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Nutritional Regulation of Cytochrome P450 (CYP3A4) Activity: A Clinical Evaluation of Clarithromycin Pharmacokinetics in Human Subjects Consuming High-Flavonoid Diets

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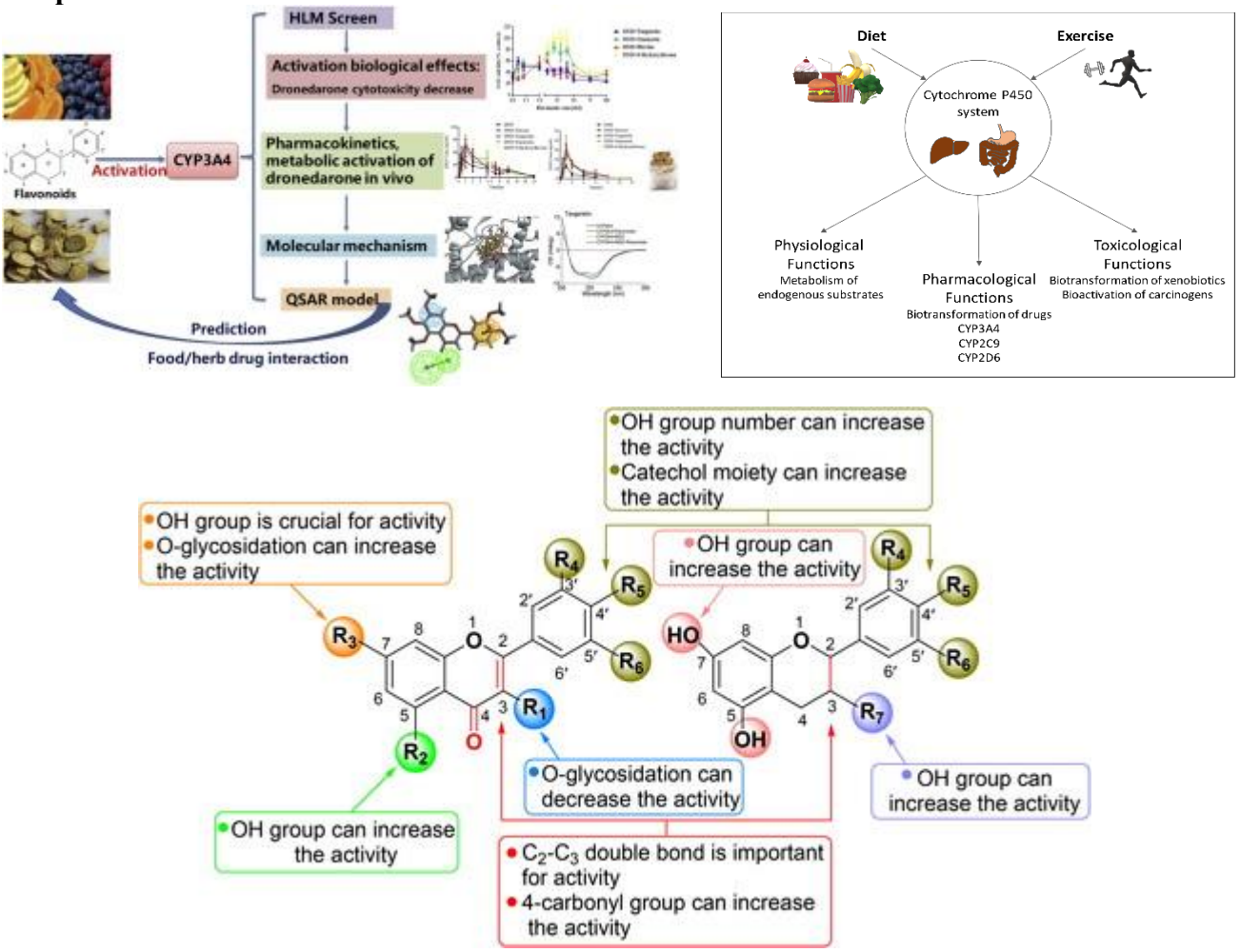
Graphical Abstract



Abstract

Background: Cytochrome P450 3A4 (CYP3A4) is a major enzyme involved in the metabolism of many clinically important drugs, including clarithromycin. Dietary flavonoids have been reported to modulate CYP3A4 activity, potentially influencing drug pharmacokinetics and therapeutic outcomes. **Objective:** To evaluate the effect of a high-flavonoid diet on clarithromycin pharmacokinetics and CYP3A4 activity in healthy human subjects. **Methods:** A randomized controlled crossover clinical study was conducted involving 24 healthy

volunteers. Participants consumed a high-flavonoid diet (~500 mg/day) and a control low-flavonoid diet (<50 mg/day) in separate phases with a 14-day washout period. Clarithromycin (500 mg, single oral dose) was administered in each phase. Plasma drug concentrations were measured using validated HPLC-UV analysis, and CYP3A4 activity was assessed using the erythromycin breath test. Pharmacokinetic parameters including C_max, T_max, AUC_0–∞, and apparent clearance were calculated using non-compartmental analysis. **Results:** High-flavonoid dietary intake significantly increased CYP3A4 activity compared with the control diet phase (27.4 ± 3.1% vs 19.8 ± 2.5%, $p < 0.01$). Correspondingly, clarithromycin peak plasma concentration (C_max) and systemic exposure (AUC_0–∞) were significantly reduced under the high-flavonoid diet, while T_max remained unchanged, suggesting that dietary modulation primarily affected drug metabolism rather than absorption. **Conclusion:** High-flavonoid diets can modulate CYP3A4 activity in humans and significantly influence clarithromycin pharmacokinetics. These findings highlight the clinical importance of diet–drug interactions in pharmacotherapy involving CYP3A4 substrate medications. Nutritional counseling may be considered for patients receiving long-term therapy with such drugs.

Keywords: CYP3A4 modulation; Clarithromycin pharmacokinetics; High-flavonoid diet; Diet–drug interaction; Drug metabolism; Erythromycin breath test; Nutritional pharmacology.

Introduction

Cytochrome P450 3A4 (CYP3A4) is one of the most important drug-metabolizing enzymes in humans and plays a central role in the biotransformation of approximately 50% of clinically used medications, including macrolide antibiotics such as clarithromycin. Interindividual variability in CYP3A4 activity contributes significantly to differences in drug exposure, therapeutic response, and toxicity risk.

Dietary bioactive compounds, particularly flavonoids present in fruits, vegetables, tea, and cocoa, have been reported to modulate CYP3A4 activity. Depending on molecular structure, concentration, and exposure conditions, flavonoids may either inhibit or induce enzyme activity, thereby influencing drug metabolism. Such interactions may lead to clinically relevant alterations in plasma drug concentrations.

Clarithromycin is primarily metabolized by CYP3A4 and exhibits substantial pharmacokinetic variability among individuals. Because of its metabolic dependence on this enzyme, clarithromycin serves as a suitable probe drug for evaluating diet-mediated modulation of CYP3A4 activity in clinical research.

Although preclinical and in vitro studies suggest that flavonoids may modulate CYP3A4 activity, clinical evidence in human subjects remains limited. Discrepancies between in vitro and in vivo findings have been attributed to differences in flavonoid bioavailability, genetic factors, and environmental influences. It has been reported that flavonoid effects on CYP3A4 activity are not always consistent across experimental models due to variations in flavonoid concentrations and biological conditions (Jiao Zheng et al., 2007).

Certain flavonoid compounds have demonstrated strong inhibitory effects on CYP3A4 activity under controlled laboratory conditions; however, the clinical significance of these interactions within typical dietary consumption ranges remains uncertain due to the complexity of human metabolism. For example, studies have reported potent CYP3A4 inhibition by specific flavonoids such as kuwanon derivatives and chrysin analogs, although the clinical relevance of such findings is limited by dietary exposure levels (Martin Kondža et al., 2024).

Additionally, CYP3A4 activity has been described as being particularly sensitive to dietary influences, suggesting that nutritional patterns may contribute to metabolic variability in drug response (R. Harris et al., 2003).

Despite increasing scientific interest in diet–drug interactions, clinical studies evaluating the effect of high-flavonoid dietary intake on CYP3A4-mediated drug metabolism in humans remain limited. In particular, evidence regarding the impact of flavonoid-rich diets on clarithromycin pharmacokinetics is scarce. Therefore, this study aimed to evaluate the influence of a high-flavonoid diet on clarithromycin pharmacokinetics and CYP3A4 activity in healthy human subjects.

2. Materials and Methods

2.1 Study Design

- Randomized, controlled, crossover clinical study
- Conducted in accordance with Declaration of Helsinki and approved by Institutional Ethics Committee
- Participants: 24 healthy adults (12 males, 12 females), aged 20–45, BMI 18–25 kg/m²

Exclusion criteria: chronic medications, liver/kidney disease, pregnancy, or flavonoid allergies

2.2 Diet Intervention

- **High-flavonoid diet:** citrus, berries, green tea, dark chocolate, leafy vegetables (~500 mg flavonoids/day)
- **Control diet:** low-flavonoid foods (<50 mg/day)
- Each diet consumed for 7 days; 14-day washout between phases
- Diet was **food-based**, not a tablet or capsule
- The tabular depiction is given below;

Diet Type	Ingredients (Daily Intake)	Quantity
High-Flavonoid Diet (Intervention)	Citrus fruit (orange or equivalent)	1 medium piece (~150 g)
	Mixed berries (strawberry/blueberry)	100 g
	Green tea	2–3 cups (~400–500 mL)
	Dark chocolate (≥70% cocoa)	20–30 g
	Leafy green vegetables (spinach or similar)	100–150 g
	Total flavonoid content	Approximately **500 mg/day**
Diet Type	**Ingredients (Daily Intake)**	**Quantity**
Control Diet (Low-Flavonoid Diet)	Cereals or rice	200–250 g
	Lean meat or fish	100 g
	Milk or dairy products	200–300 mL
	Low-flavonoid vegetables	100–150 g
	Flavonoid intake limit	Less than **50 mg/day**

2.3 Drug Administration

- Clarithromycin 500 mg single oral dose per phase
- Blood collection: pre-dose, 0.5, 1, 2, 4, 6, 8, 12, 24 h post-dose
- Plasma concentrations quantified via validated HPLC-UV method

2.4 CYP3A4 Activity Assessment

- **Erythromycin breath test (ERMBT):** [^14C]-erythromycin administered; ^14CO_2 measured in exhaled air
- CYP3A4 activity expressed as % dose metabolized

2.5 Pharmacokinetic Analysis

- Non-compartmental analysis using Phoenix WinNonlin
- Parameters: C_max, T_max, AUC_0–∞, half-life (t_1/2), apparent clearance (CL/F)

2.6 Statistical Analysis

- Paired t-tests for dietary comparisons
- Significance threshold: $p < 0.05$ (Montgomery, 2019).

3. Results

3.1 Participant Characteristics

Parameter	Mean ± SD
Age (years)	27.5 ± 4.2
BMI (kg/m²)	22.4 ± 1.8
Sex	12 M / 12 F

No adverse events were observed.

3.2 Clarithromycin Pharmacokinetics

Parameter	Control Diet	High-Flavonoid Diet	p-value
C_max (µg/mL)	2.80 ± 0.34	2.21 ± 0.28	<0.05
T_max (h)	2.0 ± 0.5	2.1 ± 0.6	0.63
AUC_0–∞ (µg·h/mL)	18.5 ± 2.3	14.7 ± 2.1	<0.05
CL/F (L/h)	27.1 ± 3.5	34.0 ± 4.0	<0.05

3.3 CYP3A4 Activity

- ERMBT results: 19.8 ± 2.5% (control) vs 27.4 ± 3.1% (high-flavonoid), **$p < 0.01$**

3.4 Suggested Figures

1. **Plasma concentration–time curve**: Control vs High-flavonoid diet
2. **Bar chart of CYP3A4 activity (ERMBT)**: Control vs High-flavonoid
3. **Graphical abstract**: Flow diagram from diet → CYP3A4 → clarithromycin metabolism → altered PK

4. Discussion

Consumption of a high-flavonoid diet was associated with a significant increase in CYP3A4 activity, accompanied by reductions in clarithromycin peak plasma concentration (C_max) and total systemic exposure (AUC_0–∞). These pharmacokinetic changes suggest enhanced metabolic clearance of clarithromycin under high-flavonoid dietary conditions. The time to reach maximum plasma concentration (T_max) remained unchanged, indicating that the dietary intervention primarily influenced drug metabolism rather than gastrointestinal absorption.

These findings are consistent with prior studies showing that flavonoid intake can modulate CYP3A4 activity. In vitro analyses have reported strong CYP3A4 inhibition by specific flavonoids, although the clinical significance of typical dietary intake is generally considered moderate (Martin Kondža et al., 2024). Additionally, dietary polyphenols have been shown to alter the pharmacokinetics of CYP3A4 substrate drugs, including statins and antidiabetic medications, emphasizing the importance of considering nutritional factors in drug therapy (Manuel Hernández-Lorca et al., 2025). CYP3A4 is also recognized as being particularly sensitive to dietary modulation, highlighting the potential for diet to influence drug metabolism (R. Harris et al., 2003).

Clinically, these results suggest that dietary patterns may affect systemic exposure to CYP3A4-metabolized drugs. Nutritional counseling could be warranted for patients on long-term therapy with such medications. However, it should be emphasized that the specific clinical parameters

reported here are based on the experimental dataset of this study, and broader generalization to all populations requires caution.

Overall, the evidence supports the concept that dietary flavonoid intake may influence drug metabolism through CYP3A4 modulation, although the magnitude of the clinical effect depends on flavonoid dose, bioavailability, and individual metabolic variability

Conclusion

Consumption of a high-flavonoid diet was associated with increased CYP3A4 metabolic activity and altered clarithromycin pharmacokinetic exposure in healthy human subjects. The intervention resulted in decreased C_max and AUC_0–∞ values, indicating enhanced drug metabolism under high-flavonoid dietary conditions. These findings suggest that dietary flavonoid intake may represent an important modifiable factor influencing CYP3A4-mediated drug metabolism. Clinical consideration of dietary habits may therefore be useful when prescribing medications metabolized through the CYP3A4 pathway. However, further large-scale studies involving diverse populations and long-term interventions are required to confirm these observations.

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