INTISARI

Kanker ovarium merupakan salah satu kanker ganas yang memiliki prognosis paling buruk karena tumbuh secara agresif. Terapi berbasis sel punca mesenkimal, khususnya sekretom *Wharthon Jelly Mesenchymal Stem Cell* (WJMSC) menunjukkan potensi efek antikanker melalui kandungan bioaktifnya. Selain itu, *peripheral blood mononuclear cell* (PBMC) juga berperan penting dalam mendukung eliminasi sel kanker. Penelitian ini bertujuan menganalisis aktivitas antikanker sekretom WJMSC secara langsung atau dengan meningkatkan sistem imun dalam melawan sel kanker ovarium SKOV-3 yang dikokultur dengan PBMC.

Penelitian ini menggunakan metode analisis *network pharmacology* (NP) dan *in vitro*. Analisis NP dilakukan untuk menentukan target protein spesifik terhadap sel kanker ovarium SKOV-3 yang kemudian divalidasi melalui analisis *in vitro*. Analisis NP menggunakan berbagai webserver seperti NCBI dan Genecard untuk mendapatkan database protein. Gen hasil irisan antar target, yaitu SKOV-3, PBMC dan Sekretom WJMSC, dianalisis *protein-protein interaction* (PPI) dengan STRING-DB dan hub gene dengan Cytoscape. Sepuluh target gen teratas dianalisis *Gene Ontology* (GO) dan *Kyoto Encyclopedia of Genes and Genomes* (KEGG) dengan WebGestalt dan SRPlot. Analisis *in vitro* dilakukan uji sitotoksik dengan MTT assay, uji apoptosis dengan annexin V-FITC/PI, dan *qRT-PCR* dengan mentargetkan *BAX*, *BCL-2*, *IL-10* dan IFN-γ. Evaluasi meliputi nilai $IC_{50,}$ persentase apoptosis dan hasil ekspresi target.

FGF2, CXCR4, FN1, IFN-γ, IGF1, BDNF, IL2, *IL-10*, HGF dan PPARG pada sekretom WJMSC terlibat dalam proliferasi sel, apoptosis, dan respons imun kanker. Analisis GO mengidentifikasi fungsi protein *binding* di *extracellular space*. Analisis KEGG, sekretom WJMSC terlibat pada jalur PI3K-Akt, JAK-STAT, MAPK, serta T *Cell Receptor signaling pathway*. Hasil analisis *in vitro*, MTT menunjukkan IC_{50} sekretom terhadap SKOV3 adalah 485; 97,26 µg/ml. Sedangkan IC_{50} sekretom terhadap SKOV3 yang dikokultur PBMC adalah 463,39; 92,40; 77,08 µg/ml. Hasil persentase apoptosis tertinggi tercatat pada perlakuan kokultur sekretom IC_{50} (95,7%), kokultur sekretom ½ IC_{50} (94,3%) dan paclitaxel (90,9%), dibandingkan kontrol sel SKOV3 (28%). Hasil uji RT-PCR, sekretom menunjukkan penurunan ekspresi gen *BAX* dan BCL2 dan peningkatan ekspresi sitokin *IL-10* dan *IFN-γ* pada PBMC yang digunakan kokultur.

Kata Kunci: *Sekretom; Kanker Ovarium; PBMC; Imunoterapi: Antikanker*

ABSTRACT

Ovarian cancer is one of the most aggressive malignant cancers with the worst prognosis. Mesenchymal stem cell-based therapy, particularly the secretome of *Wharthon Jelly Mesenchymal Stem* (WJMSC), shows potential anticancer effects through its bioactive components. In addition, peripheral blood mononuclear cells (PBMC) also play an essential role in supporting the elimination of cancer cells. This study aims to analyze the anticancer activity of the WJMSC secretome, either directly or by enhancing the immune system, in combating SKOV-3 ovarian cancer cells mediated by PBMC.

This research uses network pharmacology (NP) and in vitro analysis methods. NP analysis is conducted to determine specific protein targets against SKOV-3 ovarian cancer cells, which are then validated through in vitro analysis. NP analysis employs various web servers such as NCBI and Genecard to obtain protein databases. The genes resulting from the intersection of targets, namely SKOV-3, PBMC, and WJMSC Secretome, were analyzed for protein-protein interaction (PPI) using STRING-DB and hub gene analysis with Cytoscape. The top ten target genes were analyzed for *Gene Ontology* (GO) and *Kyoto Encyclopedia of Genes and Genomes* (KEGG) using WebGestalt and SRPlot. In vitro analysis was conducted using cytotoxicity tests with the MTT assay, apoptosis tests with annexin V-FITC/PI, and qRT-PCR targeting *BAX*, *BCL-2*, *IL-10*, and IFN-γ. Evaluation included IC50 values, percentage of apoptosis, and target expression results.

FGF2, *CXCR4*, *FN1*, *IFN-γ*, *IGF1*, *BDNF*, *IL2*, *IL-10*, *HGF*, and *PPARG* in the WJMSC secretome are involved in cell proliferation, apoptosis, and cancer immune response. GO analysis identified protein binding functions in the extracellular space. KEGG analysis showed that the WJMSC secretome is involved in the PI3K-Akt, JAK-STAT, MAPK, and T Cell Receptor signaling pathways. The results of the in vitro analysis, MTT showed that the IC50 of the secretome against SKOV3 was 485; 97.26 µg/ml. Meanwhile, the IC50 of the secretome against SKOV3 mediated by PBMC was 463.39; 92.40; 77.08 µg/ml. The highest percentage of apoptosis was recorded in the treatment of coculture with secretome IC_{50} (95.7%), coculture with secretome ½ IC_{50} (94.3%), and paclitaxel (90.9%), compared to the control of SKOV3 cells (28%). RT-PCR test results showed that the secretome decreased the expression of *BAX* and BCL2 genes and increased the expression of cytokines *IL-10* and *IFN-γ* in PBMCs used in co-culture.

Keywords: Secretome; Ovarian Cancer; PBMC; Immunotherapy; Anticancer