

PENGARUH PEMBERIAN ASAM KLOROGENAT TERHADAP *VASCULAR REMODELLING*, FIBROSIS PERIVASKULAR, EKSPRESI mRNA *ENDOTHELIN-1* DAN EKSPRESI mRNA *ENDOTHELIAL NITRITE OXIDE SYNTHASE* PADA MENCIT DENGAN *UNILATERAL URETERAL OBSTRUCTION*

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INTISARI

Latar Belakang: Fibrosis ginjal adalah tahap akhir dari penyakit gagal ginjal kronik yang melibatkan *vascular remodelling* karena ketidakseimbangan faktor vasokonstriksi dan vasodilatasi yaitu *Endothelin-1* (ET-1) dan *Endothelial Nitric Oxide Synthase* (eNOS), serta adanya fibrosis perivaskular. Asam klorogenat adalah antioksidan yang dikenal sebagai agen renoprotektif tetapi efek yang melibatkan *vascular remodelling* melalui modulasi ET-1 dan eNOS dan fibrosis perivaskular belum pernah dianalisis.

Tujuan: Mengkaji efek asam klorogenat terhadap aspek vaskular khususnya *vascular remodelling* melalui modulasi ET-1 dan eNOS, serta fibrosis perivaskular pada fibrosis ginjal.

Metode: Penelitian ini adalah penelitian *true experimental*. Unilateral ureteral obstruction (UUO) dilakukan pada mencit galur *swiss webster* (n=25, usia 2-3 bulan, berat 20-30 g) untuk menginduksi fibrosis ginjal. Mencit dibagi menjadi 5 kelompok, yaitu kelompok SO (*Sham Operation*/kontrol), U7 (UUO hari ke-7), U14 (UUO hari ke-14), UC7 (UUO+asam klorogenat hari ke-7) dan UC14 (UUO+asam klorogenat hari ke-14). Asam klorogenat 14 mg/kgBB/hari diberikan intraperitoneal. *Vascular remodelling* dengan parameter *lumen area* (LA), *mean wall thickness* (MWT), *wall/lumen area ratio* (WLAR), serta area fibrosis perivaskular dikuantifikasi menggunakan pewarnaan *Sirius Red*. Ekspresi mRNA ET-1 dan eNOS dikuantifikasi menggunakan *Reverse Transcriptase-PCR*.

Hasil: Pada kelompok perlakuan UUO (U7 dan U14) terjadi *vascular remodelling* yang signifikan ditandai dengan LA lebih sempit, MWT lebih tinggi and WLAR lebih tinggi, dan fibrosis perivaskular ditandai dengan area lebih luas dibandingkan kelompok SO (p<0,05). Hal ini terkait dengan ekspresi mRNA ppET-1 lebih tinggi dan eNOS lebih rendah (p<0,05). Pada kelompok UUO dan pemberian asam klorogenat (UC7 dan UC14) signifikan terjadi perbaikan *vascular remodelling* ditandai dengan LA lebih luas, WLAR lebih rendah dan perbaikan fibrosis perivaskular ditandai dengan area lebih sempit, serta ekspresi mRNA ppET-1 lebih rendah dan eNOS lebih tinggi dibanding kelompok UUO (p<0,05). *Mean wall thickness* lebih rendah tetapi data tidak berbeda signifikan.

Kesimpulan: Asam klorogenat memperbaiki *vascular remodelling* melalui penurunan ekspresi mRNA ET-1 dan peningkatan ekspresi mRNA eNOS, dan fibrosis perivaskular pada keadaan fibrosis ginjal.

Kata kunci: Fibrosis Ginjal, Asam Klorogenat, *Vascular remodelling*, Fibrosis perivaskular, ET-1, eNOS

THE EFFECT OF CHLOROGENIC ACID ADMINISTRATION TO VASCULAR REMODELLING, PERIVASCULAR FIBROSIS, ENDOTHELIN-1 AND ENDOTHELIAL NITRITE OXIDE SYNTHASE mRNA EXPRESSION IN MICE WITH UNILATERAL URETERAL OBSTRUCTION

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ABSTRACT

Background: Kidney Fibrosis is the common pathway final of Chronic Kidney Disease which is characterized by vascular remodelling due to imbalance between vasoconstrictor and vasodilator such as Endothelin-1 (ET-1) and Endothelial Nitric Oxide Synthase (eNOS), and perivascular fibrosis. Chlorogenic Acid (CGA) is an antioxidant as renoprotective agent. However, fibrosis perivascular and vascular remodelling with modulation ET-1 and eNOS involves has not been analyzed yet.

Objective: Examined the effect of CGA in vascular aspects, spesifically vascular remodelling through ET-1 and eNOS modulation, and perivascular fibrosis in kidney fibrosis.

Methods: This research was a true experimental study. Unilateral Ureteral Obstruction (UUO) was performed in swiss webster background mice (n=25, 2-3 months old, 20-30 g weight) to induce kidney fibrosis. The mice were divided into 5 groups, SO (*Sham Operation*/control), U7 (UUO day-7), U14 (UUO day-14), UC7 (UUO+CGA day-7) and UC14 (UUO+CGA day-14). CGA 14 mg/kg body weight/day was induced intraperitoneally. Vascular remodelling based on lumen area, mean wall thickness, and wall/lumen area ratio (WLAR) and perivascular fibrosis of intrarenal arteries were quantified using Sirius Red staining. ET-1 and eNOS mRNA expressions were quantified using Reverse Transcriptase-PCR.

Result: UUO groups (U7 and U14) had significantly higher vascular remodelling as shown by lower lumen area, higher mean wall thickness and higher WLAR, and perivascular fibrosis as shown by higher area compared to SO group ($p<0.05$). These findings associated with higher ppET-1 and lower eNOS mRNA expression ($p<0.05$). On the other hand, CGA groups (UC7 and UC14) revealed lower vascular remodelling as shown by higher lumen area, lower WLAR and perivascular fibrosis as shown by lower area associated with lower ppET-1 and higher eNOS mRNA expression significantly compared to UUO group ($p<0.05$). *Mean wall thickness* was lower but the data was not significantly different.

Conclusion: CGA ameliorates kidney fibrosis through vascular remodelling with reduction of ET-1 and upregulation of eNOS mRNA expression, and perivascular fibrosis.

Keywords: Kidney Fibrosis, CGA, vascular remodelling, perivascular fibrosis, ET-1, eNOS