# INTISARI

Obat kemoterapi dapat meningkatkan level ROS intraseluler yang bersifat toksik terhadap organ tubuh, salah satunya ginjal. Sumber utama ROS pada ginjal diantaranya $H_2O_2$ yang diproduksi NADPH oksidase 4 (NOX4). *Citrus* flavonoid merupakan komponen pada jeruk yang memiliki aktivitas sebagai antioksidan dan antiinflamasi. Penelitian ini bertujuan untuk mengungkap potensi *citrus* flavonoid sebagai agen pencegah kerusakan ginjal akibat obat kemoterapi dengan target NOX4 dan protein yang terlibat pada kerusakan ginjal. Studi meta analisis bioinformatika dilakukan melalui *database online* dan penggunaan *software*. Level ekspresi NOX *family* pada gagal ginjal kronis diperoleh dari *database* Nephroseq. *Database* CMAUP digunakan untuk memperoleh profil metabolomik *Citrus* sp. *Software* KNIME dan *database* ChEMBL digunakan untuk mengetahui potensi *inhibitor* NOX4. Protein target dari *citrus* flavonoid diperoleh dari *database* SwissTargetPrediction. Selanjutnya, analisis protein-protein *interaction network* (PPIN) NOX4 dilakukan dengan *database* STRING. Penelusuran literatur dilakukan untuk memperoleh *signaling* NOX4 pada kerusakan ginjal. Hasil menunjukkan overekspresi NOX *family* pada kondisi gagal ginjal kronis. Beberapa metabolomik dalam *Citrus* sp. seperti diosmin, hesperidin, tangeretin, nobiletin, hesperetin, naringenin, dan naringin memiliki aktivitas *tissue protective*. Senyawa khas pada *Citrus sp.* terutama *citrus* flavonoid dapat menghambat NOX4 dengan nilai prediksi diantara 0,75-0,86. *Citrus* flavonoid berpotensi mencegah terjadinya kerusakan ginjal melalui penghambatan NOX4 dan protein-protein yang terlibat pada proses fibrosis (*SRC, EGFR, HIF1α, AGTR1*), apoptosis (*CASP3*), dan inflamasi (*MAPK14*, *COX2, TNFα*) pada ginjal. Formulasi kulit jeruk yang kaya *citrus* flavonoid dapat dikembangkan sebagai agen kokemoterapi, antipenuaan, dan peningkat sistem imun dalam bentuk produk kesehatan layak edar.

**Kata kunci**: *Citrus* flavonoid, NOX4, antigenotoksik, kerusakan ginjal, bioinformatika

# ABSTRACT

Chemotherapy drugs increase intracellular ROS levels that are toxic to body organs, one of which is the kidneys. The main source of ROS in the kidney is $H_2O_2$ which is produced by NADPH oxidase 4 (NOX4). Citrus flavonoids are components in oranges that have antioxidant and anti-inflammatory activity. This study aims to reveal the potential of citrus flavonoids as agents to prevent kidney injury caused by the side effect of chemotherapy drugs with NOX4 and other proteins involved in kidney injury as targets. Bioinformatics meta-analysis studies were carried out through online databases and software. NOX family expression levels in renal injury were obtained from the Nephroseq database. The CMAUP database was used to obtain the metabolomic profile of *Citrus* sp. KNIME software and the ChEMBL database were used to determine the potential of NOX4 inhibitors. Target proteins for citrus flavonoids were obtained from the SwissTargetPrediction database. Furthermore, analysis of the NOX4 protein-protein interaction network (PPIN) was performed by STRING database. A literature search was carried out to obtain NOX4 signaling in kidney injury. The results showed that NOX family were overexpressed in chronic kidney disease. Some metabolomics in *Citrus* sp. such as diosmin, hesperidin, tangeretin, nobiletin, hesperetin, naringenin, and naringin have protective tissue activity. Citrus flavonoids inhibit NOX4 especially with predictions value between 0.75-0.86. Citrus flavonoids have the potential to prevent kidney injury through inhibition of NOX4 and proteins involved in fibrosis (SRC, EGFR, HIF1α, AGTR1), apoptosis (CASP3), and inflammation (MAPK14, COX2, TNFα) in the kidney. The formulation of orange peel which is rich in citrus flavonoids can be developed as a co-chemotherapy agent, anti-aging, and immune system enhancer in the form of health products.

**Keywords:** Citrus flavonoids, NOX4, antigenotoxic, kidney injury, bioinformatics