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Optimal control strategies for SGLT2 inhibitors as a novel anti-tumor agent and their effect on human breast cancer cells with the effect of time delay and hyperglycemia

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ABSTRACT

Breast cancer is the most frequent cancer in the world, and it continues to have a significant impact on the total number of cancer deaths. Recently, oncology findings hint at the role of excessive glucose in cancer progression and immune cells' suppression. Sequel to this revelation is ongoing researches on possible inhibition of glucose flow into the tumor micro-environment as therapeutics for malignant treatment. In this study, the effect of glucose blockage therapeutics such as SGLT-2 inhibitors drug on the dynamics of normal, tumors and immune cells interaction is mathematically studied. The asymptomatic nature of the breast cancer is factored into the model using time delay. We first investigate the boundedness and non-negativity of the solution. The condition for existence of critical equilibrium point is determined, and its global stability conditions are derived using Lyapunov function. This revealed that a timely administration of the SGLT-2 inhibitors drug can eliminate tumor cells. Secondly, we determine the sufficient and necessary conditions for optimal control strategy of SGLT-2 inhibitors so as to avert side effects on normal cells using a Pontryagin's Minimum Principle. The results showed that if the ingestion rate of the inhibitor drug is equal to the digestion rate, the tumor cells can be completely eliminated within 9 months without side effects. The analytical results were numerically verified and the qualitative views of interacting cells dynamics is showcased.

1. Introduction

Breast cancer is the manifestation of malignancies in the mammary gland. These malignancies evolve due to alteration of signal pathways that govern mammary gland cells' proliferation, death, differentiation and motility [1,2]. The proliferation and uncontrollable growth of breast cancer cells in the midst of immune system interaction are aided by under-aerobic tumors' micro-environment. This upshots, the increase in tumor's glucose uptakes to boost it energy providing glycolysis [3,4]. Glycolysis is one of the main processes of glucose metabolism which allow glucose entry into cancer cells through glucose transporters. Consequently, multi-various glucose metabolites of diverse metabolic pathways are produced [5]. Moreover, there is a revelation of recent that glycolytic tumors interferes with lactate export in cytotoxic T cells, which brews the inhibition of metabolism, proliferation, and production of immune cells such as IFN-γ, DCLs, NKs [6]. Glucose excess (hyperglycemia) is considered one of the risk factors which increase the population of cancer cells and suppress immune cells performance rapidly in breast cancer cells' micro-environment [7–9]. Therefore, the inhibition of glucose uptake may be an effective treatment in eliminating cancer cells, and also help in enhancing the efficiency of the immune cells [10,11].

Sodium-glucose co-transporter-2 (SGLT-2) accounts for about 90% of glucose re-absorption, and the remaining is accomplished by SGLT-1 [12,13]. Recently, attentions of oncologists recently have been on possible inhibition of glucose uptake as a possible effective treatment in the elimination of cancer and the improvement of the immune cells' efficiencies [14–16]. Sodium Glucose transporter-2 has being a culprit channel through which excessive glucose flow into the breast cancer micro-environment [17,18]. The incorporation of Sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) in breast cancers therapeutics has brought about reductions in the dosage of chemotherapy, radiotherapy, or surgery when used as adjunct therapy [17,19–21]. Also, Sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) has shown a promising effect in

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the inhibition glucose in treatment of diabetes and heart failure patients [22]. This has prompted the adoption of Sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) as a possible anti-cancer therapy in the case of liver, pancreatic, prostate, bowel, lung and breast cancers [23]. SGLT-2 inhibitors randomly capture SGLT-2 and block the pathway of glucose reabsorption into the blood circulation, as the affinity between them is much greater than that of glucose so that the excess glucose is removed through urine, leading to reduced blood glucose [12]. Despite, the admiration of Sodium-glucose co-transporter-2 inhibitors (SGLT-2 inhibitors) proficiency in diabetes and health failure treatment, there are fears of her aggravating side effects.

Mathematical models have played a critical role in enriching the clinical knowledge of breast cancer dynamics including possible therapeutics options using different mathematical approaches [24–29]. Optimal control theory has been exploit to study the minimization of infectious diseases including cancer and the optimal dosage required to avoid therapeutics-induced adversity [30–35]. Mufudza et al. [36] developed a deterministic model to study the interactive dynamics of the breast cancer cells, the immune cells and the normal cells with incorporation of estrogen. Their findings highlights the role of estrogen in cancer progression. Alblowy et al. [37] modified the model in [36] to study the glucose factors mechanism in breast cancer. Their results indicate the role of glucose risk factor in promoting breast cancer proliferation and uncontrollable growth as well as immune cells suppression. Also the challenges of non-instantaneous manifestation which make breast cancer asymptomatic have been studied using delay differentiation equation in [26].

Motivated by the biological evidences on the need for inhibition of sodium glucose transporter-2 as an emerging therapeutic option for cancer treatment, this works extends the model in [26] to study the efficacy of SGLT-2 inhibitor drugs in prevention of breast cancer proliferation and consequently, the enhancement of immune cells performance. The rest of this work is organized as follows: Section 2 captures the dynamical interactions among normal cells, tumors cells and effector cells with incorporation of time delay and SGLT-2 inhibitor drug. In Section 3, the qualitative analysis of the model is carried out. The numerical simulation of the model is done in Section 4. Section 5 presents the formulation of the optimal control problem as well as finding the sufficient and necessary conditions of the optimal control. Detailed discussion of the results is considered in Section 6 by using numerical simulations. The work is wrapped up with conclusion and direction for future work in Section 7.

2. Mathematical model

In this section, the mathematical model is developed based on a model presented in [26,37]. The first contribution is to include the effect of time delay on the interaction between tumor cells and immune cells to make the model close to reality. Immune cells, such as natural killer cells, macrophages, and CD8+T cells, are critical components of the immune system that destroy tumor cells by a kinetic process in which tumor cells come into contact with immune cells, rendering them functionally inactive. To avoid immune surveillance, cancer cells release immunosuppressive cytokines [25,38]. Both the secretion of cytokines by effector cells and derivation of suppressive cytokines by the tumor undertake biological processes which take time for the consequent to manifest. This time lag is significant in the dynamics of their interaction as it suggests non-instantaneous of tumor modulation of immune cells leading to effector cells suppression. Therefore, the time delay denoted by τ is used to describe the interaction delay between immune cells and tumor cells which happens due to the biological process involved in the tumor-immune system interaction. Consequently, we modify the model in [37] with incorporation of time delay to model non-instantaneous effect of tumor-immune cells interaction as well as the novel sodium-glucose co-transporter-2 [SGLT-2] inhibitor drug which is considered the second contribution of this work. This will afford the opportunity to unravel the efficacy of SGLT-2 inhibitor drug on breast cancer using mathematical modeling. Based on the description above, the dynamics of normal cells, tumor cells and immune cells with incorporation of time delay and SGLT-2 inhibitor drug is given as follows:

$$\begin{aligned}
\frac{dN}{dt} &= N(t)\left(\alpha_1 - \mu_1 N(t)\right) - \phi_1 N(t)T(t),\\
\frac{dT}{dt} &= T(t)\left(\alpha_2 - \mu_2 T(t)\right) + gT(t) - \gamma_1 M(t-\tau)T(t-\tau) + \phi_2 N(t)T(t) - \nu_1 T(t)G(t)\\
\frac{dM}{dt} &= s + \frac{\rho M(t)T(t)}{\omega + T(t)} - \gamma_2 M(t-\tau)T(t-\tau) - \mu_3 M(t) - gM(t) + \nu_2 M(t)G(t)\\
\frac{dG}{dt} &= uG(t) - \mu_4 G(t).
\end{aligned} \tag{1}$$

where the dependent variables N, T, and M represent the population of normal cells, tumor cells, and immune cells, respectively, while G represents sodium-glucose co-transporter-2 [SGLT-2] inhibitor drug. τ is used to describe the interaction delay between immune cells and tumor cells. All the parameters in model (1) are positive with the initial conditions

$$N_0 = \phi_1(\xi), \quad T_0 = \phi_2(\xi), \quad M_0 = \phi_3(\xi), \; G_0 = \phi_4(\xi) \; for \; \xi \in [-\tau, 0].$$

The description of the model parameters are provided in Table 1.

Fig. 1 shows a schematic diagram for the cells' population interaction in the proposed model with the effect of time delay, τ, and SGLT-2 inhibitor drug. τ describes the interaction delay between tumor and immune cells.

3. Model analysis

3.1. Boundness theorem

Theorem 1. *The feasible region $\Delta \subset R_+^4$ of the dynamic system (1) is positively invariant, and bounded positive solution exists for all time t.*

Proof. Standard comparison theory is used to show that the model is bounded and biologically feasible. Solving for $N(t)$, $T(t)$, $M(t)$ and $G(t)$ in System (1), we have:

Firstly, for $N(t)$

$$\frac{dN}{dt} = N(t)\left(\alpha_1 - \mu_1 N(t)\right) - \phi_1 N(t)T(t) \leq \alpha_1 N - \mu_1 N^2.$$

Integration of the above leads to

$$N(t) \leq \frac{\alpha_1}{\mu_1 + C\alpha_1 e^{-\alpha_1 t}} \Rightarrow \lim_{t\to\infty} sup(N(t)) \leq \frac{\alpha_1}{\mu_1}.$$

Table 1
Model parameters description.

Parameter	Description
α_1	Growth rate of normal cells
μ_1	Death rate of normal cells
ϕ_1	Competition-induced death rate of normal cells
α_2	Growth rate of tumor cells
μ_2	Inhibition rate of tumor cells
γ_1	Reduction of tumor cells by immune cells action
ρ	Immune response rate
ω	Immune threshold rate
γ_2	Reduction of the immune cells by tumor cells action
μ_3	Natural death rate of immune cells
ϕ_2	Competition-induced growth rate of tumor cells
s	Source rate of immune cells
g	Glucose excess rate
ν_1	The anti-proliferation rate against breast cancer cells by SGLT-2 inhibitor drug
ν_2	The rate at which the glucose transporter inhibitor [SGLT-2] enhances the viability of immune cells, counteracting the suppressive effects of glucose.
μ_4	Digestion rate of SGLT-2 inhibitor drug
u	Ingestion rate of SGLT-2 inhibitor drug

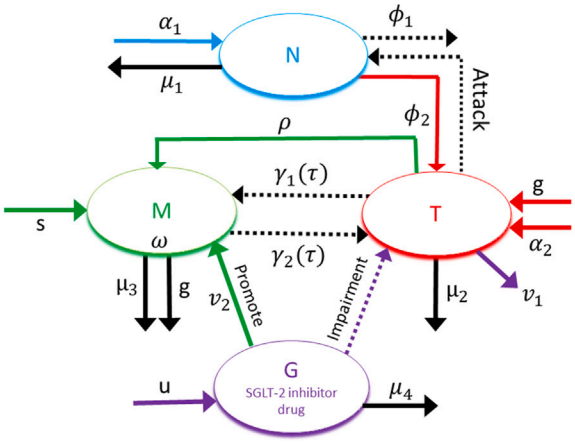

Fig. 1. Schematic diagram for the cells' population competition in the proposed model with the effect of time delay, τ, and SGLT-2 inhibitor drug.

Now, solving the second equation of System (1),

$$\begin{aligned}\frac{dT}{dt} &= T(t)\left(\alpha_2 - \mu_2 T(t)\right) + gT(t) - \gamma_1 M(t-\tau)T(t-\tau) + \phi_2 N(t)T(t) - \nu_1 G(t)T(t)\\ &\leq \alpha_2 T - \mu_2 T^2 + gT.\end{aligned}$$

Proceeding as above, we have

$$T \leq \frac{\alpha_2 + g}{\mu_2 + (\alpha_2 + g)Ce^{-(\alpha_2+g)t}} \Rightarrow \lim_{t\to\infty} sup(T(t)) \leq \frac{\alpha_2 + g}{\mu_2}.$$

Similarly, we find for the third equation of System (1)

$$\begin{aligned}\frac{dM}{dt} &= s + \frac{\rho M(t)T(t)}{\omega + T(t)} - \gamma_2 M(t-\tau)T(t-\tau) - \mu_3 M(t) - gM(t) + \nu_2 G(t)M(t)\\ &\leq s - \mu_3 M - gM\end{aligned}$$

then the solution of this equation will give

$$M \leq \frac{s}{\mu_3 + g} + Ce^{-(\mu_3+g)t} \Rightarrow \lim_{t\to\infty} sup(M(t)) \leq \frac{s}{\mu_3 + g}.$$

Finally, solving for G we have

$$\frac{dG}{dt} = uG(t) - \mu_4 G(t)$$

integrating the above equation gives

$$G(t) = e^{(u-\mu_4)t+c}$$

We assume that $u = \mu_4$, so we get

$$G(t) = e^c \Rightarrow \lim_{t\to\infty} sup(G(t)) = e^c.$$

where c is a constant. To obtain the value of c, substitute by the initial value of $G(t)$, which definitely produces a positive number.

Therefore, the solution of N, T, M, G is always bounded. Consequently, we get the bounded set

$$\Delta = \left\{ (N(t), T(t), M(t)) \in R_+^3 : 0 < N \le \frac{\alpha_1}{\mu_1}, 0 \le T \le \frac{\alpha_2 + g}{\mu_2}, 0 < M \le \frac{s}{\mu_3 + g}, 0 < G = e^c \right\}.$$

So, the solutions of System (1) is bounded.

Next is to show that the solution of System (1) are non-negative for all $t \in [t-\tau, t]$.

3.2. Existence of non-negative solution

Theorem 2. *Suppose $N(t)$, $T(t)$ and $M(t)$ are bounded and positive under the initial conditions in System (1), then, there exist non-negative solutions $N(t)$, $T(t)$, $M(t)$ and $G(t)$ of System (1) $\forall t \in [t-\tau, t]$.*

Proof. Solving for $N(t)$, $T(t)$, $M(t)$ and $G(t)$ in System (1).

Firstly, for $N(t)$

$$\frac{dN}{dt} + (\phi_1 T(t) - \alpha_1) N(t) = -\mu_1 N^2(t). \tag{2}$$

Eq. (2) is obviously Bernoulli equation, solving this equation we obtain the solution of $N(t)$ as follows

$$N(t) = \frac{N(0) e^{-\int (\phi_1 T(t) - \alpha_1) dt}}{e^{-\int (\phi_1 T(t) - \alpha_1) dt} + N(0) \int_0^t \mu_1 e^{-\int (\phi_1 T(t) - \alpha_1) dt} dt}. \tag{3}$$

Applying the same method to find the solutions of $T(t)$, $M(t)$ and $G(t)$ in System (1) yields the following results:

$$T(t) = \frac{T(0) e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G] dt}}{e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G] dt} + T(0)[\int_0^t \mu_2 e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G] dt} dt + \int_{-\tau}^0 \gamma_1 M(t-\tau) T(t-\tau) [T(t)]^{-2} e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G] dt} dt]} \tag{4}$$

$$M(t) = \frac{M(0) e^{-\int [\frac{\rho T(t)}{\omega + T(t)} - \mu_3 - g + \nu_2 G] dt} + \int_0^t s dt - \int_{-\tau}^0 \gamma_2 M(t-\tau) T(t-\tau) dt}{e^{-\int [\frac{\rho T(t)}{\omega + T(t)} - \mu_3 - g + \nu_2 G] dt}}. \tag{5}$$

$$G(t) = e^{(u - \mu_4)t} \tag{6}$$

We conclude that since $N(0) > 0$, $T(0) > 0$, $M(0) > 0$, Eqs. (3), (4) and (5) have positive solutions. For $G(t)$, it is obvious from Eq. (6), it has a positive solution for all t. Therefore, System (1) has a non-negative solution.

3.3. Equilibrium points

Since the main goal in this work is to incorporate a treatment to the model proposed in [26], the concentration is on co-existing equilibrium point where all the interacting cells in the model are present in the dynamics of treatment incorporation. Hence, to find the coexisting equilibrium point, we solve System (1) as following: setting each equation in System (1) to be equal to zero yields

$$\begin{aligned}
N^*(t)\left(\alpha_1 - \mu_1 N^*(t)\right) - \phi_1 N^*(t) T^*(t) &= 0 \\
T^*(t)\left(\alpha_2 - \mu_2 T^*(t)\right) + g T^*(t) - \gamma_1 M^*(t-\tau) T^*(t-\tau) + \phi_2 N^*(t) T^*(t) - \nu_1 T^*(t) G^*(t) &= 0 \\
s + \frac{\rho M^*(t) T^*(t)}{\omega + T^*(t)} - \gamma_2 M^*(t-\tau) T^*(t-\tau) - \mu_3 M^*(t) - g M^*(t) + \nu_2 M^*(t) G^*(t) &= 0 \\
u G^*(t) - \mu_4 G^*(t) &= 0
\end{aligned} \tag{7}$$

Solving for N^*, T^*, M^* & G^* in (7), we have

$$\begin{aligned}
N^* &= \frac{1}{\mu_1}(\alpha_1 - \phi_1 T^*) \\
T^* &= \frac{1}{\mu_2}\left[\alpha_2 + g + \phi_2 N^* - (\gamma_1 M^* + \nu_1 G^*)\right] \\
M^* &= \frac{s(\omega + T^*)}{(\omega + T^*)\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right] - \rho T^*} \\
&if\ G^* \neq 0,\ then\ \ u = \mu_4.
\end{aligned}$$

Since T^* contains N^*, M^* and G^*, the coexisting equilibrium point takes the form

$$E^* = \left(N^*, T^*, M^*, G^*\right) = \left(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right), T^*, \frac{s(\omega + T^*)}{(\omega + T^*)\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right] - \rho T^*}, G^*\right), \tag{8}$$

where $T^* = \frac{1}{\mu_2}\left[\alpha_2 + g + \phi_2 N^* - (\gamma_1 M^* + \nu_1 G^*)\right]$

3.4. Stability analysis

Here, the global stability analysis of co-existence equilibrium point $E^* = (N^*, T^*, M^*, G^*)$ is performed. Firstly, the linearization of System (1) at the equilibrium point E^* using Jacobian matrix is performed to have

$$J\left(E^*\right) = \begin{bmatrix} \alpha_1 - 2\mu_1 N^* - \phi_1 T^* & -\phi_1 N^* & 0 & 0 \\ \phi_2 T^* & -\gamma_1 M^* e^{-\lambda\tau} + \phi_2 N^* - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^* & -\gamma_1 T^* e^{-\lambda\tau} & -\nu_1 T^* \\ 0 & M^*\left(\frac{\rho\omega}{(\omega+T^*)^2} - \gamma_2 e^{-\lambda\tau}\right) & T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^* & \nu_2 M^* \\ 0 & 0 & 0 & u - \mu_4 \end{bmatrix}. \tag{9}$$

Therefore, the characteristics equation of (9) becomes

$$\begin{aligned} &\left[(\lambda - (u-\mu_4))\right]\left[\lambda^3 - (\alpha_1 - 2\mu_1 N^* - \phi_1 T^* - \gamma_1 M^* e^{-\lambda\tau} + \phi_2 N^* - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*\right. \\ &+ T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*)\lambda^2 + [(\alpha_1 - 2\mu_1 N^* - \phi_1 T^*)(-\gamma_1 M^* e^{-\lambda\tau} + \phi_2 N^* \\ &- 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*) + (T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*)(\alpha_1 - 2\mu_1 N^* - \phi_1 T^*) \\ &- (-\phi_1 N^*)(\phi_2 T^*) + (\gamma_1 M^* e^{-\lambda\tau} + \phi_2 N^* - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \\ &\left(\mu_3 + g\right) + \nu_2 G^*) - (M^*\left(\frac{\rho\omega}{(\omega+T^*)^2} - \gamma_2 e^{-\lambda\tau}\right))(-\gamma_1 T^* e^{-\lambda\tau})]\lambda - (\alpha_1 - 2\mu_1 N^* - \phi_1 T^*) \\ &(-\gamma_1 M^* e^{-\lambda\tau} + \phi_2 N^* - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \\ &\left(\mu_3 + g\right) + \nu_2 G^*) - (\alpha_1 - 2\mu_1 N^* - \phi_1 T^*)(M^*\left(\frac{\rho\omega}{(\omega+T^*)^2} - \gamma_2 e^{-\lambda\tau}\right))(-\gamma_1 T^* e^{-\lambda\tau}) \\ &+ (-\phi_1 N^*)(\phi_2 T^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*)\Big] = 0. \end{aligned} \tag{10}$$

At the co-existing equilibrium point with treatment;

$$E^* = \left(N^*, T^*, M^*, G^*\right) = \left(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right), T^*, \frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*}, G^*\right),$$

Eq. (10) takes the form of:

$$\begin{aligned} &\left[(\lambda - (u-\mu_4))\right]\Big[\lambda^3 - (-\alpha_1 + \phi_1 T^* - \gamma_1(\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*})e^{-\lambda\tau} \\ &+ \phi_2(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^* + T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) \\ &- \left(\mu_3 + g\right) + \nu_2 G^*)\lambda^2 + [(-\alpha_1 + \phi_1 T^*)(-\gamma_1(\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*})e^{-\lambda\tau} \\ &+ \phi_2(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*) + (T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) \\ &- \left(\mu_3 + g\right) + \nu_2 G^*)(-\alpha_1 + \phi_1 T^*) - (-\phi_1(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)))(\phi_2 T^*) \\ &+ (\gamma_1(\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*})e^{-\lambda\tau} + \phi_2(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)) - 2\mu_2 T^* + g + \alpha_2 \\ &- \nu_1 G^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*) - ((\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*}) \\ &\left(\frac{\rho\omega}{(\omega+T^*)^2} - \gamma_2 e^{-\lambda\tau}\right))(-\gamma_1 T^* e^{-\lambda\tau})]\lambda \\ &- (-\alpha_1 + \phi_1 T^*) - \gamma_1(\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*})e^{-\lambda\tau} + \phi_2((\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)) \\ &- 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*) \\ &- (-\alpha_1 + \phi_1 T^*)((\frac{s(\omega+T^*)}{\left[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*\right](\omega+T^*) - \rho T^*})\left(\frac{\rho\omega}{(\omega+T^*)^2} - \gamma_2 e^{-\lambda\tau}\right))(-\gamma_1 T^* e^{-\lambda\tau}) \\ &+ (-\phi_1(\frac{1}{\mu_1}\left(\alpha_1 - \phi_1 T^*\right)))(\phi_2 T^*)(T^*\left(\frac{\rho}{\omega+T^*} - \gamma_2 e^{-\lambda\tau}\right) - \left(\mu_3 + g\right) + \nu_2 G^*)\Big] = 0. \end{aligned} \tag{11}$$

The simplified form of (11) becomes

$$(\lambda - \upsilon_1)\left[\lambda^3 + (\upsilon_{21} + \upsilon_{22}e^{-\lambda\tau})\lambda^2 + (\upsilon_{31} + \upsilon_{32}e^{-\lambda\tau} + \upsilon_{33}e^{-2\lambda\tau})\lambda + (\upsilon_{41} + \upsilon_{42}e^{-\lambda\tau} + \upsilon_{43}e^{-2\lambda\tau})\right] = 0, \tag{12}$$

then

$$\begin{aligned} &\lambda^4 + (\upsilon_{21} + \upsilon_{22}e^{-\lambda\tau})\lambda^3 + (\upsilon_{31} + \upsilon_{32}e^{-\lambda\tau} + \upsilon_{33}e^{-2\lambda\tau})\lambda^2 + (\upsilon_{41} + \upsilon_{42}e^{-\lambda\tau} + \upsilon_{43}e^{-2\lambda\tau})\lambda \\ &- \upsilon_1\left[\lambda^3 + (\upsilon_{21} + \upsilon_{22}e^{-\lambda\tau})\lambda^2 + (\upsilon_{31} + \upsilon_{32}e^{-\lambda\tau} + \upsilon_{33}e^{-2\lambda\tau})\lambda + (\upsilon_{41} + \upsilon_{42}e^{-\lambda\tau} + \upsilon_{43}e^{-2\lambda\tau})\right] = 0, \end{aligned} \tag{13}$$

where

$$
\begin{aligned}
\upsilon_1 &= u - \mu_4,\\
\upsilon_{21} &= [\alpha_1 + 2\mu_2 T^* + \nu_1 G^* + (\mu_3 + g)] - [\phi_1 T^* + \frac{\phi_2}{\mu_1}(\alpha_1 + \phi_1 T^*) + g + \alpha_2 + \nu_2 G^*\\
&\quad + T^* \frac{\rho}{\omega + T^*}],\\
\upsilon_{22} &= \gamma_1 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) + T^* \gamma_2,\\
\upsilon_{31} &= -(\alpha_1 - \phi_1 T^*)[\phi_2 (\frac{1}{\mu_1}(\alpha_1 - \phi_1 T^*)) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*] + (\frac{T^* \rho}{\omega + T^*}\\
&\quad - (\mu_3 + g) + \nu_2 G^*)(-\alpha_1 + \phi_1 T^*) + \frac{\phi_1 \phi_2 T^*}{\mu_1}(\alpha_1 - \phi_1 T^*)\\
&\quad + \frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*) - 2\mu_2 T^* + g + \alpha_2\\
&\quad - \nu_1 G^* (T^* \left(\frac{\rho}{\omega + T^*}\right) - (\mu_3 + g) + \nu_2 G^*),\\
\upsilon_{32} &= (\alpha_1 - \phi_1 T^*)[\gamma_1 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) e^{-\lambda\tau} + T^* \gamma_2 e^{-\lambda\tau}]\\
&\quad + (\frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*)(-T^* \gamma_2 e^{-\lambda\tau})\\
&\quad + \gamma_1 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) e^{-\lambda\tau} (T^* \left(\frac{\rho}{\omega + T^*}\right))\\
&\quad + ((\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) \left(\frac{\rho\omega}{(\omega + T^*)^2}\right))(\gamma_1 T^* e^{-\lambda\tau}),\\
\upsilon_{33} &= -\gamma_1 \gamma_2 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*})(T^* \left(e^{-2\lambda\tau}\right))\\
&\quad - \gamma_1 \gamma_2 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*})(T^* e^{-2\lambda\tau}),\\
\upsilon_{41} &= (\alpha_1 - \phi_1 T^*)(\frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*)\left[\left(\frac{T^* \rho}{\omega + T^*}\right)\right.\\
&\quad \left. - (\mu_3 + g) + \nu_2 G^*\right] - (\frac{\phi_1 \phi_2 T^*}{\mu_1}(\alpha_1 - \phi_1 T^*))\left[\left(\frac{T^* \rho}{\omega + T^*}\right)\right.\\
&\quad \left. - (\mu_3 + g) + \nu_2 G^*\right],\\
\upsilon_{42} &= -(\alpha_1 - \phi_1 T^*)\gamma_1 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) \left(\frac{T^* \rho}{\omega + T^*}\right)\\
&\quad - (\alpha_1 - \phi_1 T^*)\gamma_1 (\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) \left(\frac{T^* \rho\omega}{(\omega + T^*)^2}\right)\\
&\quad + (\alpha_1 - \phi_1 T^*)(\frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*) - 2\mu_2 T^* + g + \alpha_2 - \nu_1 G^*) T^* \left(\gamma_2 e^{-\lambda\tau}\right)\\
&\quad + \frac{T^* \phi_1 \gamma_2}{\mu_1}(\alpha_1 - \phi_1 T^*)\phi_2 T^*,\\
\upsilon_{43} &= (\alpha_1 - \phi_1 T^*)(\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*}) \left(\gamma_1 \gamma_2 T^* e^{-2\lambda\tau}\right)\\
&\quad + (\alpha_1 - \phi_1 T^*)(\frac{s(\omega + T^*)}{[\gamma_2 T^* + \mu_3 + g - \nu_2 G^*](\omega + T^*) - \rho T^*})(\gamma_1 \gamma_2 T^* e^{-2\lambda\tau}).
\end{aligned}
\tag{14}
$$

Following the approach in [31], the scalar equation of the characteristic equation (13) supposing $\lambda = x$ is defined as follows:

$$
\begin{aligned}
x^4 &= -(\upsilon_{21} + \upsilon_{22}(t-\tau))x^3 - (\upsilon_{31} + \upsilon_{32}(t-\tau) + \upsilon_{33}(t-2\tau))x^2 - (\upsilon_{41} + \upsilon_{42}(t-\tau)\\
&\quad + \upsilon_{43}(t-2\tau))x + \upsilon_1 \Big[x^3 + (\upsilon_{21} + \upsilon_{22}(t-\tau))x^2 + (\upsilon_{31} + \upsilon_{32}(t-\tau)\\
&\quad + \upsilon_{33}(t-2\tau))x + (\upsilon_{41} + \upsilon_{42}(t-\tau) + \upsilon_{43}(t-2\tau))\Big].
\end{aligned}
\tag{15}
$$

The global stability sufficient condition for co-existing equilibrium point will be determined using Lyapunov function. The basic necessary conditions for the Lyapunov function are given below:

Definition. Let $V(x)$ is a continuous scalar function, then $V(x)$ is said to be Lyapunov function if the following conditions are hold:

1. $V(x^*) = 0$, x^* is the equilibrium point.
2. $V(x)$ is positive definite i.e. $V(x) > 0$, $x \neq 0$.

Accordingly, a generic positive Lyapunov function for nonlinear system composed of three variables can be proposed as follows:

$$V(x,y,z)=\frac{1}{2}(ax^2+by^2+cz^2)=\frac{1}{2}\sum_{i=1}^{3}a_ix_i^2, i=1,2,3 \tag{16}$$

where a,b,c are appropriate positive constants, and the dynamical system becomes asymptotic stable only when the derivative of positive Lyapunov function in Eq. (16) with respect to time is negative i.e. $\frac{dV(x,y,z)}{dt}<0$.

Remark. From the Definition above, it can be concluded that the trivial Lyapunov function is on the form:

$$V(x)=\frac{x^2}{2}, x\neq 0 \tag{17}$$

Definition. let $V(x)$ be a Lyapunov function. The steady state is said to be globally asymptotically stable if the following condition is hold:

$$\frac{dV(x)}{dt}<0, \forall x\in \tag{18}$$

Definition. [31] If the function $V(t,x_t)$ is radially unbounded and positive definite globally such that it has a globally negative time derivative, then

$$V'(t,x_t)<0,\ \forall x_t\in\mathbb{R}^* \tag{19}$$

and the invariant set is defined as follow;

$$\mathfrak{J}=\{x_t\in\mathbb{R}^*: V'(t,x_t)=0\}. \tag{20}$$

Suffices to say from the above that, if $\mathfrak{J}$ contains only x^*, then the equilibrium point is globally stable.

Hence, the global stability conditions of System (1) is presented in Theorem 3 below.

Theorem 3. *The co-existence equilibrium point of System (1) is globally asymptotically stable if and only if the following conditions:*

$$\begin{aligned}&u\leq\mu_4,\quad \alpha_1-\phi_1T^*\geq\frac{\phi_2}{\mu_1}(\alpha_1-\phi_1T^*),\quad 2\mu_2T^*+\nu_1G^*\geq g+\alpha_2,\\ &\mu_3+g\geq\nu_2G^*+T^*\frac{\rho}{\omega+T^*},\quad \gamma_2T^*\geq\frac{T^*\rho\omega}{(\omega+T^*)^2},\quad T^*=0,\ \&\ s=0.\end{aligned} \tag{21}$$

hold in (14).

Proof. Assume that

$$V(t,x_t)=\frac{x^2(t)}{2}, x\neq 0 \tag{22}$$

is a Lyapunov function.

Differentiating Eq. (22), and then multiplying it by the scalar Eq. (15) gives

$$\begin{aligned}\acute{V}x^4=&-(\upsilon_{21}+\upsilon_{22}(t-\tau))x^4-(\upsilon_{31}+\upsilon_{32}(t-\tau)+\upsilon_{33}(t-2\tau))x^3-(\upsilon_{41}+\upsilon_{42}(t-\tau)+\upsilon_{43}(t-2\tau))x^2\\ &+\upsilon_1\Big[x^4+(\upsilon_{21}+\upsilon_{22}(t-\tau))x^3+(\upsilon_{31}+\upsilon_{32}(t-\tau)+\upsilon_{33}(t-2\tau))x^2+(\upsilon_{41}+\upsilon_{42}(t-\tau)\\ &+\upsilon_{43}(t-2\tau))x\Big].\end{aligned} \tag{23}$$

Since $x^4(t-\tau)$ appears in Eq. (23), we need to generate a term like $-x^4(t-\tau)$ in Eq. (23) to complete the square of the quadratic function $V(x)$. This suggests that, using Lemma (5.1) in [39], the following function is tried:

$$V(t,x_t)=\frac{x^2(t)}{2}+p\int_{t-\tau}^{t}x^4(\theta)d\theta, \tag{24}$$

where p is a non-negative constant. Differentiating Eq. (24) gives

$$\acute{V}(t,x_t)=x(t)+px^4(t)-px^4(t-\tau). \tag{25}$$

Hence, Eq. (23) becomes

$$\begin{aligned}\acute{V}(x_t)=&-(\upsilon_{21}+\upsilon_{22}(t-\tau)-p)x^4-(\upsilon_{31}+\upsilon_{32}(t-\tau)+\upsilon_{33}(t-2\tau))x^3-(\upsilon_{41}+\upsilon_{42}(t-\tau)+\\ &\upsilon_{43}(t-2\tau))x^2+\upsilon_1\Big[x^4+(\upsilon_{21}+\upsilon_{22}(t-\tau))x^3+(\upsilon_{31}+\upsilon_{32}(t-\tau)+\upsilon_{33}(t-2\tau))x^2\\ &+(\upsilon_{41}+\upsilon_{42}(t-\tau)+\upsilon_{43}(t-2\tau))x\Big]-px^4(t-\tau),\end{aligned} \tag{26}$$

Clearly, $\acute{V}(x_t)<0$ in Eq. (26) if the following conditions hold:

$$\begin{aligned}&u<\mu_4,\quad \alpha_1-\phi_1T^*>\frac{\phi_2}{\mu_1}(\alpha_1-\phi_1T^*),\quad 2\mu_2T^*+\nu_1G^*>g+\alpha_2,\\ &\mu_3+g>\nu_2G^*+T^*\frac{\rho}{\omega+T^*}\ \&\ \gamma_2T^*>\frac{T^*\rho\omega}{(\omega+T^*)^2}.\end{aligned} \tag{27}$$

Table 2
Model parameter values.

Parameter	Value	Unit	Reference
α_1	0.7	day^{-1}	[32,36,37]
μ_1	$0.1 \rightarrow 1$	day^{-1}	[36,37,40]
ϕ_1	0.1	day^{-1}	[28,37]
α_2	0.98	day^{-1}	[36,37]
μ_2	0.4	day^{-1}	[36,37]
γ_1	0.8	day^{-1}	[36,37]
ρ	0.8	day^{-1}	[37]
ω	0.3	day^{-1}	[36,37]
γ_2	0.29	day^{-1}	[37]
μ_3	0.15	day^{-1}	[37,40]
ϕ_2	0.5	day^{-1}	[37]
s	0.4	day^{-1}	[36,37]
g	$0 \rightarrow 0.5$	mmol/L	[37]
ν_1	1.38	day^{-1}	Assumed
ν_2	0.55	day^{-1}	Assumed
u	1(100)	tablet(mg)\day	Assumed[a]
μ_4	1(100)	tablet(mg)\day	Assumed

[a] The value of u was assumed based on the approved medical dose of SGLT-2 inhibitor drugs for diabetics.

Likewise, $\acute{V}(x_t) = 0$, if $T^* = 0 \implies \nu_1 G^* = \frac{1}{\mu_2}\left[\alpha_2 + g\right]$, & $s = 0$, such that the following hold:

$$u = \mu_4, \quad \alpha_1 - \phi_1 T^* = \frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*), \quad 2\mu_2 T^* + \nu_1 G^* = g + \alpha_2,$$
$$\mu_3 + g = \nu_2 G^* + T^* \frac{\rho}{\omega + T^*} \ \& \ \gamma_2 T^* = \frac{T^* \rho \omega}{(\omega + T^*)^2}. \tag{28}$$

The condition for having $\acute{V}(x_t) = 0$ translates to having $N^* = T^* = M^* = G^* = 0$. Hence, the largest invariant set with respect to System (1) is

$$\xi = \left\{(N^*, T^*, M^*, G^*) \in R^* : \acute{V}(x_t) = 0\right\}. \tag{29}$$

This completes the proof.

Biological interpretation of the global stability conditions for System (1):

- $u \leq \mu_4$: The does rate of SGLT2 inhibitor drug (u) and the digestion rate ($\mu 4$) should be equal. This can be justified by the fact that when $u > \mu_4$ it means the ingestion of the drug is more than the digestion rate resulting in an excessive dose (overdose) which could lead to adverse effects. Conversely,, if $u < \mu_4$, it indicates under-dosage, potentially rendering the treatment ineffective.
- $s = 0$: The biological meaning is that when the treatment has caused the tumour to relapse, then s will be zero, as there is no tumor antigen remaining.
- $T^* = 0$: The global stability conditions indicate that tumor rate equal to zero which means that SGLT2 inhibitors drug caused tumor fading.
- $2\mu_2 T^* + \nu_1 G^* \geq g + \alpha_2$: It is assumed that the rate of tumour cells inhibition has to be greater than or equal to the rate of its growth due to the presence of an SGLT-2 inhibitor drug.
- $\mu_3 + g \geq \nu_2 G^* + T^* \frac{\rho}{\omega + T^*}$: The rate of immune cells decreasing should be greater than or equal to the rate at which glucose transporter inhibitor[SGLT2] promote immune cells viability against glucose-induces suppression.
- $\alpha_1 - \phi_1 T^* \geq \frac{\phi_2}{\mu_1}(\alpha_1 - \phi_1 T^*)$: This means the rate at which normal cells proliferate is greater than or equal to the rate at which tumors compete with normal cell by its death rate or carrying capacity.
- $\gamma_2 T^* \geq \frac{T^* \rho \omega}{(\omega + T^*)^2}$: This implies the rate at which the immune attacks the tumor is greater than or equal to the immune response threshold such that the immune secretion would not be excessive.

4. Numerical simulation

In this section, the numerical verification of the global stability conditions obtained in Theorem 3 is done using Matlab version R2021b with DDE23 solver and the parameter values provided in Table 2. The purpose is to confirm the accuracy of the analytical findings.

Fig. 2(a) describes the behavior of the dynamic system when there is no delay ($\tau = 0$). The tumor cells grow up while the immune cells decrease and normal cells are stable. It is obvious that from the figure the immune cells failed to eliminate the cancer cells during the interaction, and thus the cancer cells were able to escape from the attack of the immune system, which led to their growth and reproduction. Since the interaction between cells in the case of $\tau = 0$ is instantaneously, the impact of treatment is invisible.

Fig. 2(b) describes the behavior of the dynamic system when there is a delay ($\tau > 0$). The figure shows that tumor cells regress, immune cells is seen transgressing toward tumor's curve before both the tumor and immune regress to zero. The normal cell is seen progress constantly. Obviously, SGLT-2 inhibitor drug reduce the amount of glucose which leads to the strengthening of the immune system and starving of cancerous cells.

5. Optimal control analysis

The objective of applying the optimal control is to determine the optimal dosage of glucose inhibitor drug that is required for the patient such that the tumor cells will be starved and immune cells will be reinvigorated. The formulation of the optimal control problem with time delay related to System (1) is given in the next subsection.

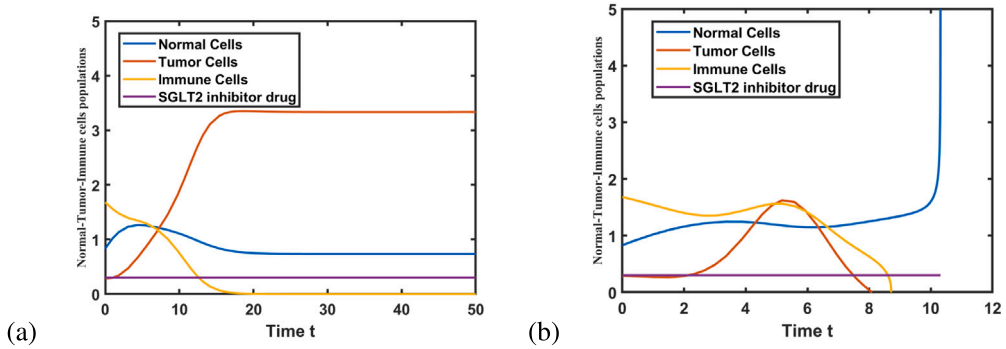

Fig. 2. Cells population when (a) $\tau = 0$, (b) $\tau > 0$, at the coexisting equilibrium-point E^* with the initial conditions $(0.83, 0.29, 1.68, 0.3)$.

5.1. Optimal control formulation

Every treatment has side effects especially if the patient has an overdose of the drug. SGLT2 inhibitor drugs, like other drugs, are harmful if taken in inaccurate doses. The mechanism of action of SGLT2 inhibitors drugs flushes the glucose out from the body through the urine instead of reabsorbing it into the body. This mechanism can lead to female genital mycotic infections, urinary tract infections and increased urination [41]. For SGLT2 inhibitors, the kidney is the main target organ is primarily affected by this substance class [42]. SGLT2 inhibitors caused toxic effects on renal function as stated in [43]. Also, filtering large amounts of glucose is a burden on the kidneys, and after several years the beneficial protein begins to come out with urine, and in late cases, it can reach the stage of kidney failure. The aim of applying optimal control here is to minimize the effect of SGLT2 inhibitor drug in order to avoid or reduce the side effects of this drug.

Therefore, the objective function of the optimal control problem is thus stated below:

$$Minimize\ J(G) = \frac{1}{2}\int_0^{t_f} G^2 dt \tag{30}$$

subject to the control system

$$\begin{aligned}
\frac{dN}{dt} &= N(t)\left(\alpha_1 - \mu_1 N(t)\right) - \phi_1 N(t)T(t),\\
\frac{dT}{dt} &= T(t)\left(\alpha_2 - \mu_2 T(t)\right) + gT(t) - \gamma_1 M(t-\tau)T(t-\tau) + \phi_2 N(t)T(t) - \nu_1 T(t)G(t)\\
\frac{dM}{dt} &= s + \frac{\rho M(t)T(t)}{\omega + T(t)} - \gamma_2 M(t-\tau)T(t-\tau) - \mu_3 M(t) - gM(t) + \nu_2 M(t)G(t)\\
\frac{dG}{dt} &= uG(t) - \mu_4 G(t).
\end{aligned}$$

with the initial conditions

$$N(t_0) = 0.83,\ T(t_0) = 0.29,\ M(t_0) = 1.68, G(t_0) = 0.3.$$
$$u \le G(t_f) \le \mu_4,$$

where t_f is the final time for control administration.

Before starting optimal control analysis, we define two important functions called Lagrangian and Hamiltonian functions. The Lagrangian, $\mathcal{L}$, of the optimal control problem is defined by:

$$\mathcal{L}(G) = \frac{1}{2}G^2 \tag{31}$$

and the Hamiltonian function, $\mathcal{H}$, associated with our optimal control problem is defined by:

$$\mathcal{H} = \mathcal{L}(G) + \lambda_N \frac{dN}{dt} + \lambda_T \frac{dT}{dt} + \lambda_M \frac{dM}{dt} + \lambda_G \frac{dG}{dt}. \tag{32}$$

This yields

$$\begin{aligned}
\mathcal{H} =& \frac{1}{2}G^2 + \lambda_N[N(t)\left(\alpha_1 - \mu_1 N(t)\right) - \phi_1 N(t)T(t)] + \lambda_T[T(t)\left(\alpha_2 - \mu_2 T(t)\right) + gT(t)\\
&- \gamma_1 M(t-\tau)T(t-\tau) + \phi_2 N(t)T(t) - \nu_1 T(t)G(t)] + \lambda_M[s + \frac{\rho M(t)T(t)}{\omega + T(t)}\\
&- \gamma_2 M(t-\tau)T(t-\tau) - \mu_3 M(t) - gM(t) + \nu_2 M(t)G(t)] + \lambda_G[uG(t) - \mu_4 G(t)].
\end{aligned} \tag{33}$$

where λ_N, λ_T, λ_M, λ_G are the adjoints variables for the states N, T, M, G, respectively.

5.2. Existence of the optimal control problem

5.2.1. Sufficient conditions for optimality

A sufficient condition is a condition or set of conditions that will produce the event. The sufficient condition for the existence of optimal control problem is presented in the following theorem.

Theorem 4. *There exists an optimal control G^* such that*

$$J(G^*) = minimize J(G) \tag{34}$$

Proof. To prove the existence of an optimal control G^* amounts to prove that the following properties hold for G^*.

1. Convexity of G^* within $[u, \mu_4]$.
   Proof: The convexity condition is satisfied if $\frac{\partial^2 \mathcal{H}}{\partial G^2} > 0$ [30]. Taking second derivative of (33) with respect to G yields
   $$\frac{\partial^2 \mathcal{H}}{\partial G^2} = 1 \tag{35}$$
   since $\frac{\partial^2 \mathcal{H}}{\partial G^2} = 1 > 0$, then the convexity condition holds.
2. Non-emptiness of G^*.
   Proof: Since the convexity condition holds in Property 1, the tangent line property for convexity condition is defined making use of definitions in [44] as given below:
   $$\frac{1}{2}G^{*2} - \frac{1}{2}G^2 \leq \frac{1}{2}(G^{*2} - G^2)\mathcal{H}_G(G^2) \quad \forall\ u \leq t_0 \ \ \& \ \ t_1 \leq \mu_4. \tag{36}$$
   Hence,
   $$J(G^*) - J(G) = \frac{1}{2}\int_{t_0}^{t_1}(G^{*2} - \frac{1}{2}G^2)dt \leq \frac{1}{2}\int_{t_0}^{t_1}(G^{*2} - G^2)\mathcal{H}_G(G^2)dt \tag{37}$$
   $\mathcal{H}_G$ denotes the optimality conditions which satisfies $\mathcal{H}_G = 0$, using this property and substitute by $\mathcal{H}_G = 0$ in Eq. (37), we have
   $$J(G^*) - J(G) = \frac{1}{2}\int_{t_0}^{t_1}(G^{*2} - \frac{1}{2}G^2)dt \leq 0 \tag{38}$$
   therefore,
   $$J(G^*) - J(G) \leq 0 \Rightarrow J(G^*) \leq J(G). \tag{39}$$
   Since $J(G^*) \leq J(G)$, then G^* is non-empty.
3. Uniqueness of G^*.
   Proof: To prove that the solution of the optimal control is unique, we assume a contradictory approach. Suppose that G^* is not the optimal control, so there exists another optimal control denoted by $\hat{G}$ on the interval $[\hat{t}, t_1]$ with $J(\hat{G}) \leq J(G^*)$. Constructing a new control G_1 on the interval $[t_0, t_1]$ as follows:
   $$G_1 = \begin{cases} G^*, & t_0 \leq t \leq \hat{t} \\ \hat{G}, & \hat{t} \leq t \leq t_1. \end{cases} \tag{40}$$
   Then
   $$J(G_1) - J(G^*) = \left(\int_{t_0}^{\hat{t}} \frac{1}{2}{G_1}^2 dt + J(\hat{G})\right) - \left(\int_{t_0}^{\hat{t}} \frac{1}{2}G^{*2}dt + J(G^*)\right) \tag{41}$$
   $$= J(\hat{G}) - J(G^*) > 0 \tag{42}$$
   Obviously, $J(G_1) - J(G^*) > 0$, which means $J(G_1) > J(G^*)$. Since $J(G_1)$ is greater than $J(G^*)$, this contradicts our hypothesis $J(\hat{G}) \leq J(G^*)$ and the existence condition of the optimal control G^*. Thus, there exists no such optimal control $\hat{G}$ and G^* is the unique for Eq. (30).
4. Boundedness of G^*.
   Proof: The boundedness of G^* can be verified from the definition of optimal control problem in Eq. (30). Since G is bounded by $u \leq G(t) \leq \mu_4$, the optimal control G^* exist within the control G. Therefore, G^* is bounded.

5.3. Characterization of the optimal control

The Characterization of the optimal control involves the derivation of optimality, adjoint and transversality conditions to maximize or minimize G^*. These will be done in the subsection below:

5.3.1. Necessary condition for optimality

A necessary condition is a condition that must be present for an event to occur. The optimal control problems, a class of optimization problems containing dynamic constraints, must satisfy a set of requirements known as Pontryagin's Minimum Principle which is applied to the Hamiltonian [45,46]. So, Hamiltonian function is used to derive the necessary conditions for the optimal control problem. We need to find the following conditions:

1. Optimality conditions which satisfies $\frac{\partial \mathcal{H}}{\partial G} = 0$.
2. adjoint equations by firstly finding the following derivatives:
   $$\acute{\lambda}_N = -\frac{\partial \mathcal{H}}{\partial N},\ \acute{\lambda}_T = -\frac{\partial \mathcal{H}}{\partial T},\ \acute{\lambda}_M = -\frac{\partial \mathcal{H}}{\partial M},\ \acute{\lambda}_G = -\frac{\partial \mathcal{H}}{\partial G}$$
   then solving them in order to obtain the values of the adjoint variables
   $$\lambda_N,\ \lambda_T,\ \lambda_M,\ \lambda_G$$
3. Transversality condition that satisfies $\lambda_i(t_f) = 0$, where $i = N, T, M, G$ and t_f is the final time.

Theorem 5. *Let G^* be the optimal control that minimizes the objective function J over G and given by $u \le G^* \le \mu_4$ with the corresponding optimal states N^*, T^*, M^* and G^*, then, there exist adjoint variables $\lambda_N, \lambda_T, \lambda_M, \lambda_G$ that satisfy:*

$$\acute{\lambda}_N = -\frac{\partial \mathcal{H}}{\partial N},\ \acute{\lambda}_T = -\frac{\partial \mathcal{H}}{\partial T},\ \acute{\lambda}_M = -\frac{\partial \mathcal{H}}{\partial M},\ \acute{\lambda}_G = -\frac{\partial \mathcal{H}}{\partial G}$$

with transversality conditions $\lambda_i(t_f) = 0$, where $i = N, T, M, G$.

Proof. The optimality condition can be found using the following equation:

$$\frac{\partial \mathcal{H}}{\partial G} = 0$$

$$\frac{\partial \mathcal{H}}{\partial G} = G^* - \lambda_T \nu_1 T(t) + \lambda_M \nu_2 M(t) + \lambda_G(u - \mu_4) = 0 \tag{43}$$

$$\Rightarrow G^* + \lambda_M \nu_2 M(t) + \lambda_G(u - \mu_4) = \lambda_T \nu_1 T(t) \tag{44}$$

$$\Rightarrow G^* = \lambda_T \nu_1 T(t) - \lambda_M \nu_2 M(t) - \lambda_G(u - \mu_4). \tag{45}$$

From Eq. (45), there are three possible cases for the optimality condition depending on the sign of G^* which can be interpreted as follows:

- **Case 1:** If $\lambda_T \nu_1 T(t) < \lambda_M \nu_2 M(t) + \lambda_G(u - \mu_4)$ then $G^* < u$.
- **Case 2:** If $\lambda_T \nu_1 T(t) = \lambda_M \nu_2 M(t) + \lambda_G(u - \mu_4)$ then $u \le G^* \le \mu_4$.
- **Case 3:** If $\lambda_T \nu_1 T(t) > \lambda_M \nu_2 M(t) + \lambda_G(u - \mu_4)$ then $G^* > \mu_4$.

Biological meaning of Case 1: The impact of SGLT2 inhibitor drug on reducing or destroying cancer cells is less than its ability to enhancing the immune cells. This means that the effect of SGLT2 inhibitor drug will promote the ability of immune cells to attack cancer cells, but it will not have a strong effect in reducing cancer cells as required, which can make a high pressure on the immune cells due to the rapid spread of cancer cells.

Biological meaning of Case 2: The effect of SGLT2 inhibitor drug in enhancing immunity is equal to its ability to destroy the cancer cells. This means that SGLT2 inhibitor drug will be effective in eliminating cancer cells as well as strengthening immune cells at the same time.

Biological meaning of Case 3: The impact of SGLT2 inhibitor drug on reducing or destroying cancer cells is greater than its ability to enhancing the immune cells. This means that the effect of SGLT2 inhibitor drug will assists the body to get rid of cancer cells, but it will not help in strengthening the immunity as required, which may make the body weak and subject to relapse and the return of the disease again.

From the above interpretations, we can conclude that if the effect of SGLT2 inhibitor drug on both cancer cells and immune cells is equal, the optimal results will occur.

Therefore, the optimal control G^* is given by:

$$u \le G^* \le \mu_4$$

For the adjoint equations, $\lambda_N, \lambda_T, \lambda_M, \lambda_G$ can be obtained by differentiating (33) with respect to the model states to obtain the following:

$$\begin{aligned}
\acute{\lambda}_N &= -\left(\lambda_N\left[\alpha_1 - 2\mu_1 N - \phi_1 T\right] + \lambda_T \phi_2 T\right)\\
\acute{\lambda}_T &= -(-\lambda_N \phi_1 N + \lambda_T\left[\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G\right])\\
&\quad - (\lambda_M\left[\frac{\rho M \omega}{(\omega + T)^2} - \gamma_2 M e^{-\lambda_T \tau}\right])\\
\acute{\lambda}_M &= -\left(-\lambda_T \gamma_1 T e^{-\lambda_M \tau} + \lambda_M\left[\frac{\rho T}{\omega + T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G\right]\right)\\
\acute{\lambda}_G &= -\left(G - \lambda_T \nu_1 T + \lambda_M \nu_2 M + \lambda_G(u - \mu_4)\right).
\end{aligned} \tag{46}$$

Using integrating factors to solve Eqs. (46), we have

$$\begin{aligned}
\lambda_N(t) &= \frac{-\lambda_T \phi_2 T}{\alpha_1 - 2\mu_1 N - \phi_1 T} + c_1 e^{-(\alpha_1 - 2\mu_1 N - \phi_1 T)t},\\
\lambda_T(t) &= \frac{-\lambda_M\left[\frac{\rho M \omega}{(\omega+T)^2} - \gamma_2 M e^{-\lambda_T \tau}\right] + \lambda_N \phi_1 N}{\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G}\\
&\quad + c_2 e^{-(\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G)t},\\
\lambda_M(t) &= \frac{-\lambda_T \gamma_1 T e^{-\lambda_M \tau}}{\frac{\rho T}{\omega + T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G}\\
&\quad + c_3 e^{-(\frac{\rho T}{\omega+T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G)t},\\
\lambda_G(t) &= \frac{-G + \lambda_T \nu_1 T - \lambda_M \nu_2 M}{u - \mu_4} + c_4 e^{-(u - \mu_4)t}.
\end{aligned} \tag{47}$$

The transversality conditions satisfy

$$\lambda_N(t) = 0,\ \lambda_T(t) = 0,\ \lambda_M(t) = 0,\ \&\ \lambda_G(t) = 0,$$

and are needed to obtain the values of the constants c_1, c_2, c_3 & c_4. Using the initial conditions $(0.83, 0.29, 1.68, 0.3)$, we obtain from (47) the following:

$$\begin{aligned}
c_1 &= \frac{\lambda_T \phi_2 T}{\alpha_1 - 2\mu_1 N - \phi_1 T} e^{(\alpha_1 - 2\mu_1 N - \phi_1 T)(0.83)},\\
c_2 &= \left[\frac{\lambda_M \left[\frac{\rho M \omega}{(\omega+T)^2} - \gamma_2 M e^{-\lambda_T \tau}\right] + \lambda_N \phi_1 N}{\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G}\right] e^{(\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G)(0.29)},\\
c_3 &= \frac{\lambda_T \gamma_1 T e^{-\lambda_M \tau}}{\frac{\rho T}{\omega+T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G} \left(e^{(\frac{\rho T}{\omega+T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G)(1.68)}\right),\\
c_4 &= \frac{G + \lambda_T \nu_1 T - \lambda_M \nu_2 M}{u - \mu_4} \left[e^{(u-\mu_4)(0.3)}\right]
\end{aligned} \tag{48}$$

Substituting c_1, c_2, c_3 and c_4 into Eqs. (47), yields

$$\begin{aligned}
\lambda_N(t) &= \frac{\lambda_T \phi_2 T}{\alpha_1 - 2\mu_1 N - \phi_1 T} \left(e^{(\alpha_1 - 2\mu_1 N - \phi_1 T)(0.83-t)} - 1\right),\\
\lambda_T(t) &= \frac{\lambda_M \left[\frac{\rho M \omega}{(\omega+T)^2} - \gamma_2 M e^{-\lambda_T \tau}\right] + \lambda_N \phi_1 N}{\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G} (e^{(\alpha_2 - 2\mu_2 T + g - \gamma_1 M e^{-\lambda_T \tau} + \phi_2 N - \nu_1 G)(0.29-t)} - 1),\\
\lambda_M(t) &= \frac{\lambda_T \gamma_1 T e^{-\lambda_M \tau}}{\frac{\rho T}{\omega+T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G} \left(e^{(\frac{\rho T}{\omega+T} - \gamma_2 T e^{-\lambda_M \tau} - \mu_3 - g + \nu_2 G)(1.68-t)} - 1\right),\\
\lambda_G(t) &= \frac{G + \lambda_T \nu_1 T - \lambda_M \nu_2 M}{u - \mu_4} \left(e^{(u-\mu_4)(0.3-t)} - 1\right).
\end{aligned} \tag{49}$$

The state variables of the optimal control G^* are N^*, T^*, M^*, G^* and given by the following equations:

$$N(t) = \frac{(0.83) e^{-\int (\phi_1 T(t) - \alpha_1) dt}}{e^{-\int (\phi_1 T(t) - \alpha_1) dt} + (0.83) \int_0^t \mu_1 e^{-\int (\phi_1 T(t) - \alpha_1) dt} dt}. \tag{50}$$

$$T(t) = \frac{(0.29) e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G^*] dt}}{e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G^*] dt} + (0.29 / \int_0^t \mu_2 e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G^*] dt} dt + \int_{-\tau}^0 \gamma_1 M(t-\tau) T(t-\tau) [T(t)]^{-2} e^{\int [\alpha_2 + \phi_2 N(t) + g - \nu_1 G^*] dt} dt]} \tag{51}$$

$$M(t) = \frac{(1.68) e^{-\int [\frac{\rho T(t)}{\omega + T(t)} - \mu_3 - g + \nu_2 G^*] dt} + \int_0^t s dt - \int_{-\tau}^0 \gamma_2 M(t-\tau) T(t-\tau) dt}{e^{-\int [\frac{\rho T(t)}{\omega + T(t)} - \mu_3 - g + \nu_2 G^*] dt}}. \tag{52}$$

$$G(t) = e^{(u-\mu_4)t} \tag{53}$$

We conclude that the optimal control is

$$G^* : u \le G^* \le \mu_4 \tag{54}$$

with the above state variables in Eqs. (50)–(53). □

6. Numerical simulation for optimal control problem

In this section, the numerical simulation of the optimal control strategies for System (1) around the coexisting equilibrium point E^* with SGLT-2 inhibitor treatment are performed with a MATLAB DDE23 solver using parameter values in Table 2. The primary objective of these numerical simulations is to authenticate the findings derived from analytical analysis and concurrently present a visual representation of the dynamic behavior of cells while implementing various optimal strategies for SGLT-2 inhibitor control. To investigate the most effective optimal control strategies pertaining to the utilization of SGLT-2 inhibitor medications, three distinct scenarios are considered:

- **Case 1:**
  $u < \mu_4$: the rate of the dose of glucose transporter inhibitors drug(SGLT2) is less than the rate of digestion of glucose transporter inhibitors drug.
  Fig. 3 describes the behavior of normal, tumor and immune cells under the effect of glucose transporter inhibitors drug (SGLT-2) when the rate of the dose of drug is less than the rate of digestion of SGLT-2 inhibitors drug. (a) shows a diminishing effect of the drug as the time changes. In (b), it can be seen that tumor cells grow uncontrollably due to the small dosage of SGLT-2 inhibitor drug which was not affected to reduce the high amount of glucose in the blood. Also, it shows a diminishing effect of the drug as the time changes. This situation produces uncontrollable tumor cells growth, immune cells suppression and impairs normal cells. Thus, glucose increasing incites non-regulating growth of tumor cells and impair the immune system, these have been recorded in many biological studies see [14–16,27,47–55].
- **Case 2:**
  $u > \mu_4$: the rate of the dose of glucose transporter inhibitors drug(SGLT-2), is greater than the rate of digestion of glucose transporter inhibitors drug.
  Fig. 4 illustrates the behavior of normal, tumor and immune cells under the effect of glucose transporter inhibitors drug (SGLT-2) in the case when the rate of the drug dose is greater than the rate of its digestion. This case can be called a drug overdose. (a) shows increasing effect of the drug as the time changes. In (b), it can be seen that the tumor cells decreased to zero, normal cells are relatively stagnated, while immune cells show uncontrolled and abnormal growth, which means that increasing the dose of treatment to be greater than the rate of digestion in the body led to a defect in the growth of immune cells. This imbalanced immune system can lead to an autoimmune disorder that causes a mismatch attack on the body's own tissues.

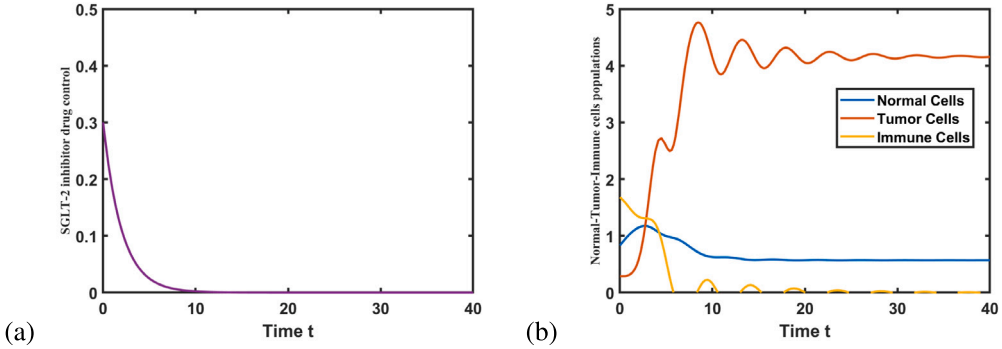

Fig. 3. Numerical result for the optimal control problem when $u < \mu_4$. (a) Drug control, (b) Cells dynamics.

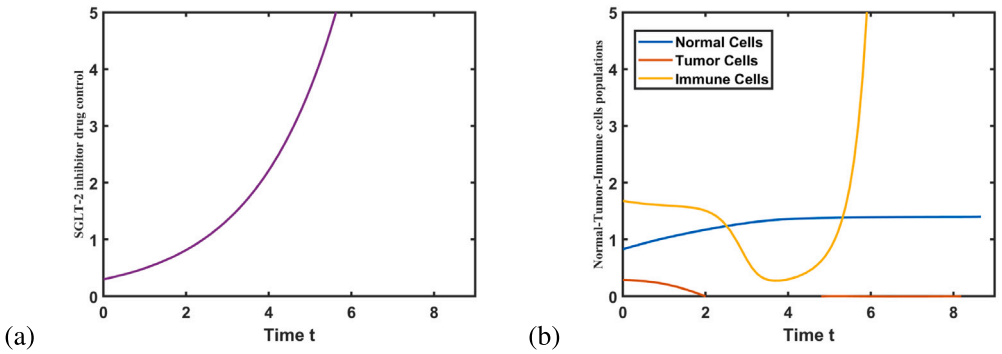

Fig. 4. Numerical result for the optimal control problem when $u > \mu_4$. (a) Drug control, (b) Cells dynamics.

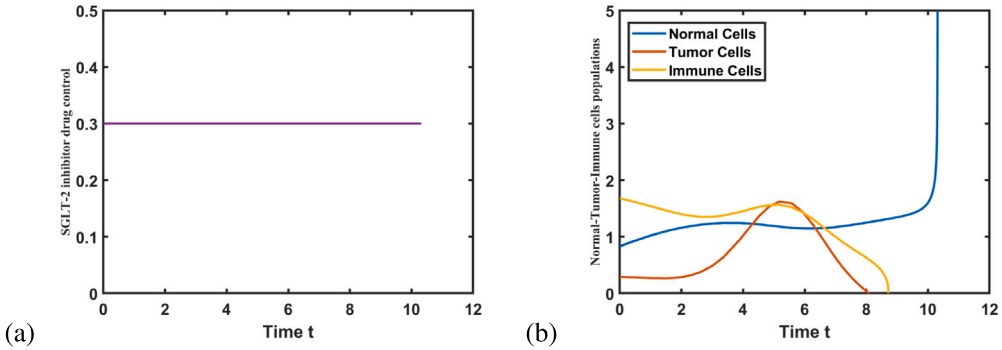

Fig. 5. Numerical result for the optimal control problem when $u = \mu_4$. (a) Drug control, (b) Cells dynamics.

- **Case 3:**
  $u = \mu_4$: the rate of the dose of glucose transporter inhibitors drug(SGLT2), is equal to the rate of digestion of glucose transporter inhibitors drug.
  Fig. 5 depicts the behavior of normal, tumor and immune cells under the effect of glucose transporter inhibitors drug (SGLT-2) in the case when the rate of the drug dose is equal to the rate of digestion of SGLT-2 inhibitors drug. (a) shows a constant effect of the drug as the time changes. (b) shows that tumor cells decrease after interacting with the immune cells while the normal cells are continuing to grow. SGLT-2 inhibitor drug reduces the amount of glucose which leads to the strengthening of the immune system and made it able to fight the tumor, in addition to starving cancer cells, and then fading them away. It also exhibits the tumor regression to zero, immune cells secretion tends to zero and normal cells continue growing healthy.

The numerical simulation showed a dynamical view of the interacting cells with treatment under different dosage controls. When $u < \mu_4$, signifying underdosage, glucose inhibition has no impact on tumor control. Immune cells become suppressed, and normal cells are impaired (see Fig. 3). Conversely, when $u > \mu_4$, biologically indicating that the drug ingestion rate surpasses the digestion rate, glucose inhibition might lead to an autoimmune disorder (see Fig. 4). Obviously, $u = \mu_4$, which biologically represents the control that ensure the ingestion rate of drug is equal to the digestion rate, is the optimal control for using SGLT2 inhibitor drug so as to eliminate cancerous cells, enhancing the effectiveness of the immune cells and ensures the healthiness of normal cells as shown in Fig. 5.

7. Conclusion

This paper has presented and analyzed a mathematical model of breast cancer cells with hyperglycemia risk factor and considering the time lag in the effect of interaction on both tumor and immune cells due to biological process involved in the secretion of cytokines by immune cells and the derivation of suppressive cytokines by the tumor. SGLT-2 inhibitors drug was incorporated in the model as a treatment, to reduce the amount of glucose in the blood. A biological meaningful co-existing equilibrium point including all the interacting cells is obtained and considered. The global stability analysis was performed using Lyapunov's function to find the global stability conditions of the coexisting equilibrium point. The analytical results were verified numerically based on global stability conditions. The results showed that for an instantaneous effect i.e. $\tau = 0$, the glucose inhibition drug has no effect on the dynamics of the interacting cells as cancer cells grow uncontrollably and both immune cells and normal cells were impaired. This indicates the need for prompt treatment intervention before the case of cancer become worst. However, in the case of non-instantaneous effect i.e. $\tau > 0$, SGLT-2 inhibitor drug under a steady-state helps in enhancing the ability of immune cells, eliminate the tumor cells and aid healthy progression of the normal cells.

The optimal control problem was also formulated for System (1) to obtain an optimal dosage control strategy for reducing the possible side effects of SGLT-2 inhibitor drug. Theoretical analysis of the optimal control model was carried out and the analytical results were verified numerically. Three different control cases for SGLT-2 inhibitor drug were obtained. First case was when the rate of the dose of SGLT-2 inhibitor drug is less than the rate of digestion of glucose transporter inhibitors drug. It was found that the effect of the drug is not appeared due to the small dosage of it which led to instability of the System. Second case was when the rate of the dose of SGLT-2 inhibitor drug is greater than the rate of digestion of glucose transporter inhibitors drug. This case showed that although the cancer cells faded away, there was an abnormal growth of the immune cells, which led to the instability of the system. The last case of optimal control problem was when the rate of the dose of SGLT-2 inhibitor drug is equal to the rate of digestion of glucose transporter inhibitors drug. The results suggested that this case is the optimal case since the behavior of cells population responded to the presence of the treatment in an ideal and desirable way. The interaction between the tumor cells and immune cells led to eliminating tumor cells while the normal cells grow healthily.

In future work, the inclusion of paclitaxel chemotherapy in the model can demonstrate how dapagliflozin (an SGLT2 inhibitor) enhances the effectiveness of paclitaxel by reducing tumor glucose uptake and extending overall survival. Additionally, other types of glucose transporter inhibitors could be investigated as potential anti-cancer drugs, and a comparison between the two inhibitor types could be made based on the results. Furthermore, exploring the effects of combining glucose transporter inhibitors with traditional treatments such as radiotherapy on tumor and immune cells would be valuable.

CRediT authorship contribution statement

Abeer Hamdan Alblowy: Conceptualization, Methodology, Software, Formal analysis, Writing – original draft. **Normah Maan:** Review and editing, Supervision, Project administration, Funding acquisition. **Abdulkareem Afolabi Ibrahim:** Methodology, Validation.

Declaration of competing interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

Availability of data and materials

The data used in this study are included and duly cited.

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