Research Article

# Pharmacokinetic Profle of Tetrahidropentagamavunon-0 (THPGV-0) in Wistar Rats Oral and Intravenous Administration

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**ABSTRACT**

Tetrahydropentagamavunon-0 (THPGV-0) is a pentagamavunon's derivative. It is also a curcuminmetabolite analog. THPGV-0 has been successfully synthesised in Faculty of Pharmacy, UGM. This research is aimed to investigate the pharmacokinetic profile of THPGV-0. The pharmacokinetic assay was carried out by oral and intravenous administrations in rats. The result showed that from the pharmacokinetic profile of THPGV-0, the bioavalability of THPGV-0 is low.

**Keywords:** THPGV-0, pharmacokinetic profile, oral, intravenous.

## INTRODUCTION

Curcumin is a natural compound isolated from *Curcuma longa,* L., (*Curcuma domestica*) and *Curcuma xanthorriza,* R. Curcumin used widely in Indonesian society as traditional medicine. Based on scientific evidences, the biological activity of curcumin are such as antioxidant, anti-inflammatory, antibacterial and anticancer.[1,2] In searching of more potent, stable, safe, effective and specific target of medicine based on curcumin, the structure modification was done. Pentagamavunon-0 (PGV-0) is one of molecules that modified from curcumin structure.[2] The modification and synthesis were done in Curcumin Research Center (CRC). CRC is a research unit in Faculty of Pharmacy, Gadjah Mada University. Our research is focused on the development of curcumin analog as medicine.

This PGV-0 has antiinflammatory activity better than curcumin. In other hand, pharmacokinetic profile of PGV-0 in the blood is erratic and even difficult to determine when taken orally by rat. Orally, PGV-0 is difficult too to evaluated in blood.[3,4] This is like what happened in curcumin pharmacokinetic profile.[5,6] Pan (1999), assumed that in blood curcumin is metabolised to its active form of tetrahydrocurcumin (THC). And this is apparently happened to our curcumin analog, PGV-0. PGV-0 in the body is assumed to transform into its metabolite's form, Tetrahydropentagamavunon-0 (THPGV-0). [7]

This research is aimed to investigate the pharmacokinetic profile of THPGV-0 which assumed that THPGV-0 is a metabolite of PGV-0.

## MATERIALS AND METHODS

### Material

Male rats as subject test, Wistar (age 2-3 months, weight 150-200 gram) from Laboratory of Pharmacology and Toxicology, Faculty of Pharmacy, Gadjah Mada University. Before treatment, rats were fasting for 18 – 24 hours, only water given *(ad libitum).* PGV-0 and THPGV-0are synthesized by Dr. Ritmaleni (Curcumin Research Center).

### Instrument

ACE homogenizer, analytical electric balance (Chyo Jupiter C3-100MI), micro pipet (Pipetman Gilson) in different volume, vortex mixer, dizzyness machine (Kokusan, Tokyo), HPLC (Shimadzu) : (column : Cartridge C-18, long 125 mm (E. Merck), mobile phase : mixture of methanol : water (70:30), 1 mL/menit, Detector UV/Vis at $\lambda$ = 294 nm.

### Method

This research was used completely one way randomized with Wistar rat as subject test. This research will be done by orally and intravenous method.

Wistar Rats were divided into four groups with seven rats each. Group I was given 200 mg/kg BW PGV-0 orally and group II was given THPGV-0 orally too with the same dose with group I. Blood sample of group I at 0, 5, 15, 30, 40, 50, 60, 70, 80, 90, 120, 240, 360 while group II was taken for 0.2 mL at 0, 5, 15, 30, 40, 50, 60, 70, 80, 90, 105, 120, 150, 180, 240, and 360 minutes. Group III was given intravenously 40 mg/kg BW PGV-0 while group IV was given THPGV-0. Blood sample was taken at 0, 2, 5, 10, 20, 30, 40, 60, 120, 240, 360 minutes.

After PGV-0 was administered, the PGV-0 and THPGV-0 were measured while for THPGV-0 blood sample, only THPGV-0 level in blood that was measured. The measurement followed the published method developed by Hakim (2004).

## RESULTS AND DISCUSSION

Table 1 showed the measurement of PGV-0 and THPGV-0 level in blood samples against time. Figure 1 showed the

curve profile after PGV-0 was administered 200 mg/kg BW on rats.

It can be seen that after 200 mg/kg BW of PGV-0 was administered orally in rats, THPGV-0 was detected in the sample, although on edge of limit detection. It means that THPGV-0 is the metabolite of PGV-0. In this case, it is assumed that a very small amount THPGV-0 detected because THPGV-0 is congated with glucoronate and sulphate so it can not be measured by this method.

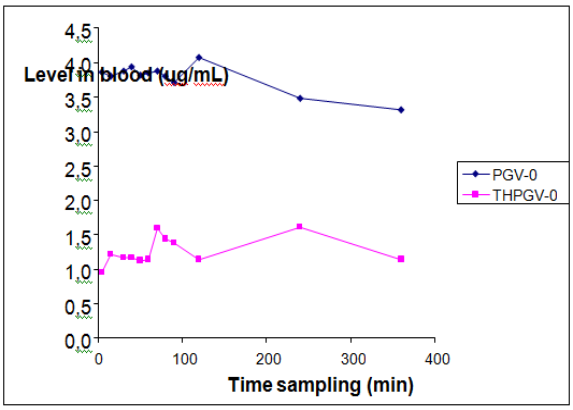


**Figure 1:** Average level profile of PGV-0 and THPGV-0 in blood sample againts time after PGV-0 was administered orally 200 mg/kg BW on rats (N=7)

Pharmacokinetic profile of PGV-0 and THPGV-0 after PGV-0 was administered orally, can be determined by calculating the pharmacokinetic parameters by using non-compartmental analysis. The data is shown on table 2.

Table 2: From this data, $C_{maks}$ of THPGV-0 is half of PGV-0's $C_{maks}$ and the time need to reach $C_{maks}$ of THPGV-0 is two times slower than ($t_{maks}$) of PGV-0. The bioavailability (F) of PGV-0 orally is 15.1 % and it means that only 15.1 % of PGV-0 given dose can reach the systemic circulation.

Table III and figure 2 showed the measurement result of PGV-0 and THPGV-0 levels in blood sample against time and profile of PGV-0 intravenously at 40 mg/kg BW in rats.

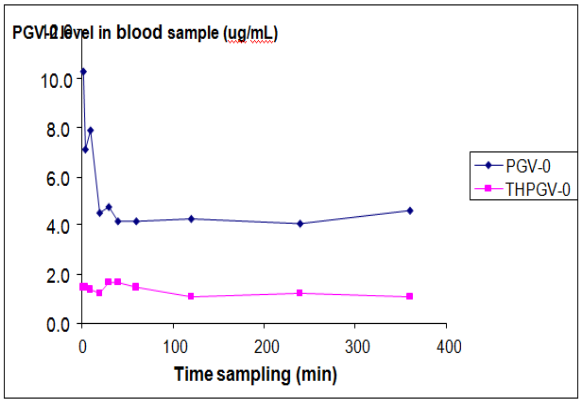


**Figure 2:** Profile of mean contain of PGV-0 and THPGV-0 in blood sample against time after PGV-0 was given intravenously 40 mg/kg BW on rats (N=7)

By given PGV-0 at 40 mg/kg BW intravenously on rats, THPGV-0 level was detected in blood sample although its content is still at edge of limit detection. THPGV-0 level found after PGV-0 was given orally at 200 mg/kg BW of dose and intravenously at 40 mg/kg BW are not really significantly different. This difference is assumed that it could be happened because of the very fast formation of THPGV-0-glucoronate or sulphate conjugations. So, the free THPGV-0 is not found in the blood except its conjugation forms.

Pharmacokinetic profile of PGV-0 and THPGV-0 level intravenously can be determined by calculating its pharmacokinetic parmeters by using non compartmental analysis. The data could be seen on table 4.

Table 4: It can be seen that clearence value of PGV-0 given orally and intravenously is not significantly different. It means that its primary clearence is not influenced by given methods.

Table 5 and figure 3 showed the measurement data of THPGV-0 level in blood sample against time and its profile after THPGV-0 was given intravenously 40 mg/kg BW and orally 200 mg/kg BW on rats. Here, THPGV-0 level was detected in blood samples while PGV-0 level was not detected. THPGV-0 level after THPGV-0 was given orally 200 mg/kg BW compared to PGV-0 which given orally and intravenously is not significantly different.

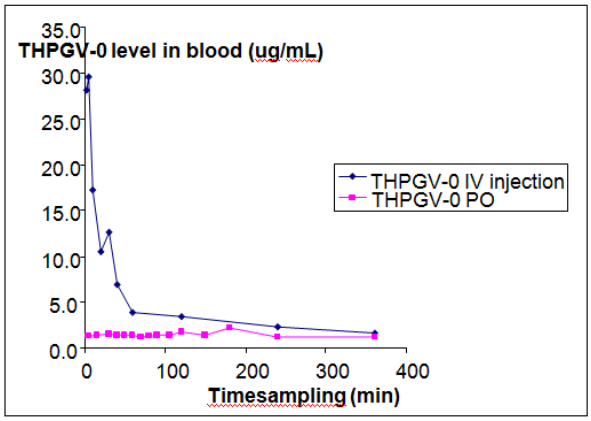


**Figure 3:** Average level of THPGV-0 in blood against time after orally adminstered at 200 mg/kg BW of dose and intravenously at 40 mg/kg BW of dose in rats (N=7)

Pharmacokinetic profile of THPGV-0 after THPGV-0 was given intravenously orally, can be determined by calculating its pharmacokinetic parameters by using non-compartemental analysis. The data is shown on table 6 below.

**Table 1:** PGV-0 and THPGV-0 level in blood sample (mean±SEM) after PGV-0 was given orally 200 mg/kg BWon rats (N=7)

| Time (min) | PGV-0 levelin blood sample (µg/mL) | | THPGV-0 levelin blood sample (µg/mL) | |
|---|---|---|---|---|
| 5 | 3.83 | ±0.32 | 1.04 | ±0.13 |
| 15 | 3.86 | ±0.34 | 0.96 | ±0.10 |
| 30 | 3.81 | ±0.31 | 1.22 | ±0.17 |
| 40 | 3.87 | ±0.37 | 1.17 | ±0.14 |
| 50 | 3.94 | ±0.28 | 1.17 | ±0.13 |
| 60 | 3.81 | ±0.34 | 1.13 | ±0.11 |
| 70 | 3.85 | ±0.26 | 1.13 | ±0.16 |
| 80 | 3.88 | ±0.31 | 1.59 | ±0.43 |
| 90 | 3.80 | ±0.17 | 1.44 | ±0.14 |
| 120 | 3.71 | ±0.27 | 1.38 | ±0.22 |
| 240 | 4.07 | ±0.31 | 1.15 | ±0.04 |
| 360 | 3.47 | ±0.11 | 1.60 | ±0.18 |

**Table 2:** Pharmacokinetic parameter values of PGV-0 and THPGV-0 (mean±SEM) after PGV-0 was administered orally 200 mg/kg BW on rats (N=7)

| Pharmacokinetic parameter | PGV-0 | | THPGV-0 | |
|---|---|---|---|---|
| $AUC_{0-t}$ (µg.menit/mL) | 1303.49 | ±50.91 | 450.43 | ±31.99 |
| $t_{maks}$ (mnt) | 67.86 | ±16.25 | 125.71 | ±29.67 |
| $Cp_{maks}$ (µg/mL) | 4.56 | ±0.35 | 2.29 | ±0.30 |
| F | 0.151 | ±0.006 | | |
| $Cl_T$ (mL/menit/kg) | 23.30 | ±0.10 | | |

**Table 3:** PGV-0 and THPGV-0 in blood sample (mean±SEM) after PGV-0 was given intravenously at 40 mg/kg BW dose on rats (N=7)

| t (mnt) | PGV-0 level in blood sample (µg/mL) | | THPGV-0 level in blood sample (µg/mL) | |
|---|---|---|---|---|
| 2 | 10.29 | ±5.65 | 1.17 | ±0.15 |
| 5 | 7.10 | ±2.60 | 1.45 | ±0.38 |
| 10 | 7.87 | ±3.76 | 1.47 | ±0.23 |
| 20 | 4.50 | ±0.48 | 1.36 | ±0.21 |
| 30 | 4.76 | ±0.66 | 1.23 | ±0.21 |
| 40 | 4.16 | ±0.19 | 1.68 | ±0.52 |
| 60 | 4.16 | ±0.23 | 1.65 | ±0.64 |
| 120 | 4.27 | ±0.29 | 1.46 | ±0.17 |
| 240 | 4.07 | ±0.21 | 1.09 | ±0.20 |
| 360 | 4.58 | ±0.60 | 1.22 | ±0.16 |

**Table 4:** Pharmacokinetic parameter values of PGV-0 and THPGV-0 (mean±SEM) after PGV-0 was given intravenously 40 mg/kg BW on rats (N=7)

| Pharmacokinetic Parameter | PGV-0 | | THPGV-0 | |
|---|---|---|---|---|
| $AUC_{0-t}$ (µg.menit/mL) | 1572.25 | ±127.10 | 440.47 | ±58.99 |
| $Cl_T$ (mL/menit/kg) | 26.29 | ±1.77 | 100.30 | ±12.87 |

**Table 5:** THPGV-0 level in blood (mean±SEM) after admintered orally at 200 mg/kg BW of dose and intravenously at 40 mg/kg BW of dose in rats (N=7)

| t (min) | THPGV-0 level after intravenously admintered (µg/mL) | | t (min) | THPGV-0 level after administered orally (µg/mL) | |
|---|---|---|---|---|---|
| 2 | 28.14 | ±11.34 | 5 | 1.18 | ±0.14 |
| 5 | 29.56 | ±15.05 | 15 | 1.32 | ±0.09 |
| 10 | 17.26 | ±8.64 | 30 | 1.45 | ±0.10 |
| 20 | 10.51 | ±4.64 | 40 | 1.54 | ±0.15 |
| 30 | 12.70 | ±5.94 | 50 | 1.49 | ±0.20 |
| 40 | 6.93 | ±2.11 | 60 | 1.46 | ±0.19 |
| 60 | 3.90 | ±0.56 | 70 | 1.44 | ±0.15 |
| 120 | 3.47 | ±0.50 | 80 | 1.26 | ±0.15 |
| 240 | 2.35 | ±0.56 | 90 | 1.37 | ±0.08 |
| 360 | 1.67 | ±0.34 | 105 | 1.51 | ±0.10 |
| | | | 120 | 1.49 | ±0.10 |
| | | | 150 | 1.75 | ±0.30 |

**Tabel 6:** Harga parameter farmakokinetika THPGV-0 (purata±SEM) setelah pemberian THPGV-0 secara oral dosis 200 mg/kg BB dan injeksi intravena dosis 40 mg/kg BB pada tikus (N=7)

| Pharmacokinetic Parameter | THPGV-0 Injection IV | | THPGV-0 PO | |
|---|---|---|---|---|
| $AUC_{0-t}$ (µg.menit/mL) | 1805.87 | ±302.05 | 527.18 | ±41.45 |
| $Cl_T$ (mL/menit/kg) | 25.02 | ±3.21 | 22.17 | ±0.04 |
| $t_{maks}$ (mnt) | | | 99.29 | ±17.81 |
| $Cp_{maks}$ (µg/mL) | | | 2.92 | ±0.78 |
| F | | | 0.058 | ±0.005 |

Table 6: It can be seen that THPGV-0 clearence value orally and intravenously are not significantly different. The method in adminitering THPGV-0 does not influence the primary clearence pharmacokinetic parameters. Another thing that can be seen also is the bioavailability of THPGV-0 orally is 5.8 %. It means that its bioavailability is very low.

## CONCLUSION

Based on pharmacokinetic profile of THPGV-0 in Wistar rats, concluded that bioavailability of THPGV-0 is very low, 5.8 %. Molecule modification of PGV-0 and THPGV-0 are needed to improve their bioavailabilities.

## REFERENCES


1. Majeed M., Badmaev V., Shivakumar V., and Rajendra, 1995, *Curcuminoids Antioxidant Photonutrients*, Nutriscience Publisher, Piscataway, New Jersey, 1-78.
2. Sardjiman, 2000, Synthesis of some new series of curcumin analogues, anti-oxidative, anti-inflammatory, antibacterial activities and qualitative structure-activity relationship, Dissertation, GadjahMada University, Yogyakarta, Indonesia.
3. Amalia, E., 2001, Profile of 2,5-*Bis*-(4'-hydroxy-3'-methoxybenzylidene) Cyclopentanone Level in Blood after administered orally in Male Sprague Dawley rats, *Skripsi*, Faculty of Pharmacy UGM, Yogyakarta.
4. Hakim L., Hakim AR., and Nugroho AE., 2004, PharmakokineticProfile of PGV-0 after Kalium-PGV-0 orally and intravenously administeredin Rats, Research Report QUE Project, Faculty of Pharmacy UGM, Yogyakarta
5. Kustaniah, 2001, Profile of 2,5-*Bis*-(4'-hydroxy-3'-methoxybenzylidene) Cyclopentanone Level in Blood after administered orally in Female Sprague Dawley rats, *Skripsi*, Faculty of Pharmacy UGM, Yogyakarta.
6. MOLNAS, 2001, Pharmakokinetic Profile of PGV-0 after orally, intravenously and Intraperitoneal administered in Female and Male, Project of MOLNAS I, in collaboration between PT Indofarma and PT Kalbe Farma with Faculty of Pharmacy UGM, Book IV, Yogyakarta
7. Pan M., Huang T., and Lin J., 1999, Biotransformation of Curcumin Through Reduction and Glucuronidation in Mice, *Drug Metab. Dispos.*, 27(1), 486-494.
8. Ritmaleni and Simbara, A., 2010, Synthesis of Tetrahidropentagamavunon-0 (THPGV-0), *Majalah Farmasi Indonesia*, 21(2), 100-105
9. Vogel, HG., 2002, Drug discovery and evaluation, pharmacological assays, 2nd ed., Spriger, Berlin.


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