

## INTISARI

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**Latar Belakang:** Kemoterapi sistemik pada karsinoma hepatoseluler mempunyai efek samping yang cukup berbahaya dengan tingkat kejadian yang cukup tinggi. Terapi bertarget molekuler menunjukkan hasil yang menjanjikan untuk pengobatan Kanker Hati. Kanker umumnya menghambat apoptosis melalui jalur intrinsik apoptosis. Beberapa protein yang meregulasi mekanisme apoptosis jalur intrinsik, yakni protein antiapoptotik BCL-XL dan BCL-W. Penambangan genom dari *Streptomyces* sp. GMY02 dapat sangat memudahkan penemuan sumber agen kemoterapi yang belum dimanfaatkan.

**Tujuan:** Mengkaji afinitas senyawa dari metabolit sekunder dari *Streptomyces* sp. GMY02 terhadap protein target BCL-XL dan BCL-W secara *in silico*, mengetahui nilai IC<sub>50</sub>, nilai indeks selektivitas, indeks apoptosis karena pengaruh ekstrak metanolik pada lini sel HepG2 dan lini sel C2C12.

**Metode:** Pendekatan *in-silico* dengan protein target BCL-XL dan BCL-W. Kemudian melalui *in-vitro* dengan bantuan MTT assay dan Annexin V-PI untuk melihat toksisitas dan apoptosis pada lini sel HepG2 dan lini sel C2C12.

**Hasil:** Interaksi BCL-XL dengan mannotriosa mempunyai afinitas sebesar -0,27, sedangkan dengan BCL-W mempunyai afinitas sebesar -0,05. Interaksi BCL-XL dengan Reductasporine mempunyai afinitas sebesar -8,95. Interaksi BCL-W dengan Hopene mempunyai afinitas sebesar -9,13. Nilai IC<sub>50</sub> lini sel HepG2 pada ekstrak metanolik GMY02 sebesar 199,66 (µg/mL). Sedangkan nilai IC<sub>50</sub> lini sel C2C12 pada ekstrak metanolik GMY02 sebesar 833,52 (µg/mL). Doksorubisin termasuk dalam kategori sangat toksik pada kedua lini sel yang digunakan, yakni 0,71 (µg/mL) pada lini sel HepG2 dan 0,55 (µg/mL) lini sel C2C12. Indeks selektivitas lini sel HepG2 pada ekstrak metanolik GMY02 sebesar 4,17 dan pada Doksorubisin sebesar 0,78. Indeks apoptosis pada lini sel HepG2 yang diberi Doksorubisin 1x IC<sub>50</sub> mempunyai perbedaan signifikan secara statistik.

**Kesimpulan:** Protein BCL-XL dan BCL-W mempunyai nilai afinitas yang cukup baik pada metabolit sekunder dari *Streptomyces* sp. GMY02. Ekstrak metanolik bersifat toksik pada lini sel HepG2. Indeks selektivitas ekstrak metanolik GMY02 pada lini sel HepG2 lebih baik daripada Doksorubisin. Indeks apoptosis pada lini sel HepG2 yang diberi Doksorubisin 1x IC<sub>50</sub> mempunyai perbedaan signifikan secara statistik.

**Kata Kunci :** BCL-XL, BCL-W, Ekstrak Metanolik, Lini Sel HepG2, Metabolit Sekunder, *Streptomyces* sp. GMY02.

## ABSTRACT

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**Background:** Systemic chemotherapy in hepatocellular carcinoma has side effects that are quite dangerous with a fairly high incidence rate. Molecular targeted therapy shows promising results for the treatment of liver cancer. Cancer generally inhibits apoptosis through the intrinsic apoptotic pathway. Several proteins that regulate the apoptotic mechanism of the intrinsic pathway, namely the antiapoptotic proteins BCL-XL and BCL-W. Genome mining of *Streptomyces* sp. GMY02 can greatly facilitate the discovery sources of untapped chemotherapeutic agents.

**Objective:** This research aimed to study the affinity of compounds from secondary metabolites of *Streptomyces* sp. GMY02 against BCL-XL and BCL-W target proteins in silico, knowing the IC<sub>50</sub> value, selectivity index value, apoptosis index due to the effect of methanolic extract on HepG2 and C2C12 cell line.

**Methods:** In-silico approach with target proteins BCL-XL and BCL-W. Then through in-vitro with the help of MTT assay and Annexin V-PI to see the level of toxicity and apoptosis in the HepG2 cell line and the C2C12 cell line.

**Results:** The interaction of BCL-XL with mannatriose has an affinity of -0.27, while with BCL-W it has an affinity of -0.05. The interaction of BCL-XL with Reductasporine has an affinity of -8.95. The interaction of BCL-W with Hopene has an affinity of -9.13. The IC<sub>50</sub> value of the HepG2 cell line in the GMY02 methanolic extract of 199.66 (µg/mL). Meanwhile, the IC<sub>50</sub> value of the C2C12 cell line in the GMY02 methanolic extract of 833.52 (µg/mL). Doxorubicin was categorized as very toxic in both cell lines, namely 0.71 (µg/mL) in HepG2 cell line and 0.55 (µg/mL) C2C12 cell line. The cell line selectivity index of HepG2 in the methanolic extract of GMY02 was 4.17 and that of Doxorubicin was 0.78. The apoptotic index in HepG2 cell lines treated with Doxorubicin 1x IC<sub>50</sub> had a statistically significant difference.

**Conclusion:** BCL-XL and BCL-W proteins have good affinity values for secondary metabolites of *Streptomyces* sp. GMY02. The methanolic extract was toxic to the HepG2 cell line. The selectivity index of the GMY02 methanolic extract on the HepG2 cell line was better than that of doxorubicin. The apoptotic index in HepG2 cell lines treated with Doxorubicin 1x IC<sub>50</sub> had a statistically significant difference.

**Keywords:** BCL-XL, BCL-W, HepG2 Cell Line, Methanolic Extract, Secondary Metabolites, *Streptomyces* sp. GMY02