STOCHASTIC MODELLING OF CANCER CELL PROLIFERATION AND DEATH IN RESPONSE TO ANTICANCER THERAPEUTICS OF THYMOQUINONE

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DOCTOR OF PHILOSOPHY

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SUPERVISOR'S DECLARATION

We hereby declare that We have checked this thesis and, in our opinion, this thesis is adequate in terms of scope and quality for the award of the degree of Doctor of Philosophy.

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STUDENT'S DECLARATION

I hereby declare that the work in this thesis is based on my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously or concurrently submitted for any other degree at Universiti Malaysia Pahang or any other institutions.

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ABSTRAK

Kajian terbaru telah mendedahkan peranan Thymoquinone (TQ) sebagai bahan aktif habbatus sauda (Nigella Sativa) dalam aktiviti apoptosis. TQ yang meransang aktiviti apoptosis (program mematikan sel) boleh memodulasi kehidupan dan kematian sel, dengan itu berpotensi sebagai terapeutik terhadap penyakit kanser. Mekanisme biologi apoptosis yang disebabkan oleh TQ masih belum difahami sepenuhnya. Model matematik berguna dalam meningkatkan pengetahuan yang efektif tentang kesan TQ terhadap pertumbuhan sel kanser dan aktiviti apoptosis. Ia memberikan maklumat penting untuk meneroka dan meramalkan pertumbuhan kanser serta tindak balas terhadap terapi. Tambahan pula, pertumbuhan sel kanser tertakluk kepada faktor yang tidak terkawal, yang dirujuk sebagai hingar putih. Model stokastik menyediakan kaedah untuk menerangkan proses yang tidak terkawal ini. Walaupun model ini sangat berguna, tiada model stokastik yang telah dibangunkan untuk mewakili pertumbuhan kanser yang terganggu disebabkan oleh terapi antikanser TQ dan aktiviti apoptosis. Penyelidikan ini bertujuan untuk membangunkan sistem persamaan pembezaan stokastik (SDEs) untuk proses apoptosis dalam pertumbuhan dan kematian sel kanser sebagai tindak balas kepada TQ. Untuk mencapai objektif ini, hukum logistik dan Gompertz pertumbuhan dinamik populasi telah dimasukkan ke dalam model mangsa-pemangsa untuk membentuk model deterministik persamaan pembezaan biasa (ODEs). TQ juga direkrut oleh sel-sel kanser melalui hukum Michaelis-Menten yang memberikan kesan tepu dalam persamaan pemangsa iaitu TQ. Deterministik model ODEs telah dikembangkan kepada bentuk stokastik yang setara dengan kemasukan proses Wiener kepada parameter kadar pertumbuhan kinetik sel kanser dan TQ. Kualitatif dinamik model logistik dan Gompertz mangsa-pemangsa menunjukkan bahawa model tersebut mempunyai sifat penyelesaian positif. Sel-sel kanser akan berkembang ke titik keseimbangan bagi kegagalan rawatan dan di bawah kejayaan rawatan, sel-sel kanser akan berkurang kepada titik keseimbangan rawatan. Model deterministik dan stokastik telah disimulasikan, dan hasilnya telah dibandingkan dengan data eksperimen sel kanser HSC-3 dan HSC-4. Eksperimen TQ sebagai tindak balas kepada sel kanser telah dijalankan di makmal Universiti Islam Antarabangsa Malaysia (UIAM) dan data eksperimen telah digunakan untuk verifikasi model. Keputusan simulasi model deterministik dan stokastik adalah konsisten dengan data eksperimen dan nilai ralat min punca kuasa dua (RMSE) yang rendah dalam model SDEs menunjukkan kesesuaian SDEs dalam memodelkan proliferasi sel kanser dengan kehadiran TQ. Pemodelan sistem diperluaskan kepada mekanisme isyarat laluan apoptosis untuk sel-sel kanser dengan kehadiran TQ. Dua laluan telah dipilih iaitu, laluan intrinsik mitokondria yang menggalakkan pengaktifan Caspase 3 (laluan 1) dan laluan intrinsik mitokondria yang menggalakkan pengaktifan Caspase 10 (laluan 2) telah dikenal pasti. Tindak balas kinetik laluan tersebut telah dikenalpasti dan model matematik sistem ODEs dibina berdasarkan tindak balas kinetik biokimia laluan 1 dan 2. Kemudian, gangguan telah dimasukkan melalui parameter kadar faktor pertumbuhan luaran (EGFR) dan apoptosis untuk membentuk sistem SDEs. Dalam penyelidikan ini, parameter kinetik telah dianggarkan menggunakan kaedah Markov Chain Monte Carlo (MCMC). Kaedah berangka stokastik Runge-Kutta peringkat 4 (SRK4) telah digunakan untuk mencari simulasi penyelesaian SDEs. Keputusan menunjukkan apabila TQ bertindak balas dengan EGFR, pengaktifan keluarga Caspase untuk laluan intrinsik 1 dan 2, membawa kepada pengaktifan mekanisme apoptosis. Ia konsisten dengan keputusan eksperimen dan pemodelan saiz kanser yang dirawat dengan menggunakan dua model persamaan, iaitu mekanisme apoptosis (peningkatan aliran dalam jumlah protein)

mengecilkan saiz sel kanser. Model stokastik yang baru dibangunkan boleh membantu pakar onkologi untuk memahami sistem dinamik dalam aktiviti apoptosis terapeutik antikanser dan boleh digunakan untuk meramalkan pertumbuhan kanser yang terjejas disebabkan kehadiran TQ dengan lebih tepat, seterusnya boleh membantu merancang strategi rawatan yang lebih baik untuk kanser.

ABSTRACT

Recent studies have revealed the role of Thymoquinone (TQ) as an active ingredient of black seed (Nigella Sativa) in apoptotic activities. TQ induced apoptotic (the program cell death) can modulate cell life and death, hence able to provide therapeutic potential in cancer disease. The biological mechanism of apoptotic induced by TQ is not yet fully understood. Mathematical model is useful in promoting effective knowledge about the effects of TQ in cancer proliferation and apoptotic activities. It provides an insightful way to explore and predict the growth of the cancer as well as the response to therapy. Furthermore, the cancer cell proliferation is subjected to uncontrolled factors, referred as white noise. Stochastic model provides a way to describe the process. Although potentially useful, no stochastic model has been formulated to represent the growth of cancer affected by anticancer therapeutic of TQ and apoptotic activities. This research is aimed to formulate a system of stochastic differential equations (SDEs) for the apoptosis process in signalling pathways of cancer cell proliferation and death in response to TQ. To achieve this objective, the logistic and Gompertz growth laws of population dynamics were included in the prey-predator model to form a deterministic model of ordinary differential equations (ODEs). Therefore, the deterministic form of logistic prey-predator and Gompertz prey-predator was developed to model the cancer cells proliferation (prey) in the presence of TQ. TQ was also recruited by the cancer cells through a Michaelis-Menten law which provided the saturation effect in the predator of the equation. The models were extended to their stochastic counterpart with the inclusion of the Wiener process to the kinetic growth rate parameters of cancer cells and TQ. The qualitative dynamic of the logistic and Gompertz prey-predator models had shown that the model possesses the properties of positive solution. Cancer cells would grow to the equilibrium point of the treatment failure, but under the success of treatment, the cancer cells would shrink to the equilibrium points of the treatment. Deterministic and stochastic models were simulated, and the results were compared with the experimental data of HSC-3 and HSC-4 lines. Laboratory experiment of TQ in response to cancer cell was carried out in International Islamic University Malaysia (IIUM) laboratory and the experimental data were used to validate the model. The simulated results of the deterministic and stochastic models were consistent with the experimental data and low values of root mean square error (RMSE) in SDEs model. This indicated good fit of the SDEs in modelling the proliferation of the cancer cells in the presence of TQ. Modelling of the system was extended to the mechanism of the apoptotic signalling pathway for cancer cells in the presence of TQ. Two pathways, which are the intrinsic mitochondrial pathway that promotes the activation of the Caspase 3 (pathway 1) and the intrinsic mitochondrial pathway that promotes the activation of the Caspase 10 (pathway 2) had been identified. The kinetic reaction of those pathways has been developed and mathematical model of a system of ODEs was constructed based on the biochemical kinetic reactions of the pathways 1 and 2. Then, the perturbation was performed through the kinetic rate parameters of external growth factor rate (EGFR) and apoptosis to form a system of SDEs. In this research, the kinetics parameter was estimated using Markov Chain Monte Carlo Method (MCMC). Numerical method of 4-stage stochastic Runge-Kutta (SRK4) was employed to simulate the solution of SDEs. The results showed that as the TQ reacted with EGFR, the activation of Caspase family for intrinsic pathways 1 and 2, led to the activation of the apoptosis mechanism. It was consistent with the results of the experimentation and modelling of the cancer size under treatment using two equations model, which was apoptosis mechanism (increasing trend in the amount of protein) that

shrank the size of the cancer cells. The newly developed stochastic model can help oncologists to understand the physical and biological barriers in apoptotic activities of anticancer therapeutic. The model can be used to predict the growth of cancer affected by TQ accurately and subsequently help to plan better treatment strategies for cancer.

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