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

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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 citation 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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STOCHASTIC MODEL OF CANCER GROWTH WITH THE EFFECT OF GLYCOSAMINOGLYCANS (GAGs) AS ANTICANCER THERAPEUTICS

MAZMA SYAHIDATUL AYUNI BINTI MAZLAN

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In dedication to:

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Tuan Hj Mazlan bin Abd Rahman and Puan Hjh Che Maimon binti Che Mansor,
Strong and gentle souls, who have taught me to trust in Allah and to earn an honest living.

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ABSTRAK

Persamaan pembezaan biasa (ODEs) dan persamaan pembezaan stokastik (SDEs) digunakan secara meluas untuk memodelkan proses biologi bagi pertumbuhan kanser. Dalam fenomena semulajadi, pertumbuhan kanser yang tidak dirawat boleh dipengaruhi oleh kesan rawak yang boleh dirujuk sebagai faktor tidak terkawal dalam badan manusia. Di samping itu, kelakuan dinamik bagi kadar pertumbuhan sel kanser bergantung bukan sahaja kepada strukturnya pada masa kini, tetapi juga pada strukturnya pada masa sebelumnya. Oleh itu, ODEs dan SDEs tidak berupaya untuk memodelkan yang tidak terkawal dan maklum balas masa lengahan untuk proses pertumbuhan kanser yang tidak dirawat. Fenomena seperti ini boleh dimodelkan melalui persamaan pembezaan stokastik dengan masa lengahan (SDDEs). Pada masa kini, kanser dirawat secara tradisional dengan pembedahan, kemoterapi dan radiasi. Walau bagaimanapun, rawatan terkini untuk kanser adalah terapi sasaran. Dalam penyelidikan ini, ubat yang digunakan adalah Glycosaminoglycans (GAGs). Kandungan GAGs menunjukkan kehadiran Chondroitin Sulfate (CS). Kesan CS dalam proses berkaitan dengan sistem biologi adalah penting untuk menggalakkan apoptosis. Bagi kajian ini, CS diambil daripada ekstrak pari bintik biru dari Jabatan Pengendalian Hidupan Liar, Selangor. Sehubungan dengan itu, bagi pertumbuhan kanser yang telah dikenalpasti, CS boleh digunakan sebagai terapi sasaran bagi kanser. Data-data bagi kanser pangkal rahim dan kanser payudara yang tidak dirawat bagi kajian ini telah diambil dari Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu. Kajian makmal berkenaan CS bagi sel kanser yang telah dikenalpasti telah dilakukan dengan menggunakan sel HeLa (pangkal rahim) dan sel MCF-7 (payudara). Data-data ujikaji bagi kanser pangkal rahim dan kanser payudara yang dirawat telah digunakan bagi mengesahkan model stokastik tersebut. CS dikenalpasti dapat mengurangkan sel hidup HeLa dan MCF-7. Selain itu, ekspresi gen mRNA dan perubahan dalam sel HeLa dan MCF-7 dikaji dengan teknik RT-qPCR. Gen apoptosis iaitu caspase3 terekspresi dalam sel HeLa sahaja. Bagi memahami kuantitatif dinamik bagi antikanser, CS bagi pertumbuhan sel kanser adalah diperlukan dalam usaha mereka bentuk rawatan yang berkesan. Model matematik boleh digunakan sebagai alat mempromosi pengetahuan yang mendalam tentang kesan CS dalam pertumbuhan sel kanser. Pertumbuhan sel kanser boleh dipengaruhi oleh kehadiran yang tidak terkawal, yang boleh dirujuk sebagai gangguan. Terkini, tiada model deterministik dan stokastik yang telah diformulasikan bagi mewakili pertumbuhan kanser kesan dari CS. Justeru, kajian ini dijalankan bagi membangunkan model berketentuan dan stokastik bagi pertumbuhan sel kanser oleh CS sebagai satu kaedah rawatan antikanser. Satu sistem stokastik yang baru untuk kanser terapi CS dibangunkan menggunakan SDEs. Parameter kinetik dianggarkan melalui pendiskretan fungsi kebolehjadian. Kaedah berangka 4 peringkat stokastik Runge-Kutta (SRK4) digunakan untuk mensimulasikan penyelesaian model. Algoritma bagi mensimulasikan penyelesaian berangka juga dibangunkan. Penyelesaian berangka model stokastik telah menghuraikan dengan secukupnya kesan CS ke atas sel HeLa dan MCF-7 berbanding deterministik model yang setanding dengannya. Pembangunan baru bagi model stokastik ini dijangka amat sesuai bagi jenis sel kanser lain. Dapatan dari kajian ini dapat membantu ahli-ahli perubatan bagi merancang strategi yang baik dalam usaha merawat kanser.

ABSTRACT

Ordinary differential equations (ODEs) and stochastic differential equations (SDEs) have been widely used to describe the biological process of cancer growth. In natural phenomena, the untreated cancer growth is influenced by random effects as the result of uncontrolled factors in the human body. In addition, the dynamical behaviour of cancer cell growth rate depends on not only its structure at the present time, but also on its structure at a previous time. Thus, ODEs and SDEs are not capable to model the uncontrolled fluctuation and delay feedback for the untreated cancer growth process. It is necessary to model the untreated cancer growth process via stochastic delay differential equations (SDDEs). Nowadays, cancers are traditionally treated with surgery, chemotherapy, and radiotherapy. However, the most advanced treatment for cancer is targeted therapies. In this research, the drug that is used is Glycosaminoglycans (GAGs). The content of GAGs indicates the presence of Chondroitin Sulphate (CS). The effects of CS on the processes related to biological systems is crucial to promote apoptosis. For this research, CS is extracted from Blue-spotted stingrays, taken from Wild Life Handler Resource, Selangor. For the treated cancer growth, CS can be employed for targeted cancer therapy. The untreated cervical and breast cancer data for this research is taken from Hospital Sultanah Nur Zahirah (HSNZ), Kuala Terengganu. Laboratory experiments of CS for treated cancer cell is done in International Islamic University Malaysia (IIUM) on HeLa (cervical cancer) and MCF-7 (breast cancer) cell lines. The experimental treated data is used to validate the stochastic model. CS has significantly reduced cell viability of Hela and MCF-7 cell lines. Futhermore, the mRNA gene expression of HeLa and MCF-7 cells are studied using the RT-qPCR technique. The apoptotic gene, activation caspase3 is only presented in HeLa cell line. Understanding the quantitative dynamics of the protective anticancer, CS to cancer cell proliferation is required in designing an effective treatment. Mathematical model can be used as a tool in promoting knowledge about the effects of CS in cancer growth. The cell growth of cancer is influenced by uncontrolled factors, which is referred to as noise. To date, no deterministic or stochastic models have been formulated to represent the growth of cancer affected by CS. Thus, this research is carried out to formulate the deterministic and stochastic models for cancerous growth affected by CS as anticancer therapeutics. A new stochastic system for the treated cancer growth affected by anticancer therapeutics of CS is formulated via SDEs. The kinetic parameters is estimated via non-parametric stimulated maximum likelihood function. Numerical method of 4-stage stochastic Runge-Kutta (SRK4) is employed to simulate the solution. The algorithms of simulating the numerical solution are then developed. Numerical solution of stochastic model is adequately described the effects of CS on HeLa and MCF-7 cell lines compare than its deterministic counterpart. The newly developed of stochastic model is expected to be appropriate for other types of cancer cells as well. The findings of this research may help physicians and biologists planning better strategies for treatment of cancer.

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