinical studies focusing on drug-drug interactions (DDIs). Current studies revealed that clarithromycin significantly enhanced the concentration-time curve (AUC) of abemaciclib compared to rifampin, a potent inhibitor of CYP3A [2].

Imperatorins and isoimperatorins are found in medicinal herbs such as *Angelica dahurica*, *Notopterygium giumincisum*, *Angelica sinensis*, *Rhodiola bupleuroides* and *Foeniculum vulgare* Mill. [6–9]. Accumulating evidence indicates that IMP and IIMP possess a wide range of pharmacological actions including diastolic vasoactivity, liver protection, anti-bacterial, anti-tumor effects and anti-inflammatory activities [10, 11]. Furthermore, previous studies have reported that IIMP possesses promising anti-viral properties *in vitro* with dose-dependent differences [12, 13]. Natural compounds have fewer side effects and are less expensive than synthetic drugs. IMP is an excellent anti-oxidant in the human diet, which may alleviate the progression of several diseases including cancer and cardiovascular disease by scavenging the production of free radicals and inflammation [14]. Chen et al. suggest that IMP inhibits myotube atrophy in the C2C12 myotube model, implying that IMP may be beneficial in treating cancer cachexia [15]. IMP and IIMP are two natural compounds commonly prescribed to treat cancer patients. Previous studies have shown that furanocoumarins can efficaciously inhibit the activity of the CYP450 enzyme [16]. IMP and IIMP strongly inhibited CYP1A2 and CYP2B6, moderately inhibited CYP2C19 and weakly inhibited CYP2C9, CYP2D6 and CYP3A.

The pharmacokinetics of IMP and IIMP on abemaciclib have been poorly explored. Thus, the inhibitory effects of IMP and IIMP on abemaciclib need to be evaluated systematically. In this study, we developed a sensitive and rapid UPLC/MS/MS technique for detecting and identifying IMP and IIMP in plasma.

2 Materials and Methods

Chemicals and Reagents

IMP and IIMP (purity > 98%) were obtained from MUST (Chengdu, China). Abemaciclib was obtained from Aladdin (USA). NADPH was provided by Roche (Shanghai, China). The manufacturer of midazolam was Jiangsu Nhwa Pharmaceutical Co., Ltd. (Jiangsu, China). Ultrapure water was obtained from a Milli-Q filtration system (Millipore, Bedford, MA, US), acetonitrile and methanol from Merck (Darmstadt, Germany).

Instruments and Conditions

Positive mode analysis was performed using an ACQUITY I-Class UPLC and an XEVO TQD triple quadrupole mass spectrometer (Waters Corp., Milford, MA, USA). The sample was run on a CORTECS UPLC C18 Column (2.10 mm x 100 mm, 1.6 meters). Mobile phases A (0.1% formic acid water) and B (20 mM ammonium acetate aqueous solution) were maintained at 40°C. The gradient elution was performed using a flow rate of 0.4 mL/min and an injection volume of 5 µL. Table 1 shows that the proportion of the mobile phase varies with time and the analytes were run for 3 min.

Table 1
The proportion of mobile phase varies with time

Time(min)	Flow Rate(mL/min)	%A	%B
0	0.4	10.0	90.0
0.5	0.4	30.0	70.0
1	0.4	95.0	5.0
2	0.4	95.0	5.0
2.3	0.4	10.0	90.0

The cone gas (50 L/h) and the desolvation gas (1000 L/h) contain nitrogen. The ion monitoring voltage was determined at the following conditions: source temperature: 150°C; desolvation temperature: 500°C; capillary voltage: 2.5 kV. Several techniques for monitoring reactions were utilized in the quantitative analysis. The transitions from midazolam to N-desethyl abemaciclib to abemaciclib are shown in Table 2.

Table 2
The transitions of Abemaciclib, N-desethylabemaciclib and midazolam

Compound	Parent(m/z)	Daughter(m/z)	Cone(V)	Collision(V)
Abemaciclib	507.300	393.100	30	25
Midazolam	325.980	291.070	50	26
N-desethylabemaciclib	479.000	393.000	40	33

Animals

Sprague-Dawley rats (SDs) weighing 200 to 220 grams were obtained from the Experimental Animal Center of Wenzhou Medical University, Zhejiang, China (ID number: wyd2019-650). The animals were controlled with an artificial light-dark cycle with an ambient temperature of 20–26°C and relative humidity of 40–60%. There was free access to water before the experiment, but food was prohibited for 12 hr.

In vivo pharmacokinetics

Male SD rats were divided into three groups to examine the impact of IMP and IIMP on the pharmacokinetics of abemaciclib. The control group (n = 6) received oral doses of 50 mg/kg/day CMC-Na solution for 14 consecutive days. The IMP group (n = 6) received an oral dose of 50 mg/kg/day IMP solution for 14 consecutive days. The IIMP group (n = 6) received an oral dose of 50 mg/kg/day of the IIMP solution for 14 consecutive days. The rats received an oral gavage of 10 mg/kg abemaciclib (dissolved in CMC-Na solution) 30 min after receiving IMP or IIMP. The tail vein was punctured at 10 min, 30 min, 1, 2, 3, 4, 6, 8,

12, 24, 36, 48, 60 and 72 hr at predetermined intervals. The plasma samples were then isolated from whole blood after centrifugation at 3000 rpm for 10 min and stored at -80°C. The pharmacokinetic parameters such as plasma clearance (CL_z/F), the area under the concentration-time curve (AUC), maximum plasma concentration (C_{max}), maximum plasma time (T_{max}) and half-life (t_{1/2}) were processed by the DAS software (Version 3.2.8, The People's Hospital of Lishui, China).

Preparation of RLM and measurement of protein concentration

Following a 12-hour overnight fast with free access to water, Sprague-Dawley (SD) rats were transferred to the procedure room and anesthetized in an induction chamber using 4–5% isoflurane in oxygen. Anesthesia was subsequently maintained with 2–3% isoflurane delivered via a nose cone until the animals reached a surgical plane of anesthesia, as confirmed by the complete absence of the pedal withdrawal and corneal reflexes. Once deep anesthesia was achieved, the animals were humanely euthanized by decapitation, allowing rapid tissue collection while minimizing postmortem biochemical alterations. Immediately following euthanasia, the abdominal cavity was opened through a midline incision, and the liver was exposed and perfused in situ with ice-cold KCl buffer (0.15 mol/L, pH 7.4) to remove residual blood. The liver was then excised, rinsed with ice-cold phosphate-buffered saline (PBS), and homogenized in ice-cold PBS using a glass-Teflon homogenizer. Rat liver microsomes (RLMs) were subsequently prepared by differential centrifugation at 9,000 × g for 30 min followed by ultracentrifugation at 105,000 × g for 60 min at 4°C. The resulting microsomal pellets were resuspended in ice-cold PBS containing 0.01 mM buffer and stored at -80°C until further analysis. Protein concentrations of the RLM preparations were determined using the Thermo Scientific BCA Protein Assay Kit according to the manufacturer's instructions.

In vitro pharmacokinetics

The RLM was prepared according to the methodology described by Wang et al. [17]. We used a 200 L incubation system containing potassium phosphate buffer (pH 7.4), 0.1 mM NADPH and 0.3 mg/mL RLMs. The half-maximal inhibitory concentrations (IC₅₀) of IMP and IIMP were determined using 10 mg abemaciclib (closely following the K_m value of this compound) as a substrate and various concentrations of IMP (0.01, 0.1, 1, 5, 10, 50 and 100 mg/ml) and IIMP (0.01, 0.1, 1, 5, 10, 50 and 100 mg/ml) as IMP and IIMP inhibitors. To analyze the inhibitory mechanisms of IMP and IIMP on abemaciclib, various concentrations of IMP (0, 1.75, 3.5, 7, 14 μM), IIMP (0, 1.625, 3.25, 6.5, 13 μM) and abemaciclib (2.5, 5, 10, 20 μM) were applied to the incubation system and the inhibition constants were obtained (K_i and αK_i).

After pre-incubation for 5 min at 37°C, 1 mM NADPH was added to a water bath. The reaction was cooled immediately to -80°C after 30 min. The working solution (IS) was added in 20 L followed by the addition of acetonitrile in 200 L. The specimens were vortexed for 1 min and then centrifuged for 5 min at 13000 rpm. Next, the samples were injected into a UPLC-MS/MS system for analysis. The Linear Lineweaver-Burk plots and the enzyme kinetic parameters (K_m, IC₅₀, K_i and αK_i) were finally analyzed using Prism 9.0 software.

The molecular docking technique

The inhibitory mechanism of these drugs was evaluated using the previously described procedures (Sevrioukova and Poulos, 2017). The 3D crystal structure of CYP3A4 was derived from the Protein Data Bank (ID: 2J0D), while the molecular structures of IMP, IIMP and abemaciclib were retrieved from PubChem. The docking of target proteins and small molecules was routinely verified using AutoDock Vina (version 1.2.0) and AutoDock Tools (version 1.5.7). Pymol software was used to calculate the binding energy (BE) between the small compounds and their targets.

Statistical analysis

The graph of IC₅₀ values and Lineweaver-Burk plots were computed using GraphPad Prism 7.0. To analyze the pharmacokinetic profiles of the drugs, we used the Drug and Statistics (DAS) software (Version 3.0, Bontz Inc., Beijing, China). All data were presented as mean standard deviation (SD) and analyzed using SPSS 24.0's unpaired t-test analysis. P < 0.05 or P < 0.01 was considered significant for comparisons between the two groups.

3 Results

Impact of IMP and IIMP inhibition on the metabolism of abemaciclib *in vitro*

Based on Fig. 1, we established a method to quantify abemaciclib and IS in RLMs without interference from other peaks. The nonlinear regression analysis indicated that abemaciclib was metabolized with a K_m of 10.48 μM for N-desethylabemaciclib in RLMs. IMP and IIMP demonstrated moderate inhibition for abemaciclib with IC_{50} values of 6.79 μM and 6.56 μM , respectively.

IMP, IIMP and abemaciclib were studied at different concentrations. In Figs. 3 and 4, Lineweaver-Burk and Dixon plots showed the inhibition constant and mechanism. The inhibition constants of IMP and IIMP were 6.26 and 10.36 for k_i ($\alpha > 1$) and 12.61 and 5.14 for k_{ik} ($\alpha < 1$). Taken together, these results indicated that the metabolism of abemaciclib was inhibited in a mixed inhibition manner by both IMP and IIMP.

The inhibitory effects of IMP and IIMP on the metabolism of abemaciclib *in vivo*

Figure 1 shows the UPLC-MS/MS chromatograms for midazolam and abemaciclib in blank and denatured sample plasma pre-infused with abemaciclib and IS and plasma samples following oral abemaciclib administration. In addition, Fig. 5 shows the plasma concentration-time curves for abemaciclib and Table 3 lists their pharmacokinetic parameters. There was a significant difference in pharmacokinetic parameters such as $\text{AUC}_{(0-t)}$, $\text{AUC}_{(0-\infty)}$, $t_{1/2}$, CLz/F and C_{max} between the control and IMP or IIMP groups.

Table 3

The major pharmacokinetic parameters of abemaciclib in control group, imperatorin group, and isoimperatorin group (n = 6)

Parameters	Units	Control group	Imperatorin Group	Rate ratio	95% CI		Isoimperatorin Group	Rate ratio	95% CI	
					Lower limit	Upper limit			Lower limit	Upper limit
$\text{AUC}_{(0-t)}$	ug/L*h	6518.532 ± 1886.361	11044.907 ± 2456.205**	1.69	1.393	1.996	10278.413 ± 1703.534**	1.58	1.368	1.786
$\text{AUC}_{(0-\infty)}$	ug/L*h	6540.731 ± 1898.879	11091.649 ± 2461.247**	1.70	1.395	1.997	10320.467 ± 1726.539**	1.58	1.367	1.789
$\text{MRT}_{(0-t)}$	h	17.929 ± 1.775	19.557 ± 1.976	1.09	1.003	1.179	20.591 ± 1.662*	1.15	1.074	1.223
$\text{MRT}_{(0-\infty)}$	h	18.09 ± 1.828	19.831 ± 1.983	1.10	1.009	1.184	20.828 ± 1.769*	1.15	1.073	1.230
$t_{1/2}$	h	5.726 ± 1.221	8.124 ± 1.736*	1.42	1.176	1.661	7.093 ± 1.179	1.24	1.074	1.403
T_{max}	h	6.667 ± 1.033	5.5 ± 1.761	0.82	0.614	1.036	5.667 ± 0.816	0.85	0.752	0.948
V_z/F	L/kg	13.018 ± 2.965	11.184 ± 4.052	0.86	0.610	1.108	10.035 ± 1.516	0.77	0.678	0.864
CLz/F	L/h/kg	1.615 ± 0.363	0.934 ± 0.18**	0.58	0.489	0.668	0.996 ± 0.197**	0.62	0.519	0.714
C_{max}	ug/L	242.315 ± 46.383	385.794 ± 65.25**	1.59	1.377	1.808	349.815 ± 76.379*	1.44	1.191	1.696
Note: Data are presented as mean ± SD.* $p < 0.05$ indicates a significant difference versus the control group. ** $p < 0.01$ indicates a significant difference versus the control group.										

The IMP group had higher $AUC_{(0-\infty)}$ and C_{max} values (0.70-fold and 0.59-fold, respectively) and lower CL_Z/F values (0.42-fold) compared to the control group. In the IIMP group, the $AUC_{(0-\infty)}$ and C_{max} values were increased by 0.58-fold and 0.44-fold, respectively, whereas the values of CL_Z/F were decreased by 0.38-fold compared to the control group. Intriguingly, the results showed that co-administration with IMP increased $t_{1/2}$ and elevated $MRT_{(0-\infty)}$ value. Taken together, these findings indicated that IMP and IIMP significantly impaired the metabolism of abemaciclib in rats.

Molecular docking prediction of IMP and IIMP

Molecular docking simulations were conducted (Fig. 6) to confirm compound-target associations [18, 19]. Abemaciclib and IMP/IIMP bind closely to CYP3A4 as shown in Fig. 6 (A, B, C, D). The minimum binding energies of CYP3A4 with IMP/IIMP and abemaciclib were both - 7.9 kcal/mol and - 10.3 kcal/mol. The IMP and IIMP form hydrogen bonds with the ALA-370 and ARG-105 amino acid residues in CYP3A4. We found that abemaciclib inhibitors IMP and IIMP are closely bound to CYP3A4. Taken together, these findings revealed that IMP/IIMP inhibited the metabolism of abemaciclib by CYP3A4 due to their proximity.

4 Discussion

A growing number of phytotherapies and herbal-drug interactions are being developed as combination therapies. It has been demonstrated that natural coumarin derivatives including IMP and IIMP possess promising pharmacological actions. IMP and IIMP are commonly used for the treatment of BC. Previous studies have revealed that IMP significantly inhibits the proliferation of BC cells MCF-7 at a concentration-dependent level. Furthermore, IMP inhibits the migration and proliferation of BC cells by regulating HMGB2 [20]. The clinical safety of herb-drug combinations has recently received considerable attention. However, the potential drug-drug interactions between IMP/IIMP and abemaciclib have not been studied.

We evaluated the effects of IIMP and IMP on the metabolism of abemaciclib *in vitro* and *in vivo*. *In vitro* studies showed that IMP and IIMP inhibited abemaciclib moderately and their IC_{50} values were 6.79 μ M and 6.56 μ M, respectively. This study is consistent with our *in vivo* results. IMP or IIMP altered the pharmacokinetic parameters of abemaciclib such as AUC, CL and C_{max} to varying degrees. The results indicated increased AUC (0-t), $AUC_{(0-\infty)}$ and C_{max} of abemaciclib. In contrast, the values of CL_Z/F were markedly decreased, indicating the inhibition of metabolism in IMP and IIMP groups compared to the control group.

Kang and co-workers showed that IMP and IIMP inhibit the activity of CYP enzymes in rat liver microsomes (RLMs) [21]. A pioneering study has shown IMP inhibits diazepam metabolism by CYP2C19 and CYP3A4 *in vitro* and *in vivo* [22]. In addition, Cao et al. showed that IIMP inhibits the function of CYP2B6 time-dependently and inactivates the enzyme concentration-dependently [23]. Based on the *in vitro* results, we found that IIMP had inhibition constants of 12.61 and 5.14 and IMP had inhibition constants of 6.26 and 10.36. The inhibitor-enzyme affinity was believed to be greater than the enzyme-substrate affinity. The inhibitors exhibited stronger affinity for enzyme-substrate complexes than free enzymes when $\alpha < 1$ [24, 25]. IMP exhibits a significant inhibitory constant than IIMP, suggesting that IMP binds to enzymes preferentially. The results from molecular docking further confirmed this finding. Binding energies less than -5 kcal/mol indicate significant binding interactions between the compound and its target [26, 27]. The combination of IMP and IIMP inhibited the metabolism of abemaciclib *in vivo* and *in vitro*. In this study, the rats were treated with abemaciclib and no metabolites were detected. However, the metabolism of this drug differs slightly in humans and rats.

We first evaluated the pharmacokinetics of abemaciclib using Chinese herbs such as IMP and IIMP. Our results showed that IMP/IIMP potentially inhibited the metabolism of abemaciclib *in vivo* and *in vitro*. Therefore, the dosage should be adjusted to decrease the possibility of adverse reactions when abemaciclib can be combined with IMP/IIMP in clinical settings.

Declarations

Ethical Approval Consent to participate

The animal procedures were approved by the Institutional Animal Care and Use Committee of Wenzhou Medical University (Approval No. wyd2019-650) and were carried out in accordance with the institutional animal care guidelines and ethics regulations of Wenzhou Medical University, Zhejiang, China. No patients are included in this study.

Human Ethics

Not applicable.

Consent for publication

Not applicable.

Competing interests

All authors declare no competing financial interests.

Clinic Trial

Not applicable.

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Author Contribution

Chengfeng Wang, Xueyi Song, Jianfeng Wang, Zebei L: Conceptualization, writing-original draft preparation, Formal analysis, Methodology, Data curation; Yu Wang, Xiuyun Peng: Visualization, Formal analysis; Peiwu Geng: Software, Validation, Investigation; Yunfang Zhou and Md Siddiqul Islam, Abdullah Al Mamun: Writing-review and editing; Shuanghu Wang: Resources, Supervision, Validation, Funding acquisition; Minzhi Xu: Conceptualization, Validation, Investigation. All the authors have read and agreed to the published version of the manuscript.

Acknowledgement

Not applicable

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Figures

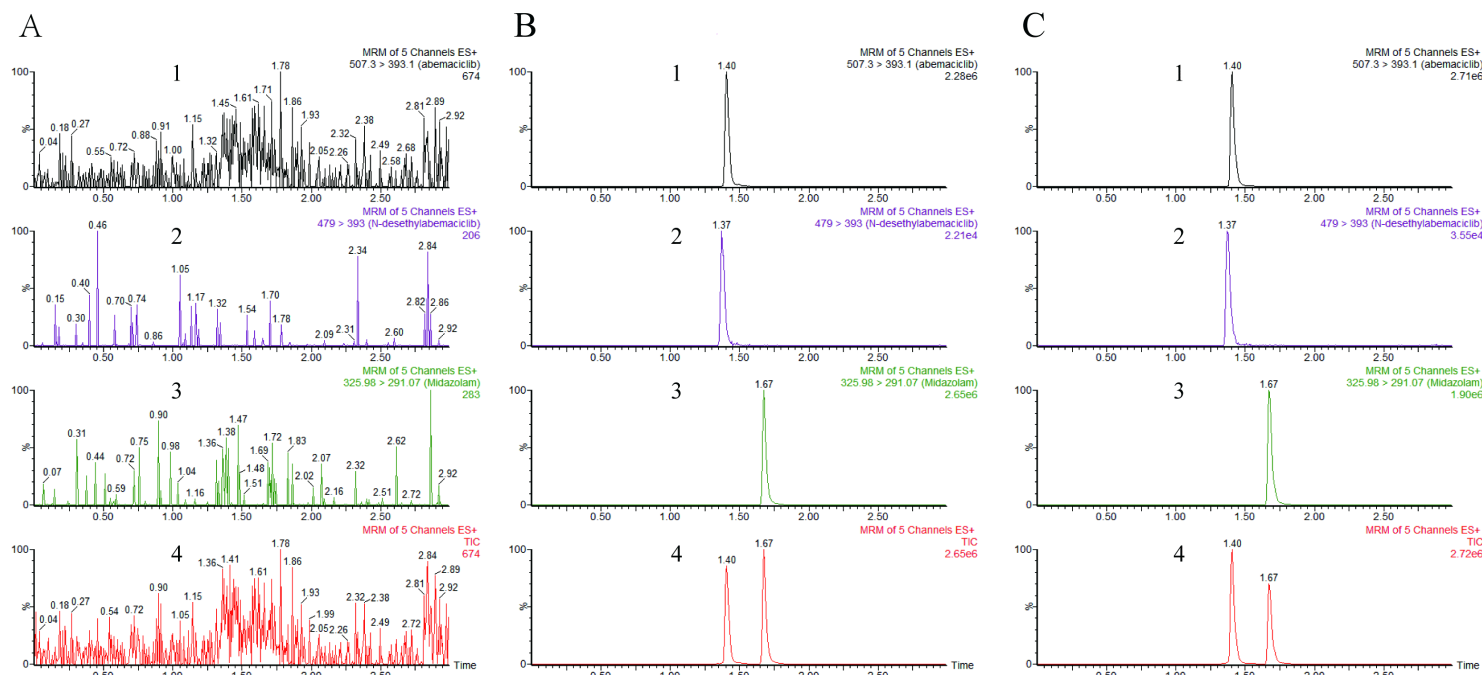


Figure 1

Representative chromatograms of abemaciclib and IS in rat plasma. (A) Blank rat plasma sample. (B) Denatured blank rat plasma sample with abemaciclib and IS. (C) Rat plasma sample after dosing abemaciclib with oral administration.

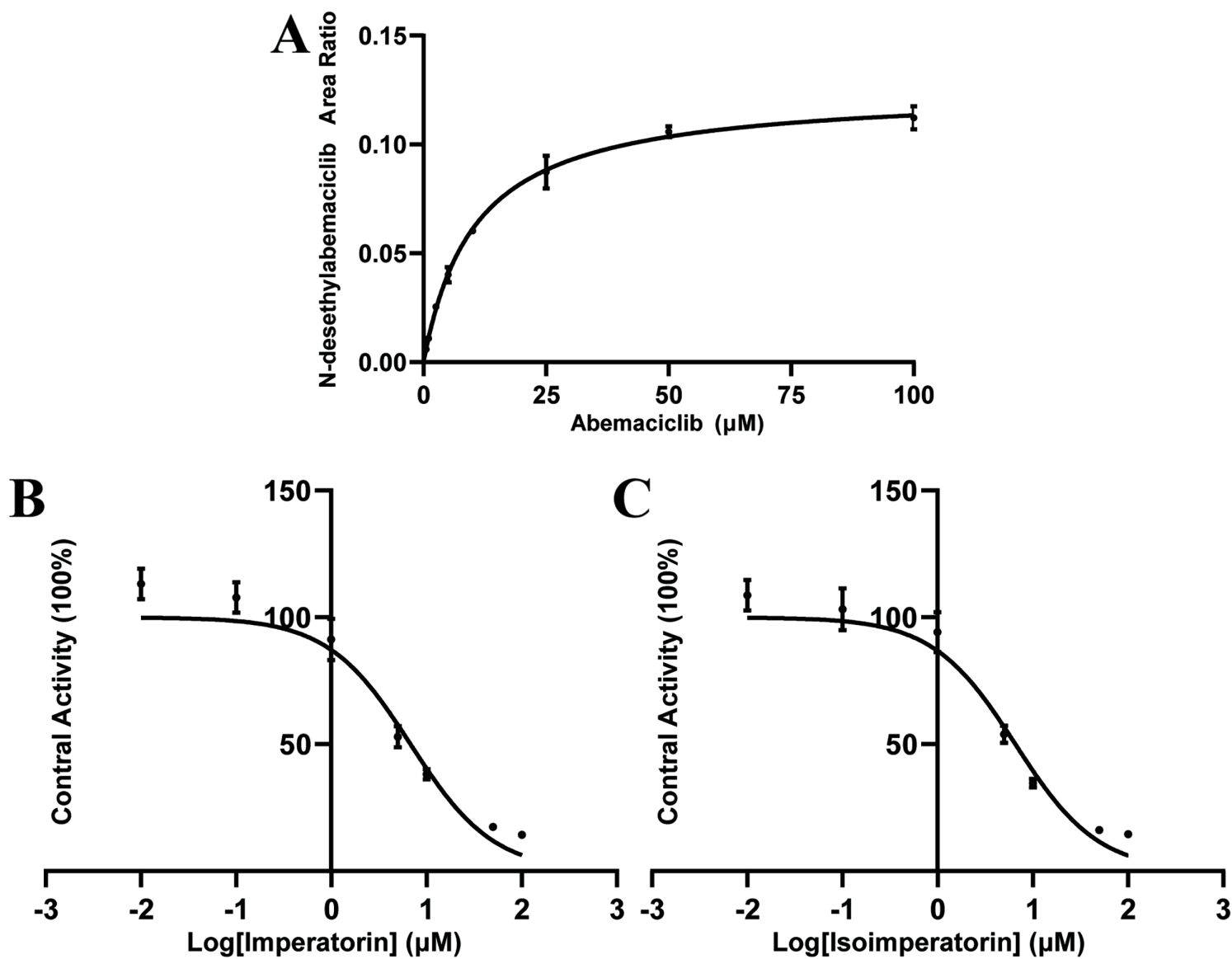


Figure 2

Michaelis-Menten curve of abemaciclib (0.01-100 μM) metabolism in RLMs (A). The half-maximal inhibitory concentration (IC_{50}) curve of imperatorin (B), isoimperatorin (C) (values are means $\pm$ standard deviations, $n = 3$).

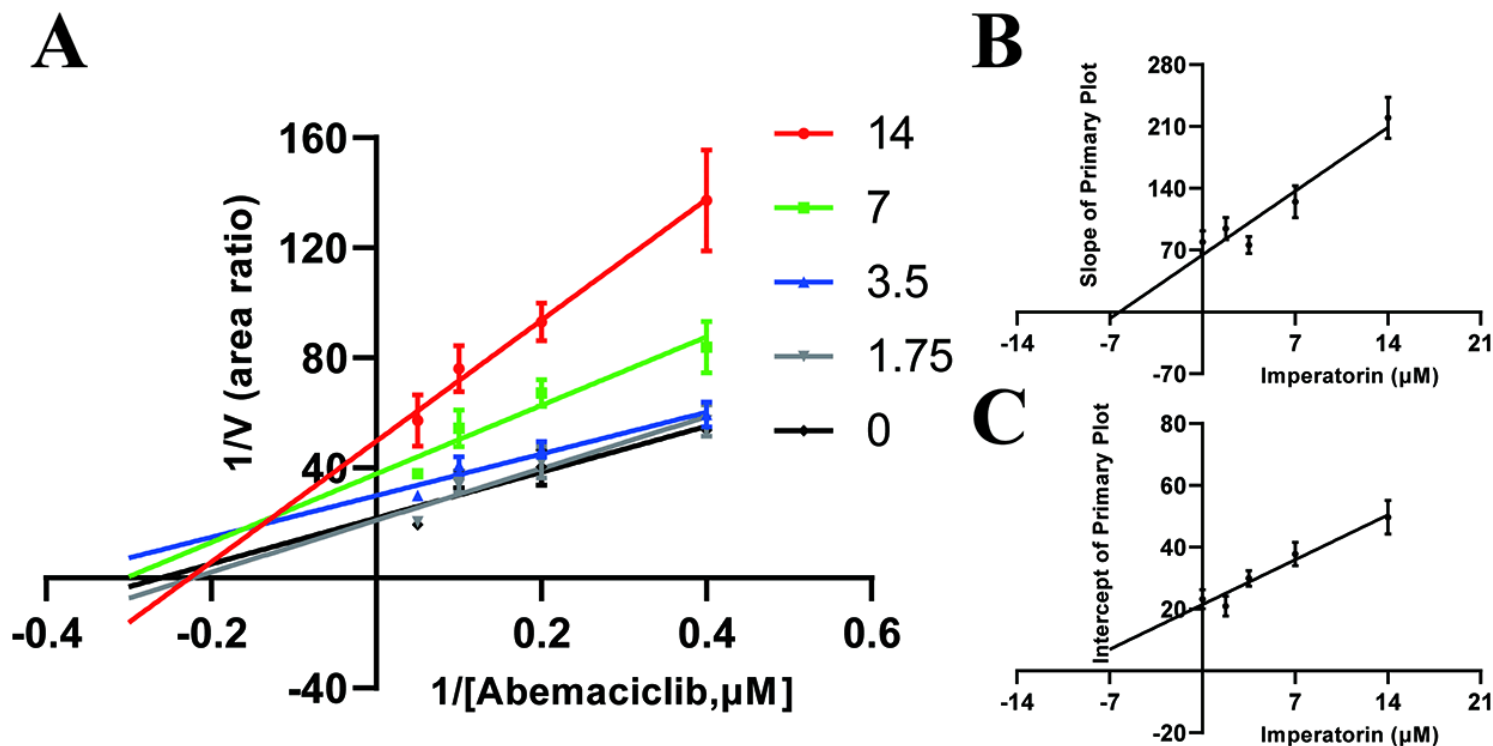


Figure 3

The Primary Lineweaver-Burk plots of imperatorin inhibition on abemaciclib (A); Slope of the primary plot of imperatorin (B); Intercept of the primary plot of imperatorin (C) (values are means $\pm$ standard deviations, $n=3$).

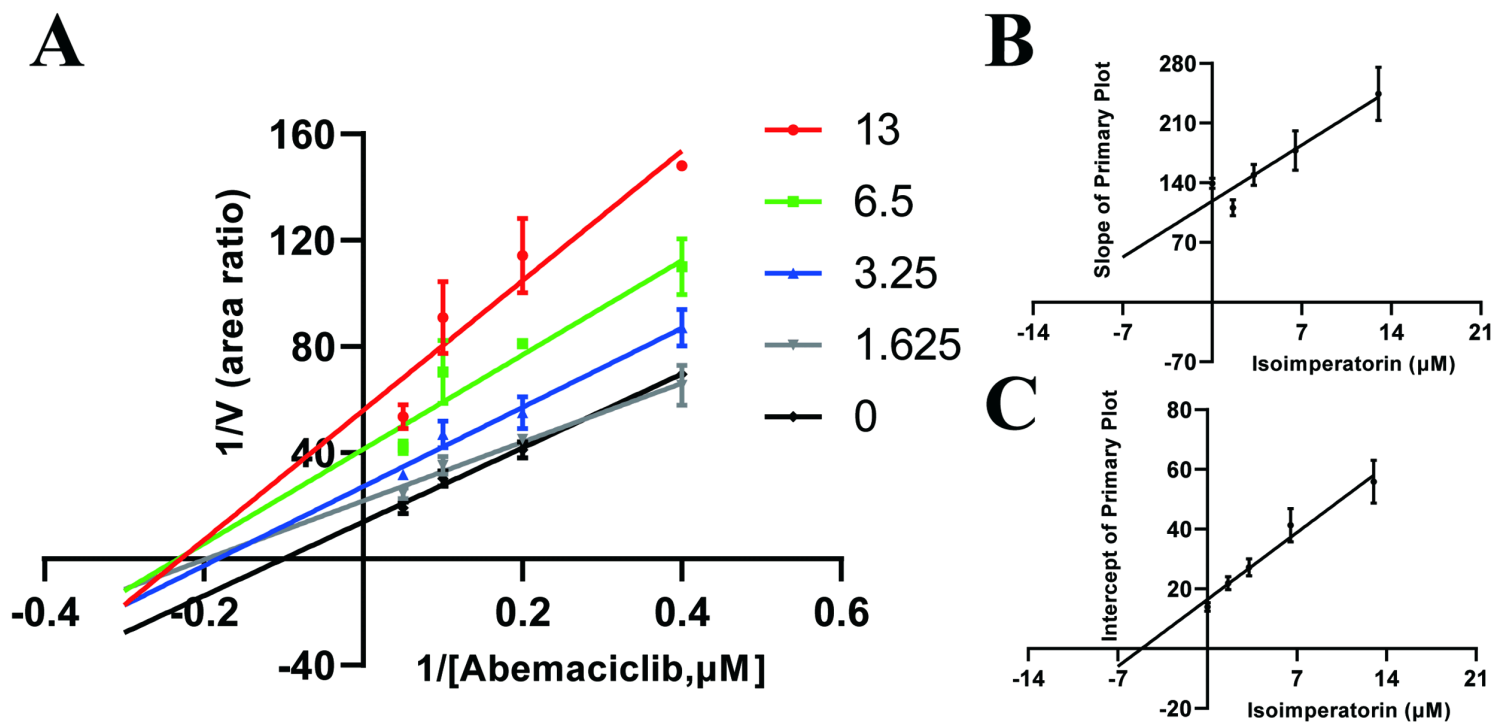


Figure 4

The Primary Lineweaver-Burk plots of isoimperatorin inhibition on abemaciclib (A); Slope of the primary plot of isoimperatorin (B); Intercept of the primary plot of isoimperatorin (C) (values are means $\pm$ standard deviations, $n=3$).

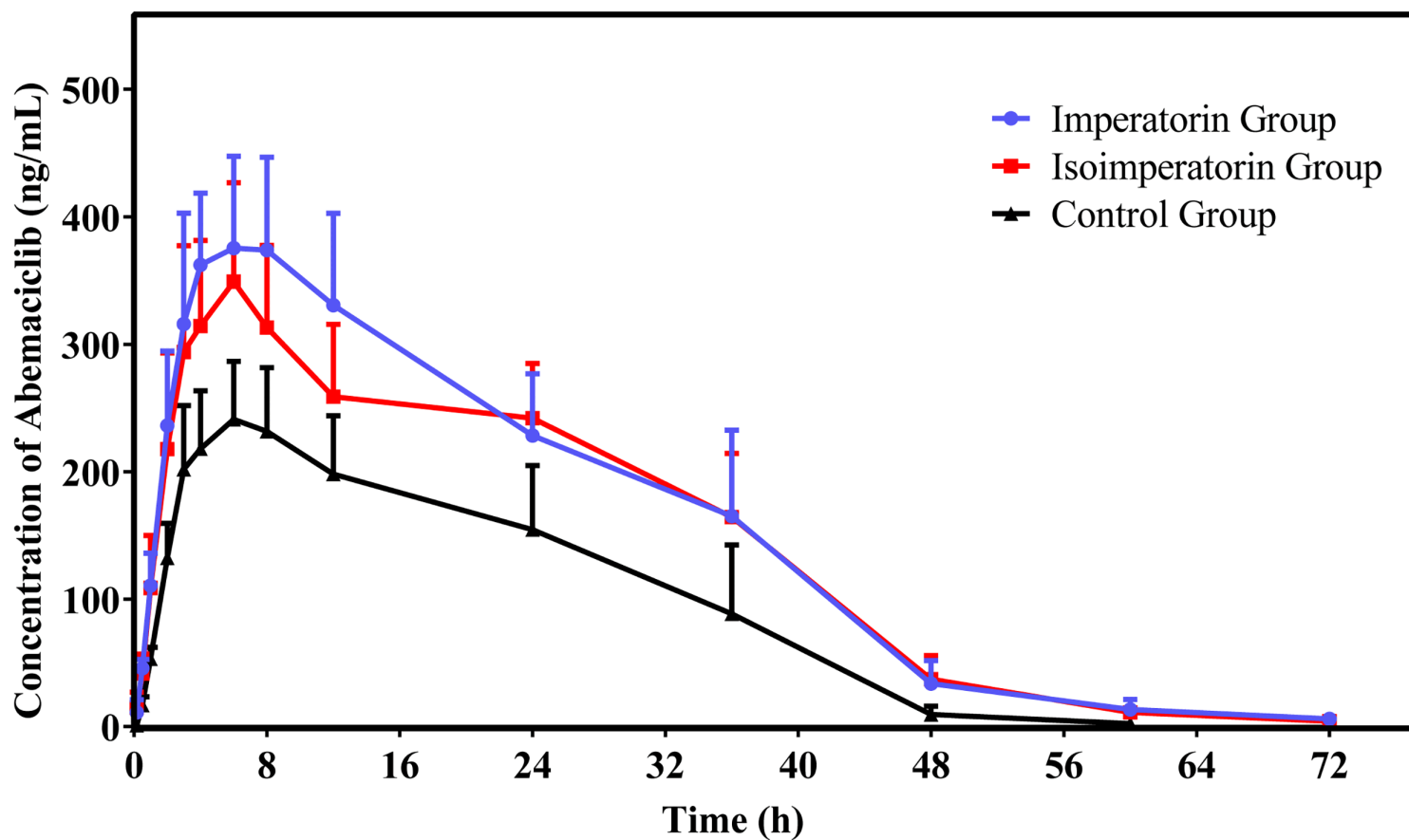


Figure 5

The mean plasma concentration-time curves of abemaciclib in control group, emperorin group, and isoimperatorin group

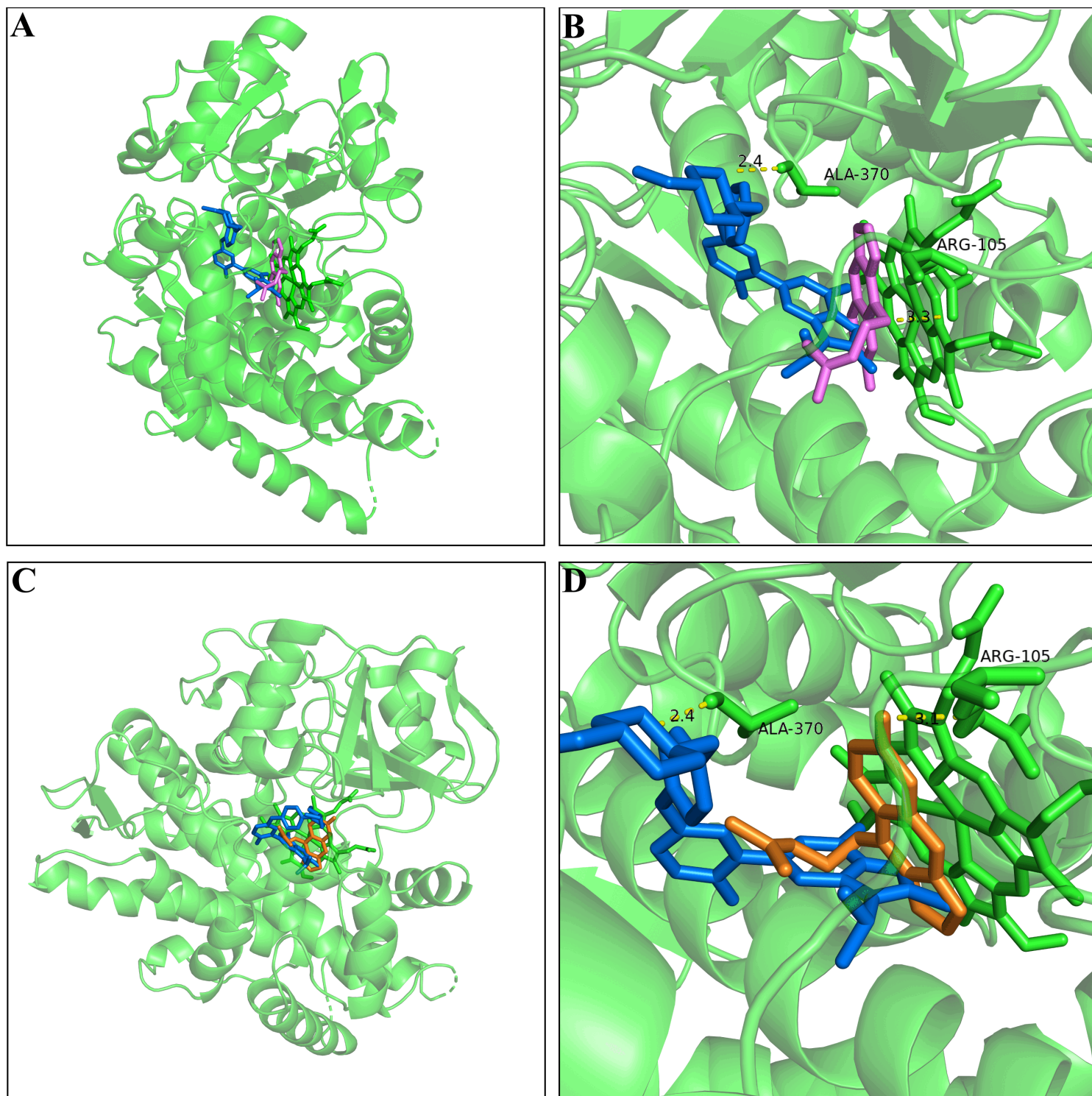


Figure 6

Molecular docking analysis of the interactions between the small molecules and target proteins. The docking simulations of imperatorin in purple (A, B), isoimperatorin in orange (C, D), (B) partially enlarged drawing of A, (D) partially enlarged drawing of C; blue represents abemaciclib, and purple/orange represent imperatorin/ isoimperatorin, respectively.