

Use of PBPK modelling to assess the drug-disease interaction of caffeine in cancer subjects and the influence of cytokine-mediated CYP1A2 suppression

Sheng Yuan Chin¹, Kenneth Hor Cheng Koh¹, James Chun Yip Chan^{1,2}

¹ Singapore Institute of Food and Biotechnology Innovation, A*STAR, Singapore, ² A*STAR Skin Research Labs, A*STAR, Singapore

Introduction

Caffeine, a psychostimulant consumed by 80% of world population every day, is predominantly metabolized by cytochrome P450 enzyme, CYP1A2 in liver. Hence, caffeine is widely used as a probe for metabolic phenotyping of CYP1A2. Elevated cytokines such as interleukin-6 (IL-6), IL-1 β and tumor necrosis factor-alpha (TNF- α) have been shown to suppress CYP1A2 activity in *in vitro* experiments. [1,2] There were also studies investigating the *in vivo* influence of induced/suppressed IL-6 levels on CYP1A2 activity using physiologically-based pharmacokinetic (PBPK) model, albeit the influence is not conclusive. A review by Grzegorzewski *et al.* suggested that the main drug-disease interaction for caffeine is liver dysfunction (Figure 5D of the paper) [3]. However, there is no direct study on the caffeine clearance (CL) differences in healthy adults and cancer subjects without liver dysfunction. **This study investigates the drug-disease interaction of caffeine in cancer subjects by accessing the impact of cytokine-mediated suppression of CYP1A2 activity and caffeine CL with PBPK modelling approach**, guided by the observations showing the elevated levels for IL-6, IL-1 β and TNF- α in some cancer populations.

Methods

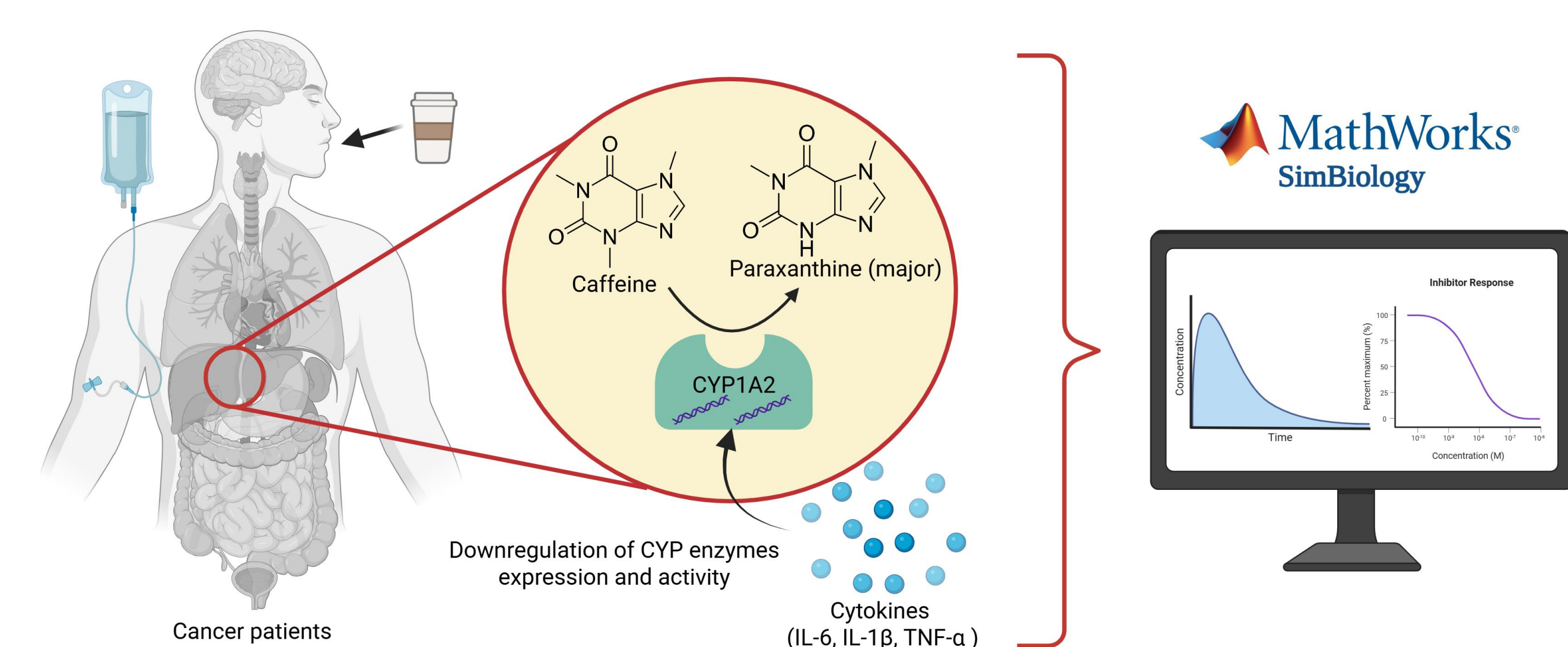


Figure 1. Illustration of the PBPK modelling for cytokine-mediated suppression of caffeine metabolism in cancer patients. Created in <https://BioRender.com>.

- Base PBPK model of caffeine was constructed for the healthy adult population in SimBiology (MathWorks, R2024a) and verified against clinical data.
- Base model was extrapolated to cancer populations by modifying the physiological parameters (age, weight, organ volumes, blood flow rates, unbound fraction in plasma (f_{up}), blood-to-plasma ratio (B/P ratio) and others) (**Figure 1**).
- The suppressions of CYP1A2 activity by IL-6, IL-1 β and TNF- α were derived with the four-parameter logistic (4PL) regression equation (**equation 1**)

$$\% \text{ of CYP1A2 activity remaining} = \text{Min} + \frac{\text{Max} - \text{Min}}{1 + \left(\frac{x}{IC_{50}}\right)^h} \quad (1)$$

where Min is minimum response, Max is maximum response, x is cytokines concentration (pg/mL), IC_{50} is half-maximal inhibition concentration (pg/mL) and h is Hill coefficient.

- CYP1A2 activity suppression was also incorporated in our model to predict the altered pharmacokinetic profile of caffeine in cancer patients.

Results & Discussion

- Clinical data of caffeine in healthy adults and cancer patients showed significant difference in PK**, particularly in metabolism with **48% decrease in CL** and **90% increase in AUC** for cancer patients (**Figure 2**).
- Our **base model was validated** against clinical data for **healthy adults** (comparisons of PK parameters are tabulated in **Table 1**).

Table 1. Comparison of predicted and observed PK parameters for caffeine (100 mg oral dose) in healthy adults.

PK parameters	Observed (clinical data)				Predicted	Fold-difference *
	Desmond 1980 [4]	Brazier 1983 [5]	Cheng 1990 [6]	Mean		
C_{max} ($\mu\text{g/mL}$)	2.61	4.01	3.62	3.41	2.79	0.82
T_{max} (h)	0.5	0.5	0.33	0.44	0.22	0.49
$AUC_{0-\infty}$ ($\mu\text{g/mL}\cdot\text{h}$)	17.01	13.94	16.61	15.85	12.32	0.78
$t_{1/2}$ (h)	5.2	4.71	4.5	4.80	3.52	0.73
CL (L/h)	5.88	7.17	6.02	6.36	8.11	1.28

* Calculated as the quotient of predicted and mean observed values.

- The validated base model was extrapolated to the cancer population by incorporating cytokine-induced CYP1A2 suppression for IL-6, IL-1 β and TNF- α separately (**Table 2**).
- Sensitivity analyses indicated **minimal changes in PK profile of caffeine due to the changes in f_{up}** (lower plasma albumin level) and **B/P ratio** (lower hematocrit) reported in cancer subjects (data not shown).

Table 2. % CYP1A2 activity remaining after suppression driven by IL-6, IL-1 β and TNF- α in cancer populations.

Cytokines	IC_{50} (pg/mL) for CYP1A2 suppression	Cytokine concentration in cancer patients (pg/mL)	% CYP1A2 activity remaining
IL-6	909.02	14.3	98
IL-1 β	13.85	5.2-19.8	42-73*
TNF- α	837.20	18.9	98

* 5.2 and 19.8 pg/mL IL-1 β levels lead to 73% and 42% of CYP1A2 activity remaining respectively.

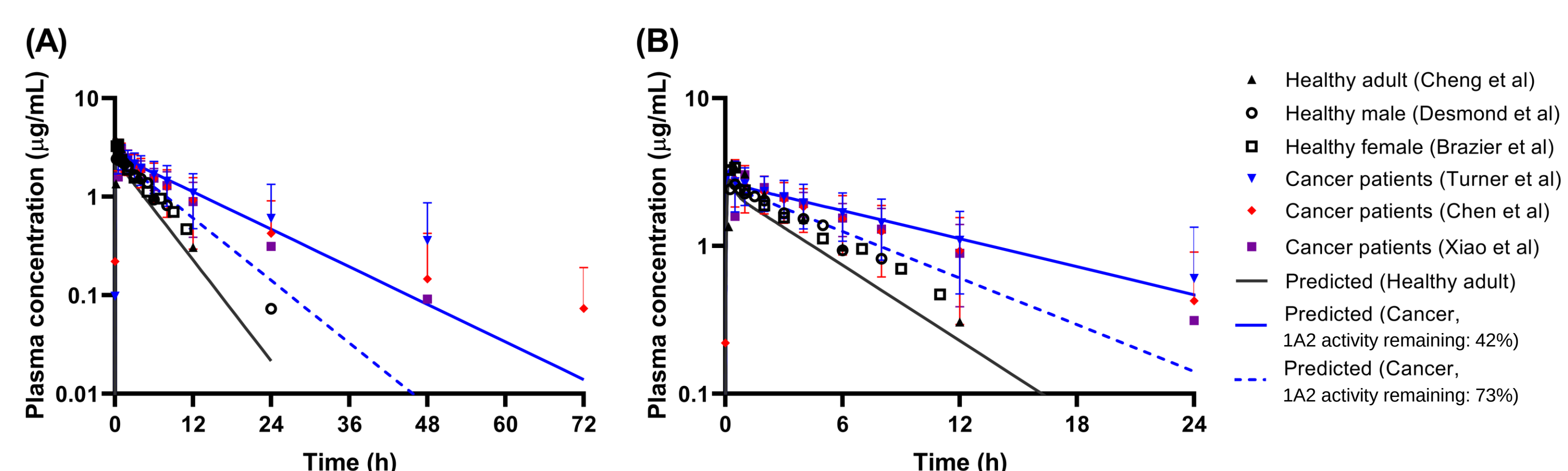


Figure 2. (A) Predicted plasma concentrations of caffeine for healthy adult and cancer patients (with IL-1 β -mediated suppression of CYP1A2 activity to 42-73%) at 100 mg oral single dose and clinical data for healthy and cancer populations. (B) Zoomed-in version of (A) corresponding to 0-24 h.

- Predicted PK parameters for IL-6 incorporation underperform the observed cancer PK data except C_{max} , showing that **IL-6 induced CYP1A2 suppression is insufficient to account for the reduction of caffeine CL in cancer subjects**.
- The effect of TNF- α on caffeine cancer PK is similar to that of IL-6.
- Predicted PK parameters for IL-1 β incorporation are comparable with the observed data, implying that the observed **reduction in caffeine CL due to CYP1A2 suppression can be explained by the highest observed IL-1 β level** (lead to 42% CYP1A2 activity remaining) (**Table 3, Figure 2**).
- Limitation: Interplay of suppression effect among IL-6, IL-1 β and TNF- α was not explored in our work, which may not be purely additive.

Table 3. Comparison of predicted and observed PK parameters for caffeine (100 mg oral dose) in cancer patients. The simulations were run for incorporation of IL-6 (98% CYP1A2 activity remaining) and IL-1 β -mediated (42-73% CYP1A2 activity remaining) CYP1A2 suppression.

PK parameters	Observed (clinical data)				Predicted (IL-6)	Fold-difference	Predicted (IL-1 β , 73% 1A2)	Fold-difference	Predicted (IL-1 β , 42% 1A2)	Fold-difference
	Xiao 2019 [7]	Turner 2020 [8]	Chen 2023 [9]	Mean						
C_{max} ($\mu\text{g/mL}$)	2.99	2.89	2.95	2.94	3.09	1.05	3.18	1.08	3.29	1.12
T_{max} (h)	0.5	0.52	0.5	0.51	0.24	0.47	0.24	0.47	0.24	0.47
$AUC_{0-\infty}$ ($\mu\text{g/mL}\cdot\text{h}$)	29.65	32.5	28.2	30.12	16.13	0.54	21.57	0.72	37.05	1.23
$t_{1/2}$ (h)	7.0	10.3	-	8.65	4.36	0.50	5.69	0.66	9.48	1.10
CL (L/h)	3.37	3.08	3.55	3.33	6.20	1.86	4.64	1.39	2.70	0.81

Conclusions

- Our model is the first to assess the deviation in caffeine PK between healthy and cancer populations by investigating cytokine-induced CYP1A2 suppression.**
- We demonstrate that IL-1 β has the most significant influence on CYP1A2 suppression among IL-6, IL-1 β and TNF- α .
- Our finding has **implications on the exposure of xenobiotics that are primarily metabolized by CYP1A2 in cancer subjects**.

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Acknowledgement

This project and travel funding are supported by the Agency for Science, Technology and Research (A*STAR) Central Funds-Council Strategic Funds (Project number C240314053). The authors declare no conflict of interest.

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