

## DAFTAR ISI

|   |      |
|---|------|
| PERNYATAAN .....                            | iii  |
| PRAKATA .....                               | iv   |
| DAFTAR ISI .....                            | v    |
| DAFTAR GAMBAR .....                         | viii |
| DAFTAR TABEL .....                          | ix   |
| DAFTAR LAMPIRAN .....                       | x    |
| DAFTAR SINGKATAN .....                      | xi   |
| INTISARI .....                              | xiii |
| <i>ABSTRACT</i> .....                       | xiv  |
| BAB I . PENDAHULUAN .....                   | 1    |
| I.1. Latar Belakang .....                   | 1    |
| I.2. Perumusan Masalah .....                | 6    |
| I.3. Tujuan Penelitian .....                | 7    |
| 1.3.1. Tujuan Umum .....                    | 7    |
| 1.3.2. Tujuan Khusus .....                  | 7    |
| I.4. Keaslian Penelitian .....              | 7    |
| I.5. Manfaat Penelitian .....               | 9    |
| BAB II. TINJAUAN PUSTAKA .....              | 10   |
| II.1. Cedera Ginjal Akut .....              | 10   |
| II.2. Diagnosis .....                       | 10   |
| II.3. Epidemiologi .....                    | 13   |
| II.4. Etiologi dan Tatalaksana .....        | 14   |
| II.5. Kreatinin .....                       | 16   |
| II.5.1. Kebermaknaan Klinis Kreatinin ..... | 17   |
| II.5.2. Nilai Rujukan Kreatinin .....       | 19   |

|  |           |
|--|-----------|
| II.5.3. Pengukuran Kreatinin .....                               | 19        |
| II.6. Cedera Tubulus .....                                       | 22        |
| II.7. Proliferasi Tubulus .....                                  | 24        |
| II.8. Patofisiologi .....  | 29        |
| II.9. Cedera Iskemia – Reperfusi .....                           | 31        |
| II.10. Karakteristik Patofisiologi Cedera Iskemi Reperfusi ..... | 35        |
| II.11. Sel Punca Mesenkim .....                                  | 37        |
| II.11.1. Media Terkondisi Sel Punca Mesenkim .....               | 38        |
| II.11.2. Manfaat Media Terkondisi Sel Punca Mesenkim .....       | 39        |
| II.11.3. Komponen MT-SPM .....                                   | 40        |
| II.12. <i>Proliferating Cell Nuclear Antigen</i> (PCNA) .....    | 41        |
| II.13. Faktor Pertumbuhan ( <i>Growth Factors</i> ) .....        | 45        |
| II.14. Landasan Teori .....                                      | 48        |
| II.15. Kerangka Teori .....                                      | 50        |
| II.16. Kerangka Konsep .....                                     | 51        |
| II.17. Hipotesis .....   | 51        |
| <b>BAB III. METODE PENELITIAN .....</b>                          | <b>52</b> |
| 3.1. Jenis dan Rancangan Penelitian .....                        | 52        |
| 3.2. Variabel Penelitian .....                                   | 52        |
| 3.3. Definisi Operasional .....                                  | 52        |
| 3.4. Bahan dan Alat Penelitian .....                             | 53        |
| 3.4.1. Alat dan Bahan untuk pemeriksaan IHC .....                | 53        |
| 3.4.2. Alat dan bahan untuk pemeriksaan Histopatologi .....      | 54        |
| 3.4.3. Pembuatan Media Terkondisi Sel Punca Mesenkim .....       | 54        |
| 3.5. Jalannya Penelitian .....                                   | 55        |
| 3.5.1. Pelaksanaan Penelitian .....                              | 55        |
| 3.5.2. Subjek Penelitian .....                                   | 56        |

|  |            |
|--|------------|
| 3.5.3. Besar Sampel .....                                | 56         |
| 3.5.4. Pengelompokan Hewan Coba .....                    | 56         |
| 3.5.5. Model Cedera Iskemia/Reperfusi (I/R) Ginjal ..... | 56         |
| 3.5.6. Terminasi Hewan Coba .....                        | 57         |
| 3.5.7. Pewarnaan <i>Periodic Acid Schiff</i> (PAS) ..... | 57         |
| 3.5.8. Pewarnaan Imunohistokimia PCNA .....              | 59         |
| 3.6. Analisis Hasil .....                                | 62         |
| 3.7. Kesulitan Penelitian .....                          | 62         |
| <b>BAB IV. HASIL DAN PEMBAHASAN .....</b>                | <b>63</b>  |
| IV.1. Hasil Penelitian .....                             | 63         |
| IV.1.1. Kadar Serum Kreatinin .....                      | 63         |
| IV.1.2. Cedera Sel Epitel Tubulus Ginjal .....           | 65         |
| IV.1.3. Proliferasi Sel Epitel Tubulus Ginjal .....      | 68         |
| IV.2. Diskusi dan Pembahasan .....                       | 72         |
| <b>BAB V. KESIMPULAN, SARAN, DAN RINGKASAN .....</b>     | <b>80</b>  |
| V.1. Kesimpulan .....                                    | 80         |
| V.2. Saran .....   | 80         |
| V.3. Ringkasan .....                                     | 82         |
| <b>DAFTAR PUSTAKA .....</b>                              | <b>95</b>  |
| <b>LAMPIRAN .....</b>                                    | <b>109</b> |

## DAFTAR GAMBAR

|  |    |
|--|----|
| Gambar 1. Fase-fase pada AKI iskemik .....                       | 36 |
| Gambar 2. Patofisiologi AKI .....                                | 43 |
| Gambar 3. Jalur AKI menuju CKD .....                             | 45 |
| Gambar 4. Jalur utama iskemi–reperfusi hingga kematian sel ..... | 46 |
| Gambar 5. Struktur Gen PCNA .....                                | 55 |
| Gambar 6. Gambaran mikroskopis ginjal dengan pewarnaan PAS ..... | 78 |
| Gambar 7. Gambaran mikroskopis ginjal dengan pewarnaan IHC ..... | 82 |

## DAFTAR TABEL

|   |    |
|---|----|
| Tabel 1. Keaslian Penelitian .....                                  | 20 |
| Tabel 2. Kriteria RIFLE .....                                       | 23 |
| Tabel 3. Kriteria AKIN ( <i>Acute Kidney Injury Network</i> ) ..... | 24 |
| Tabel 4. Etiologi AKI .....   | 28 |
| Tabel 5. Deskripsi hasil serum kreatinin .....                      | 76 |
| Tabel 6. Grafik batang hasil uji kreatinin .....                    | 77 |
| Tabel 9. Deskripsi skor cedera tubulus ginjal .....                 | 79 |
| Tabel 10. Grafik batang hasil uji skor cedera tubulus .....         | 80 |
| Tabel 13. Deskripsi hasil PCNA .....                                | 83 |
| Tabel 14. Grafik Batang Hasil Uji PCNA .....                        | 84 |

## DAFTAR LAMPIRAN

|   |     |
|---|-----|
| Tabel 7. Hasil Uji Anova variabel serum kreatinin .....             | 122 |
| Tabel 8. Hasil Uji <i>post hoc</i> LSD serum kreatinin .....        | 122 |
| Tabel 11. Hasil Uji <i>ANOVA</i> variabel skor cedera tubulus ..... | 122 |
| Tabel 12. Hasil Uji <i>post hoc</i> LSD skor cedera tubulus .....   | 123 |
| Tabel 15. Hasil Uji <i>ANOVA</i> variabel PCNA .....                | 123 |
| Tabel 16. Hasil Uji <i>post hoc</i> LSD PCNA .....                  | 123 |
| Lampiran 1 <i>Ethical Clearance</i> .....                           | 124 |

## DAFTAR SINGKATAN

|               |   |
|---------------|---|
| $\alpha$ -GST | : $\alpha$ -glutathione-S-transferase                           |
| $\gamma$ -GT  | : $\gamma$ -glutamyl transpeptidase                             |
| AAP           | : Alanine aminopeptidase  |
| AEC           | : Alveolar epithelial cells                                     |
| AP            | : Alkaline phosphatase  |
| ACE           | : Angiotensin-converting enzyme                                 |
| AKIN          | : Acute Kidney Injury Network                                   |
| ANCA          | : Anti-neutrophil cytoplasmic antibody                          |
| ADMSC         | : Adipose-derived mesenchymal stem cell                         |
| AKI           | : Acute Kidney Injury   |
| ATP           | : Adenosine 5'-Triphosphate                                     |
| BB            | : Berat badan   |
| BDNF          | : Brain-derived neurotrophic factor                             |
| bFGF          | : Basic fibroblast growth factor                                |
| BMSC-CM       | : Bone marrow-derived mesenchymal stem cells-conditioned medium |
| BUN           | : Blood Urea Nitrogen   |
| cc            | : Cubic centimeter (1 cc = 0,001 liter)                         |
| CKD           | : Chronic Kidney Disease  |
| CYR-61        | : Cysteine-rich protein   |
| DAB           | : 3,3'-Diaminobenzidine   |
| DAMP          | : Danger-associated molecular pattern                           |
| DNA           | : Deoxyribonucleic acid   |
| EBV           | : Epstein Barr Virus  |
| ELISA         | : Enzyme-linked immunosorbent assay                             |
| EGF           | : Epidermal Growth Factor                                       |
| ESRF          | : End Stage Renal Failure                                       |
| ET-1          | : Endothelin-1  |
| EV            | : Extracellular vesicle   |
| FABP          | : Fatty acid binding protein                                    |
| FENa          | : Fractional excretion of sodium                                |
| FGF-2         | : Fibroblast Growth Factor-2                                    |
| FK            | : Fakultas Kedokteran   |
| FKH           | : Fakultas Kedokteran Hewan                                     |
| GBM           | : Glomerular Basement Membrane                                  |
| GFR           | : Glomerular filtration rate (laju filtrasi glomerulus)         |
| GN            | : Glomerulonefritis   |
| HEGF          | : Human Epidermal Growth Factor                                 |
| HGF           | : Hepatocyte growth factor                                      |
| HGMB-1        | : High mobility group box protein 1                             |
| HIF           | : Hypoxia-inducible factor                                      |
| HS            | : Heparan sulphate  |
| HUC-MSCs      | : Human umbilical cord – mesenchymal stem cells                 |
| HUCB-MSCs     | : Human umbilical cord blood-derived mesenchymal stem cells     |
| ICAM-1        | : Intercellular Adhesion Molecule 1                             |
| ICU           | : Intensive care unit   |
| IGF-I         | : Insulin-like growth factor-1                                  |

|        |   |
|--------|---|
| IHC    | : <i>Immunohistochemistry</i>   |
| IL-6   | : <i>Interleukin-6</i>  |
| ip     | : <i>Intraperitoneal</i>  |
| I/R    | : <i>Iskemik / Reperfusi</i>  |
| IRI    | : <i>Ischemic Reperfusion Injury</i>                                    |
| JNK    | : <i>c-Jun N-terminal kinases</i>                                       |
| KGf    | : <i>Keratinocyte growth factor</i>                                     |
| LIF    | : <i>Leukemia Inhibitory Factor</i>                                     |
| LPPT   | : <i>Laboratorium Penelitian dan Pengujian Terpadu</i>                  |
| LSD    | : <i>Least Significance Different (beda nyata terkecil)</i>             |
| MCP-1  | : <i>Monocyte Chemotactic Protein-1</i>                                 |
| mg     | : <i>Miligram</i>   |
| MSH    | : <i>Melanocyte-stimulating hormone</i>                                 |
| MT-SPM | : <i>Media terkondisi sel punca mesenkim</i>                            |
| MSCs   | : <i>Mesenchymal stem cells</i>   |
| NCAM   | : <i>Neural cell adhesion molecule</i>                                  |
| NF-κB  | : <i>Nuclear factor kappa-light-chain-enhancer of activated B cells</i> |
| NGAL   | : <i>Neutrophil Gelatinase Associated Lipocalin</i>                     |
| NSAIDs | : <i>Non-steroidal Anti-inflammataory Drugs</i>                         |
| OPN    | : <i>Osteopontin</i>  |
| PARP   | : <i>Poly ADP-ribose polymerase</i>                                     |
| PAS    | : <i>Periodic Acid Schiff</i>   |
| PBS    | : <i>Phosphate-buffered saline</i>                                      |
| PCNA   | : <i>Proliferating Cell Nuclear Antigen</i>                             |
| PDGF   | : <i>Platelet-derived growth factor</i>                                 |
| pH     | : <i>Potential of Hydrogen (kadar keasaman)</i>                         |
| PIGF   | : <i>Placental growth factor</i>  |
| RBP    | : <i>Retinol Binding Protein</i>  |
| RIFLE  | : <i>Risk, Injury, Failure, Loss, and End-stage renal failure</i>       |
| RNA    | : <i>Ribonucleic acid</i>   |
| ROS    | : <i>Reactive oxygen species</i>  |
| RRT    | : <i>Renal Replacement Therapy</i>                                      |
| SAEC   | : <i>Small airway epithelial cells</i>                                  |
| SDGs   | : <i>Sustainable development goals</i>                                  |
| SO     | : <i>Sham Operation</i>   |
| SPM    | : <i>Sel Punca Mesenkim</i>   |
| STCs   | : <i>Scattered tubular cells</i>  |
| TGF-β  | : <i>Transforming Growth Factor-beta</i>                                |
| TLR    | : <i>Toll like receptor</i>   |
| UGM    | : <i>Universitas Gadjah Mada</i>  |
| UPHP   | : <i>Unit Pelayanan Hewan Percobaan</i>                                 |
| USG    | : <i>Ultrasonografi</i>   |
| VCAM-1 | : <i>Vascular Cell Adhesion Molecule 1</i>                              |
| VCD    | : <i>4-Vinyl cyclohexene diepoxide</i>                                  |
| VEGF-A | : <i>Vascular Endothelial Growth Factor-A</i>                           |
| WBC    | : <i>White blood cell</i>   |