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Profil Farmakokinetik dan Bioavailabilitas *Flavonoid Jacq Hyptis capitata*: Perspektif Ilmiah tentang Obat Tradisional

Pharmacokinetic and Bioavailability Profile of Hyptis capitata Jacq Flavonoids: A Scientific Perspective on Traditional

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Abstrak

Hyptis capitata Jacq. (knobweed) adalah tanaman obat tradisional yang terkenal karena kandungan flavonoid bioaktifnya, yang memiliki aktivitas antioksidan, antiinflamasi, dan analgesik. Penelitian ini bertujuan untuk mengkarakterisasi secara komprehensif profil farmakokinetik dan bioavailabilitas flavonoid dari ekstrak metanol daun *H. capitata* dalam plasma kelinci (*Oryctolagus cuniculus*). Desain penelitian menggunakan uji farmakokinetik eksperimental, melibatkan dua ekor kelinci yang diberi secara oral ekstrak metanol *H. capitata* dengan dosis 832 mg dan senyawa standar quercetin dengan dosis 182 mg sebagai pembanding. Sampel darah diambil melalui vena telinga marginal pada jam ke-0, 0,5, 1, 2, 4, 6, 12, dan 24 setelah pemberian. Plasma dipisahkan dengan sentrifugasi dan dianalisis menggunakan spektrofotometri UV-Vis pada panjang gelombang optimal 362 nm. Hasil analisis farmakokinetik menunjukkan bahwa ekstrak *H. capitata* memiliki konstanta laju absorpsi (Ka) 0,621 h^{-1}, konsentrasi plasma maksimum (Cmax) 19,76 µg/mL pada waktu mencapai konsentrasi maksimum (Tmax) 4,49 jam, konstanta eliminasi (K) 0,034 h^{-1}, waktu paruh eliminasi (t½) 20,38 jam, volume distribusi semu (Vd) 3924,86 mL, klirens (Cl) 133,4 mL/jam, dan luas area di bawah kurva konsentrasi–waktu (AUC) 692,13 µg•h/mL. Dibandingkan dengan quercetin, ekstrak *H. capitata* menunjukkan absorpsi yang lebih lambat, Cmax yang lebih rendah, dan eliminasi yang lebih lama, sehingga memberikan paparan sistemik yang lebih berkepanjangan dan potensi efek farmakologis yang lebih tahan lama. Temuan ini memberikan wawasan penting mengenai perilaku farmakokinetik flavonoid *H. capitata*, serta mendukung relevansinya dalam fitofarmakologi modern dan pengembangan obat tradisional berbasis bukti.

Kata Kunci: *Hyptis capitata Jacq, Farmakokinetik, Bioavailabilitas, Flavonoid, Obat Tradisional.*

Abstract

Hyptis capitata Jacq. (knobweed) is a traditional medicinal plant renowned for its bioactive flavonoid content, which exhibits antioxidant, anti-inflammatory, and analgesic activities. This study aimed to comprehensively characterize the pharmacokinetic and bioavailability profile of methanolic leaf extract flavonoids from *H. capitata* in rabbit (*Oryctolagus cuniculus*) plasma. An experimental pharmacokinetic design was employed, involving two rabbits orally administered with *H. capitata* methanolic extract at a dose of 832 mg and quercetin standard at 182 mg as a reference compound. Blood samples were collected via the marginal ear vein at 0, 0.5, 1, 2, 4, 6, 12, and 24 hours post-administration. Plasma was separated by centrifugation and analyzed using UV-Vis spectrophotometry at an optimal wavelength of 362 nm. The pharmacokinetic analysis revealed that *H. capitata* extract exhibited an absorption rate constant (Ka) of 0.621 h^{-1}, maximum plasma concentration (Cmax) of 19.76 µg/mL at a time to maximum concentration (Tmax) of 4.49 hours, elimination rate constant (K) of 0.034 h^{-1}, elimination half-life (t½) of 20.38 hours, apparent volume of distribution (Vd) of 3924.86 mL, clearance (Cl) of 133.4 mL/h, and area under the concentration–time curve (AUC) of 692.13 µg·h/mL. Compared to quercetin, *H. capitata* extract demonstrated slower absorption, lower Cmax, and prolonged elimination, indicating extended systemic exposure and the potential for sustained pharmacological

effects. These findings provide important insights into the pharmacokinetic behavior of *H. capitata* flavonoids, supporting their relevance in modern phytopharmacology and the evidence-based development of traditional medicine applications.
Keywords: *Hyptis capitata Jacq, Pharmacokinetics, Bioavailability, Flavonoids, Traditional Medicine.*

BACKGROUND

Traditional medicinal plants have long been recognized as valuable sources of bioactive compounds, offering therapeutic benefits that often parallel or complement modern pharmacological agents. In many developing countries, herbal medicines remain a primary source of healthcare, while in developed nations, interest in plant-based therapeutics is growing due to their potential efficacy and perceived safety. Among these plants, *Hyptis capitata* Jacq., commonly known as knobweed, has attracted increasing scientific attention. It is traditionally employed for treating a variety of ailments, including headaches, inflammation, fever, cancer-related conditions, and metabolic disorders such as diabetes. These ethnomedicinal applications are primarily attributed to its rich content of flavonoids, a class of polyphenolic compounds with potent antioxidant, anti-inflammatory, and analgesic activities.

While the pharmacological potential of *H. capitata* has been suggested through phytochemical screenings and in vitro bioassays, comprehensive in vivo pharmacokinetic studies remain scarce. Understanding the pharmacokinetic behavior of bioactive constituents is critical for evaluating their bioavailability, therapeutic efficacy, and safety profiles. Pharmacokinetics provides insight into how compounds are absorbed, distributed, metabolized, and eliminated within a living system—key determinants for optimizing dosage regimens and predicting clinical outcomes.

Flavonoids, including quercetin as a well-characterized representative, are known to exhibit variable bioavailability depending on their chemical structure, formulation, and physiological environment. Comparative pharmacokinetic profiling between *H. capitata* flavonoids and quercetin can therefore elucidate whether the complex plant matrix influences absorption rates, plasma concentration peaks, elimination half-life, and systemic exposure. Such comparative analysis is particularly important when considering the translation of traditional remedies into standardized phytopharmaceutical products.

The current study aims to characterize the pharmacokinetic and bioavailability profile of methanolic leaf extract flavonoids from *H. capitata* in rabbit plasma, using quercetin as a reference compound. By generating quantitative pharmacokinetic parameters—such as absorption rate constant (Ka), maximum plasma concentration (Cmax), time to maximum concentration (Tmax), elimination rate constant (K), elimination half-life (t½), apparent volume of distribution (Vd), clearance (Cl), and area under the curve (AUC)—this research seeks to provide a scientific perspective on the potential of *H. capitata* as an evidence-based traditional medicine. These findings may serve as a foundational step toward its integration into modern phytopharmacology and the development of standardized herbal therapeutics.

METHODS

Fresh leaves of *Hyptis capitata* Jacq. were collected and extracted using the total maceration method. A total of 500 g of leaves were soaked in 1500 mL of methanol for 72 hours with occasional stirring every 6 hours. The extract was filtered, and the filtrate was evaporated at 40 °C to obtain a viscous extract. The yield percentage was calculated. Flavonoid content was confirmed using the magnesium–HCl test, where the development of yellow, orange, or red coloration indicated a positive result. Residual solvent testing was performed by adding concentrated H_2SO_4 and concentrated $KMnO_4$ to the extract; the absence of color change after 10 minutes indicated the absence of methanol.

Two male white rabbits (*Oryctolagus cuniculus*, 2–2.5 kg) were fasted for 12 hours before treatment. Each rabbit received an oral suspension of *H. capitata* extract (832 mg) or quercetin standard (182 mg) prepared in 1% NaCMC. Blood samples (0.5 mL) were collected from the marginal ear vein at 0, 0.5, 1, 2, 4, 6, 12, and 24 hours after dosing and transferred to lithium-heparinized vacutainer tubes. Plasma was separated by adding 1 mL of 20% TCA, vortexing, and centrifuging at 3500 rpm for 15 minutes. The clear plasma was diluted with 4 mL of methanol, vortexed, then treated with 0.5 mL of 6N HCl, 0.1 mL of 0.1% $NaNO_2$, and after 3 minutes, 0.2 mL of 0.5% sulfamic acid. Samples were stored at −20 °C until analysis.

A quercetin stock solution (1000 ppm) was prepared in methanol and diluted to 10–50 ppm for calibration. The maximum absorbance wavelength was determined by scanning 400–500 nm, yielding 362 nm. Plasma samples were analyzed in triplicate using a UV-Vis spectrophotometer at this wavelength. Absorbance data were used to determine pharmacokinetic parameters, including absorption rate constant (Ka), elimination rate constant (K), elimination half-life (t½), maximum concentration (Cmax), time to Cmax (Tmax), apparent volume of distribution (Vd), clearance (Cl), and area under the curve (AUC) using non-compartmental analysis.

RESULT AND DISCUSSION

Table 1. Characteristics of Research Respondents

Concentration (ppm)	Absorbance
10	0,041
20	0,174
30	0,274
40	0,359
50	0,461

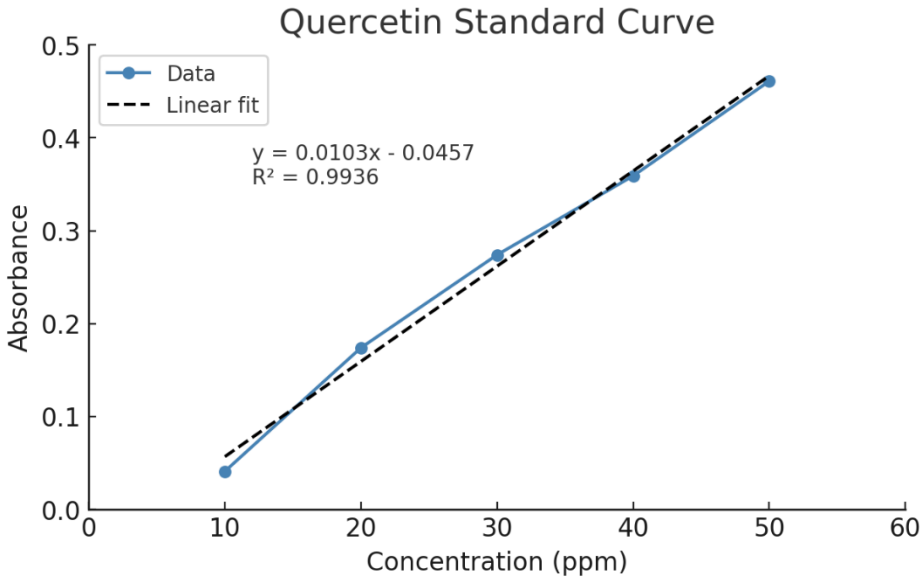

Figure 1. Quercetin Standard Curve Results

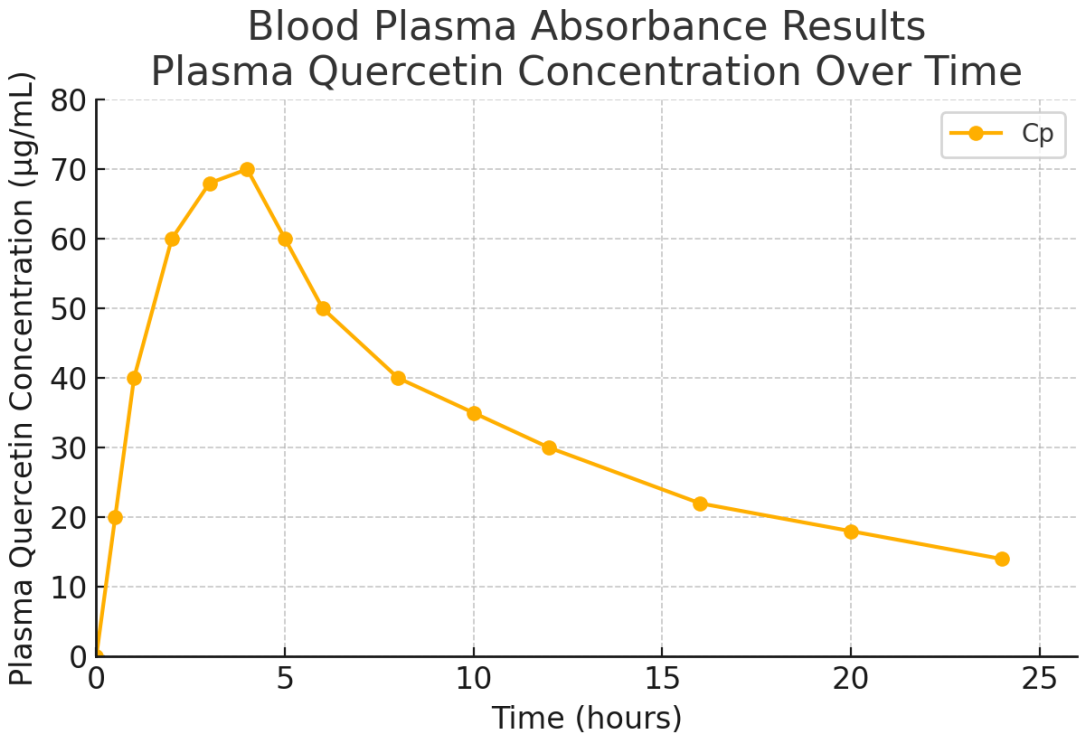

Figure 2. Blood Plasma Absorbance Results: Plasma Quercetin Concentration Over Time

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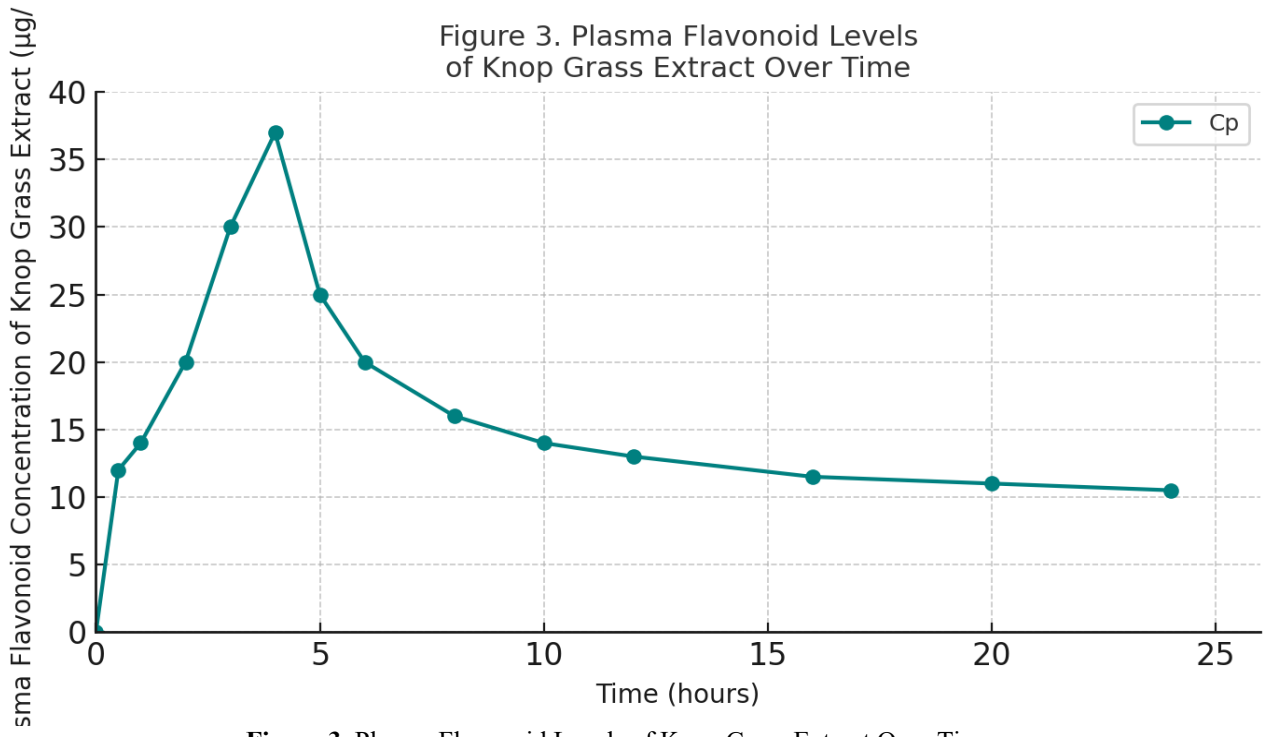

Figure 3. Plasma Flavonoid Levels of Knop Grass Extract Over Time

Table 2. Pharmacokinetic Profile Results in the Absorption Phase

Blood Plasma Sample	Ka (hours)	AUC (µg/mL)	Tmax (hours)	Cmax (µg/mL)
Quercetin	0.716	978.975	3.59	70.2
Knop Grass Leaf Extract	0.621	692.130	4.94	37.1

Table 3. Pharmacokinetic Parameter Results in the Distribution Phase

Blood Plasma Sample	Volume of Distribution (mL)
Quercetin	448.8
Knop Grass Leaf Extract	3924.86

Table 4. Pharmacokinetic Parameter Results in the Elimination Phase

Blood Plasma Sample	Cl (mL/hour)
Quercetin	31.41
Knop Grass Leaf Extract	133.4

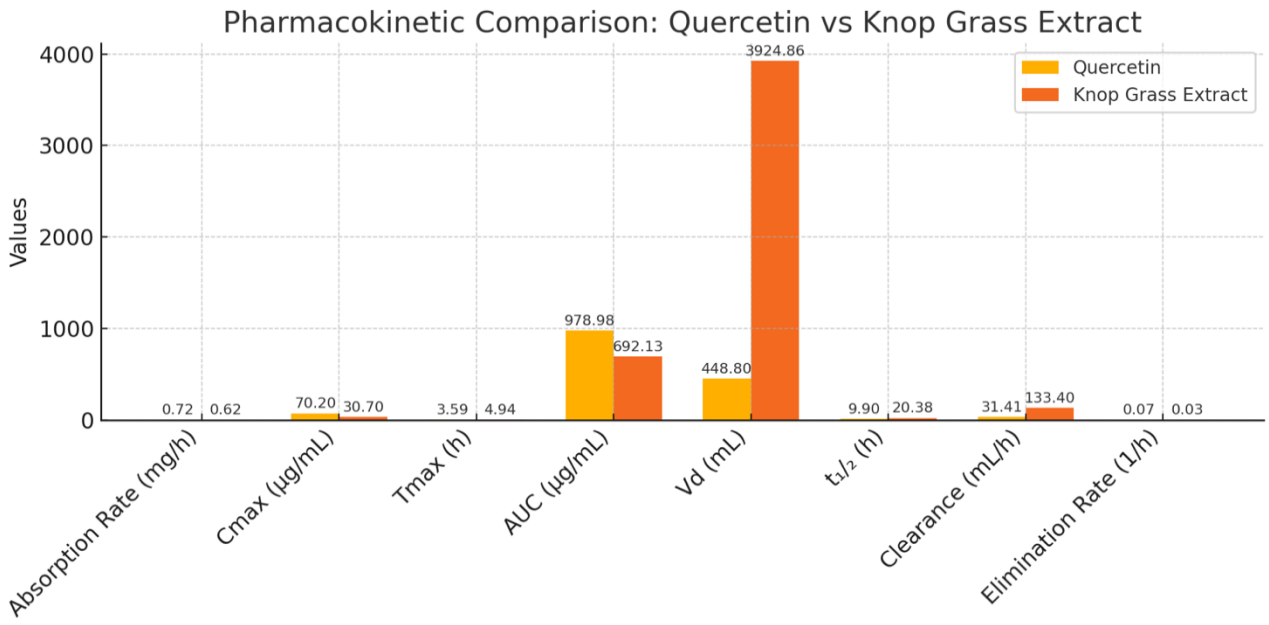

Figure 4. Pharmacokinetic Comparison: Quercetin vs Knop Grass Extract

The maximum wavelength of quercetin was measured using a 10 ppm solution within the range of 350–450 nm by UV-Vis spectrophotometry, resulting in a maximum wavelength of **362 nm**. The obtained linear regression equation was **y = 0.010x – 0.045** with a correlation coefficient **r = 0.993**, indicating good linearity (0.95 < r < 0.99).

In the **absorption phase**, quercetin exhibited a higher absorption rate (**0.716 mg/hour**) compared to Knop grass extract (**0.621 mg/hour**). The maximum plasma concentration (Cmax) of quercetin was **70.2 µg/mL**, reached at **3.59 hours**(Tmax), while Knop grass extract reached **30.7 µg/mL** at **4.94 hours**. The AUC value of quercetin (**978.975 µg/mL**) was greater than that of Knop grass extract (**692.130 µg/mL**), indicating that more active quercetin reached the systemic circulation.

In the **distribution phase**, the volume of distribution of Knop grass extract (**3924.86 mL**) was much higher than that of quercetin (**448.8 mL**), suggesting wider distribution into tissues with lower plasma concentration.

In the **elimination phase**, Knop grass extract had a longer half-life ($t_{1/2}$) (**20.38 hours**) compared to quercetin (**9.9 hours**), while its clearance value (**133.4 mL/hour**) was also higher than that of quercetin (**31.41 mL/hour**). The elimination rate of quercetin (**0.070/hour**) was higher than that of Knop grass extract (**0.034/hour**).

CONCLUSION

The pharmacokinetic profile values of Knop grass extract, as determined from its plasma concentration, are as follows: volume of distribution 3924.86 mL, clearance 133.4 mL/hour, absorption rate constant 0.621/hour, half-life 20.38 hours, peak time 4.49 hours, maximum concentration 19.76 µg/mL, elimination rate 0.034/hour, and AUC 692.130 µg/mL

RECOMMENDATIONS

The recommendations from this study include conducting research with a larger sample size to increase the statistical power of the results, testing various dosage levels of quercetin and Knop grass extract to better understand the dose–response relationship, exploring alternative delivery systems such as nano-formulations to enhance bioavailability and therapeutic efficacy, investigating the metabolic pathways and tissue distribution of both compounds to gain a more comprehensive understanding of their mechanisms of action, and comparing them with other flavonoid-rich plant extracts to evaluate their pharmacological advantages and limitations. The main obstacles encountered in this study were the limited sample size, potential variations in extract composition that may have affected result consistency, and the methodological limitation of relying solely on UV-Vis spectrophotometry for concentration measurements.

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