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RESEARCH ARTICLE

A Computational Study of Efficient Combinations of FDA-Approved Drugs and Dietary Supplements in Endometrial Cancer

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ABSTRACT Endometrial cancer (EC) develops in the uterine lining, and in 2024, there will be approximately 67,880 reported cases of uterine cancer in the USA, with 90% of them being EC. Many unfit or elderly cancer patients are unable to undergo standard treatments for EC such as surgery, chemotherapy, or radiation therapy. For such patients, targeted therapies and immunotherapy drugs that have received approval from the FDA and have demonstrated significant efficacy in treating EC, offer a viable alternative. Dietary supplements, which are known for their lower toxicity, are increasingly becoming a complementary treatment option, alongside conventional primary therapies for patients battling many cancers. Additionally, individuals with a family history of EC or those focused on maintaining their overall well-being often include these supplements in their daily diet as a proactive measure. However, the consumption of random inefficient supplements may elevate the risk of other health issues, such as headaches, nausea, and fatigue. Since combination therapy has been already shown to be a successful treatment for EC, it makes sense to consider finding the optimal combinations of targeted therapies and dietary supplements in treating EC. This paper uses a Boolean Network approach to find such combinations. Our computational analysis predicts that combining Pembrolizumab (FDA-approved immunotherapy for EC) with dietary supplements like Epigallocatechin Gallate (EGCG), Melatonin, Curcumin, and Baicalein significantly enhances its efficacy, showing improvements ranging from 71.22% to 99.99% across different combinations. This demonstrates the potential for synergistic effects when supplements are combined with a commonly used immunotherapy treatment (Pembrolizumab) in EC.

INDEX TERMS Endometrial cancer, FDA approves drugs, dietary supplements, Pembrolizumab, Lenvatinib, Afinitor, EGCG, Curcumin, Melatonin, Aspirin, Baicalein, Boolean network, targeted therapy, immunotherapy, combination therapy.

I. INTRODUCTION

Endometrial cancer is a type of cancer that develops in the lining of the uterus, known as the endometrium. It is the most common gynecological cancer in developed countries [1] and the fourth most common cancer among postmenopausal women in general. People living longer, eating unhealthier, and other living conditions are all factors that could lead to an increase in the number of people developing EC [1]. In 2024, an estimated 67,880 cases of cancer of the uterine corpus

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(body of the uterus) will be diagnosed in the USA, the other 10% being uterine sarcomas [2]. Out of these, 13,250 women will die from uterine cancer which can be referred to as EC as 90% of the uterine cancer cases occur in the endometrium [2]. Based on histology, and differences in molecular and clinical characteristics, EC is classified into two separate groups. One is type I, which is estrogen-dependent and the other one is less common but clinically fatal type II, which is estrogen-independent [3]. Type II tumor risk factors are poorly understood since most studies do not have enough cases to individually examine these less common malignancies [3]. Being more prevalent and well-studied, we focus our attention in this paper only on type I EC.

EC diagnosis is more invasive than screening for other forms of commonly diagnosed cancers in women. In the USA, the primary treatment for EC consists of the removal of the uterus, cervix, fallopian tubes, and ovaries [4]. For younger women who want to keep their fertility active, progestin-containing intrauterine devices (IUDs) can be a potential course of treatment [4], [5]. Candidates who have undergone surgeries and have been assessed for cancer development staging, ranging from stages 1 to 4, are treated with adjuvant radiotherapy, chemotherapy, or hormonal therapy, based on their specific risk factors and the stage of cancer development. Many women especially with metastatic EC, have an overall poor prognosis and a survival period of less than 1 year [6]. Immunotherapy drugs, that attack the immune checkpoints are also gaining popularity in treating EC [7]. Targeted therapies constitute another approach to EC treatment [8]. This therapy attacks specific cancer cells' unique genes or proteins that contribute to tumor growth and survival, sparing most normal cells. The selection of the unique gene or protein depends on the specific therapeutic agent used in the treatment. Thus, if the cancer mutations are known, corresponding therapeutic agents can be provided in the treatment. Thus, these targeted approaches not only focus on the cancer's specific molecular characteristics, leading to potentially fewer side effects but also mark a significant shift towards more personalized cancer treatment strategies [9]. Targeted therapies in EC, such as Lenvatinib block the formation of new blood vessels essential for tumor growth (angiogenesis) and target proteins that facilitate cancer cell proliferation [10]. For Type 1 EC, treatments such as Lenvatinib, often in combination with Pembrolizumab, have shown promise, especially in advanced cases previously unresponsive to treatment. Combining anti-cancer medications increases effectiveness over monotherapy because it targets important pathways in a way that is typically additive or synergistic. This strategy exhibits therapeutic anti-cancer effects, such as reducing tumor growth with metastases and triggering apoptosis. In conclusion, the combination of targeted immunotherapy, and dietary supplements presents a promising approach for EC treatment, a possibility that is explored in detail in this paper [11].

Natural products, such as dietary supplements, are a potential way to treat cancer because they are affordable, easy to use, and do not cause as many side effects as other drugs [12]. One of the key reasons dietary supplements are an interesting complementary and alternative medicine therapy to investigate is their potential synergy with traditional cancer therapies [13]. In recent work [14], we have investigated the combination of dietary supplements in treating EC. In this paper, our focus is on extending our prior work on EC to understand the improvement of efficacies of FDA-approved drugs when used in conjunction with dietary supplements.

Cancer is an umbrella term for many diseases caused by breakdowns in the cell cycle control system that regulates the cell numbers in a multicellular organism. Advancements in next-generation sequencing (NGS) and multispectral analyses have significantly improved the understanding of the molecular mechanisms in cancer [14], [15]. These technologies have discovered how signaling pathways intertwine to form complex networks within cells. These networks provide scientists with the information needed to identify precise molecular targets for endometrial cancer treatment. This knowledge is key to designing targeted therapies that specifically address the genetic molecular basis of cancer and paves the way for precision medicine approaches in EC treatment [15].

Although marginal, such pathway information can provide potential therapeutic pointers for diseases that result from a simple breakdown of such signaling. However, in the case of cancer, the success of this approach has been very limited mainly because of the complexity of the possible breakdowns in signaling pathways resulting in the manifestation of the disease [12], [14], [15]. However, modeling multivariate interactions via genetic regulatory networks provides the opportunity to pinpoint potential disease-causing breakdown points and can even suggest possible therapeutic interventions [15].

Many strategies have emerged for identifying cancer therapies through the understanding of gene interactions within cancer pathways - encompassing the utilization of established pathways from public databases, network-based methodologies, and the creation of cancer pathways from the ground up [16]. In this paper, we use one of those approaches, namely Boolean Networks (BNs). The paper is organized as follows. In Section II, we provide a brief introduction to BNs. The pathways and the gene interactions in Type I EC are discussed in Section III. Section IV describes the mechanism and intervention points of the drugs and supplements. The results obtained, pertaining to predicted therapeutic efficacy, are presented in Section V. Section VI discusses the significance of the results while outlining possible directions for future research.

II. METHODS

Gene regulatory network (GRN) [17] represents biological phenomena through diverse interactions among genes, proteins, and various biological molecules. While this paper employs Boolean networks for GRN modeling, it is important to note that GRNs can also be effectively modeled using

Bayesian networks [18], neural networks [19], and various other computational approaches. In this paper, we model GRNs using Boolean networks. We confine ourselves to binary-valued logic in order, to facilitate our understanding of complex biological interactions [20]. Some benefits of regulatory network modeling are (1) incorporating the disease-causing genes and their mutations [21], [22]; and (2) analyzing therapeutic responses for target identification and drug discovery [23].

Boolean Networks (BN) have become one of the most popular methods of modeling gene regulatory networks. They provide coarse-scale modeling for the biological phenomenon of interest and do not require any external datasets for inference. Boolean models have been extensively used as a method for theoretical computations in Pancreatic cancer [24], Prostate cancer [25], and Triple-negative breast cancer [26] to name a few. Before delving into the application of Boolean networks for identifying optimal combinations of dietary supplements and FDA-approved drugs for endometrial cancer treatment, we start our discussion with a necessary overview of the model implementation. Fig.1(a) and 1(b) show a toy gene regulatory network and its Boolean equivalent representation, respectively. Utilizing this toy example, we next present a detailed discussion of the Boolean network approach and its utility in theoretically studying diseases and carrying out the associated drug discovery.

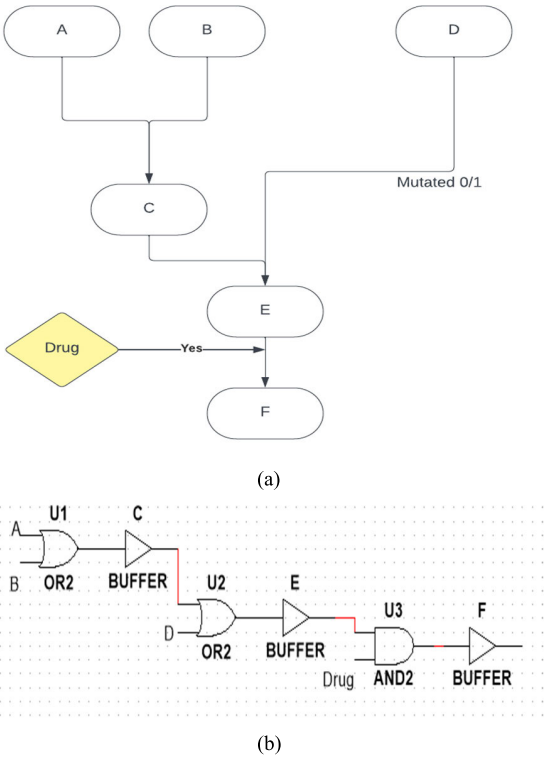

FIGURE 1. (a) Example of gene regulatory network. (b) Boolean equivalent of the example gene regulatory network of FIGURE 1. (a).

A. BOOLEAN NETWORK (BN)

Boolean Networks consist of nodes that can take on binary values, 0 and 1, depending on the activity status of the biological variable represented by that node. If the Boolean network represents interaction between genes, a '0' indicates that the corresponding gene is down-regulated while a '1' indicates that the corresponding gene is up-regulated. In addition, a Boolean network has directed edges that connect any pair of nodes that have a direct interactive relationship. In a biological system, a gene can be influenced by external factors, other genes, etc. The binary regulatory behavior interactions can easily be represented with the help of Boolean logic functions [27]. The Boolean paradigm is a suitable modeling choice for comprehending signaling pathways because it simplifies complex interactions into binary on/off states, making it effective for capturing the essential dynamics of signaling events and aiding in the identification of key regulatory components and their roles in pathway function. Thus, binarization of gene interactions is a very useful mathematical tool for understanding the genetic pathways.

B. MODELING ABNORMALITIES

Due to any external (e.g. UV rays, toxic chemicals) or internal influences (e.g. old age, genetic predisposition) the genes within cells can undergo alterations. Such cells with altered signaling logic are called abnormal cells. Abnormal cells with aberrant signaling can lead to the development of cancer. These cells can produce more abnormal cells. Over time, they continue to grow and accumulate more genetic abnormalities. Some of these abnormalities can lead to uncontrolled cell proliferation resulting in the formation of tumors, damage to organs, and disruption of the immune systems. In our Boolean network model, we simulate genetic mutations as "stuck at faults," where a gene (node) is permanently fixed in an active (stuck at 1) or inactive (stuck at 0) state, independent of the status of its upstream regulators. For instance, in Fig. 1(a) and 1(b), node D represents a critical gene (a proto-oncogene) that is 'stuck at 1,' and, it simulates a mutation causing the gene to be continuously active, which can lead to uncontrolled cell proliferation. Conversely, if the node 'stuck at 0' implies a mutation that permanently turns off a (tumor suppressor) gene, potentially blocking any braking action on cell division, leading once again to uncontrolled cell proliferation. Along these lines, the BN approach allows us to understand the impact of specific genetic mutations on the entire regulatory network. Referring to the toy gene regulatory model introduced in Fig. 1(a), genes A and B act as independent inputs and together activate gene C. This explains the initial layer of the toy network's regulatory mechanism. In the downstream, genes C and D collaboratively activate gene E, which in turn is responsible for the activation of gene F. This sequential activation explains the interconnected nature of gene regulation within the model.

C. MODEL DRUG INTERVENTIONS

Targeted therapies can be thought of as working by binding to targets in cancer cells. Unlike chemotherapy, targeted

therapies have fewer side effects and, in some cases, can differentially target cancer cells. Targeted therapies aim to mitigate cancerous signaling triggered by mutations. Thus, they inhibit the abnormal behavior of cancer cells, possibly leading to the induction of apoptosis, and do not attempt to cure the underlying genetic alterations. In Boolean networks, drugs are incorporated to mitigate the effects of mutations. For instance, if a gene is mutated to '1' (stuck at 1 fault), i.e., overexpressed, after interacting with the therapeutic drug applied at a suitable intervention point, the output gene product can be brought back to '0' [20].

This paper discusses the modeling of gene regulatory networks using the Boolean paradigm. Now, let us consider a scenario where gene D becomes dysfunctional, modeled as being 'stuck at 0' or 'stuck at 1', due to genetic mutations. Thus, the downstream effects on the network are disrupted, affecting the activation of gene E and subsequently gene F. This brings us to the topic of intervention; for instance, if a drug is designed to interact with gene E, it aims to restore the normal function at gene F.

The results of this paper are based on the placement of drugs and dietary supplements at their appropriate intervention point. Starting from that point and referring to the toy example, we see that for the corresponding Boolean network in Fig 1(b), C is the output of an OR gate with inputs A and B. Subsequently, E is the output of an OR gate with inputs C and D. Since the drug is supposed to bind with E to inhibit it and then the signal activates F, the gene F the output of an AND gate with inputs E and the complement of the drug. The Boolean network modeling just discussed allows us to simulate and intervene in the pathways disrupted by genetic mutations, offering insights into potential therapeutic targets.

III. SIGNALING PATHWAY IN EC

Many biological researchers have studied the signaling pathways to improve targeted therapies in endometrial cancer. Signaling pathways are marginal cause-effect relationships that transmit signals from the cell surface to the cytoplasm and nucleus [28]. Fig. 2 and Table 1 show a summary of the reporter genes and pathways of interest and reporter genes respectively in endometrial cancer type I. We next briefly describe these pathways and the associated reporters.

A. WNT/BETA-CATENIN PATHWAY

Almost 40% of endometrial cancers report abnormal gene mutations in the Wnt signaling pathway [29]. Frizzled protein (FZL), T cell factor (TCF7), Lymphoid enhancer-binding factor (LEF1), and beta-catenin which are part of the Wnt signaling pathway are found to be overexpressed in beta-catenin mutated tumors [29], [30]. The recruitment of protein Disheveled (Dvl) by the complex FZD-LRP complex phosphorylates LRP and attracts Axin to receptors. Beta-catenin gathers and moves towards the nucleus where it attaches to TCF [29]. The reporter genes of this pathway are Cyclin D1 (CCND1) and cMyc [29].

B. ECAD

Cadherins are responsible for maintaining cell-to-cell junction. Loses of E cadherin adhesion can influence epithelial-to-mesenchymal transition (EMT) and mesenchymal-to-epithelial transition (MET), which are important indicators for cancer progression [31]. Dissociation of adheren junctions can influence E-cadherin endocytosis, β-catenin levels, and β-catenin substrate levels available downstream for the Wnt pathway [28], [31].

C. NF-Kb PATHWAY

When the immune system is dysregulated by the nuclear factor kappaB (NF-kB), it results in abnormal chemokine and cytokine production, which contributes to the development of endometriosis (endometrial cancer) and other endometrial diseases [32]. Activation of NF-kB encourages migration, invasion, and metastasis of tumor cells in endometrial cancer [32]. CCND1, matrix metalloproteinases (MMP9), and B-cell lymphoma 2 protein (Bcl2) are the reporter genes for this pathway [32], [33].

D. PI3k/AKT/mTOR PATHWAY

The signaling pathway known as PI3K/AKT/mTOR is commonly disrupted in endometrial cancer. A less explored aspect in endometrial cancer research pertains to comprehending how mTOR signaling impacts its principal downstream mechanism [34]. mTOR can influence tumor cell proliferation, survival, and angiogenesis. According to the KEGG database, the main reporter genes for this pathway are CCND1, Bcl2, cMyc [33], [34].

E. NOTCH PATHWAY

Forkhead box A1 (FOAX1) promotes cell proliferation by androgen receptor (AR) and activates the NOTCH pathway by overexpressing NOTCH1 and HES1 [35]. Studies have shown that in breast cancer patients' overexpression of NOTCH receptors and ligands is associated with poor prognosis. Many patients show oncogenesis with dysregulation of NOTCH 1, NOTCH 2, and NOTCH 4 [36]. CCND1 is the reporter gene for this pathway [33], [36].

F. NrF2 PATHWAY

Nuclear factor erythroid 2-related factor 2 (NFE2L2 or NRF2) is a modulator of oxidative responses in cells. The inhibition of NRF2 ubiquitination and the binding to ARE induces transcription in the nucleus [37]. As a component of an E3 ubiquitin ligase, Kelch-like ECH-associated protein 1 (KEAP1) closely regulates the transcription factor NRF2 by pushing it toward ubiquitination. KEAP1's multiple stress sensors and inactivation modalities, enable a variety of cellular inputs that dysregulated NRF2 activity [37], [38]. The reporter gene of this pathway is *NAD(P)H quinone oxidoreductase 1* (NQO1) [38]. Other reporter genes of this pathway are MMP9 and Bcl2 [33] [37], [38].

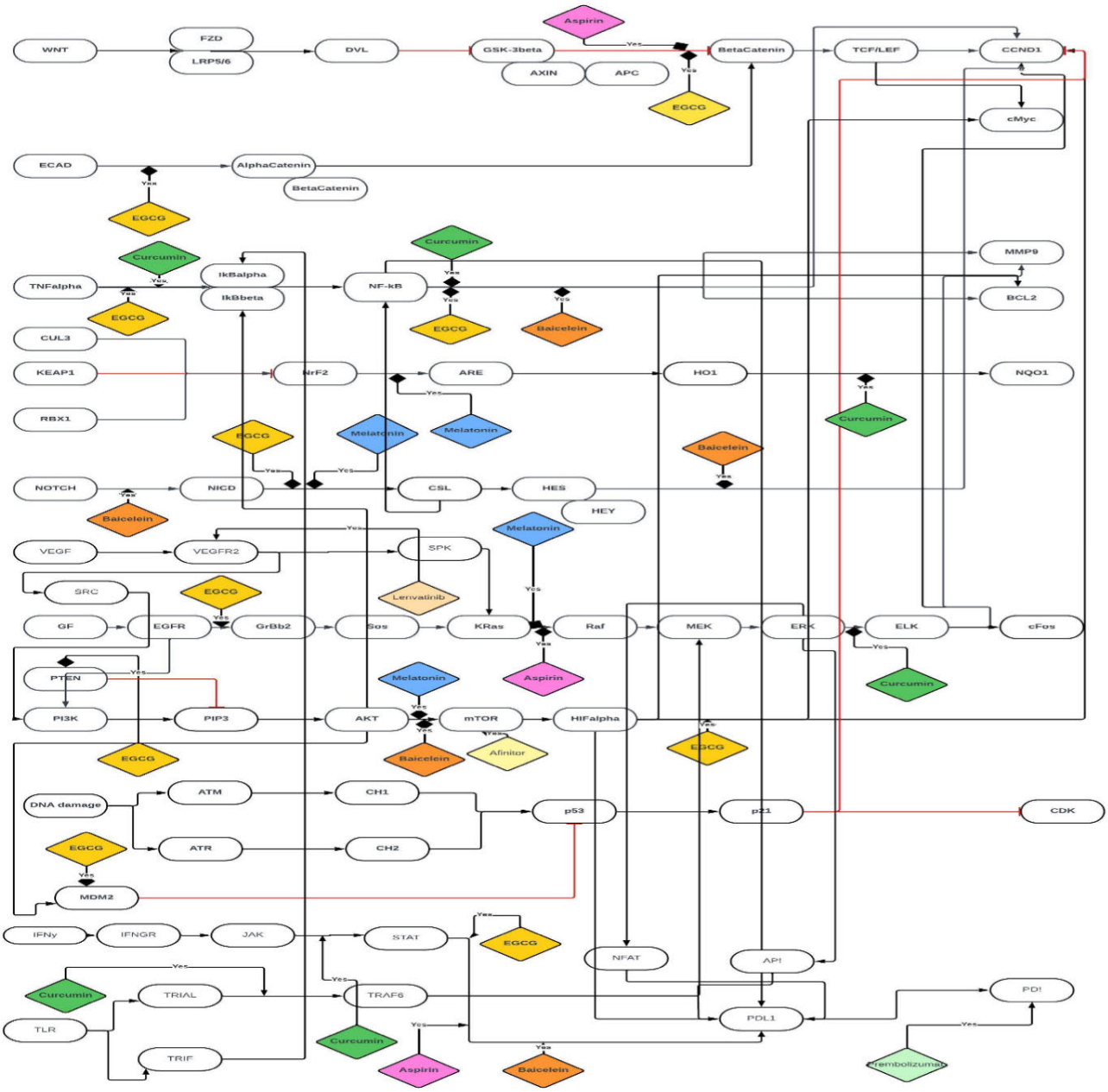

FIGURE 2. Signaling pathway in endometrial cancer Type I.

G. MAPK PATHWAY

The initial set of cytosolic mediators responsible for initiating the phosphorylation cascade in the *Mitogen-activated protein kinase* (MAPK) pathway consists of the Rat- Sarcoma (RAS) superfamily of GTPases, encompassing Harvey -Ras (HRAS), Kirsten – RAS (KRAS), Neuroblastoma – RAS (NRAS), and various others [39]. Following the activation of the *epidermal growth factor receptor* (EGFR), the RAS GTPase is triggered through the assistance of the EGFR-associated nucleotide exchange factor known as Son of Sevenless 1 (SOS1) [40]. Reporter genes of this pathways are CCND1, cFos and MMP9 [33], [40], [41].

H. P53 PATHWAY

Mutations in the tumor protein 53 (TP53) gene are detected in 17–61% of endometrioid cancers and 93–100% of serous types. The presence of TP53 gene mutations correlates with statistically significant reductions in patient survival [39]. Reporter genes of this pathway are CCND1 and Cyclin-dependent kinase (CDK) [33], [42].

I. VEGF PATHWAY

The primary inducer of endometrial tumor angiogenesis is vascular endothelial growth factor (VEGF), which may be a target for therapy given the prevalence and long-term mortality of endometrial carcinomas [43]. VEGF controls

TABLE 1. Endometrial cancer Type I pathway and their reporter genes.

Pathway	Reporter gene
Wnt/beta-catenin	CCND1, cMyc
NFkB	CCND1, MMP9, Bcl2
PI3k/AKT/mTOR	BCL2, CCND1, cMyc
NOTCH	CCND1
NRf2	NQO1
MAPK	cFos, CCND1, MMP9 ,PD1
P53	CCND1, CDK
VEGF	CCND1
INFy	PD1
TLR	cMyc, MMP9, Bcl2, cFos, CCND1

TABLE 2. Drug-supplements and their intervention nodes.

Drugs and Supplements	Intervention nodes
Pembrolizumab	PD1
Lenvatinib	VEGFR2
Afinitor	mTOR
EGCG	GSK3-Axin, ECAD, TNFalpha, NFkB, NICD, EGFR, PTEN, HIF alpha, MDM, STAT
Melatonin	NICD, KRAS, AKT, NrF2
Aspirin	GSK3-Axin-APC, KRAS , STAT
Curcumin	TNFalpha, NFkB, ERK,HO1, JAK, TRIAL
Baicalein	NFkB, AKT, NOTCH, HES ,STAT

angiogenesis in endometrial cancer [44]. VEGF interconnects with the MAPK pathway at KRAS and the PI3K pathway at PI3K [29]. Thus, it affects the reporter genes- CCND1, cMyc, Bcl2, cFos and MMP9 [14].

J. INF-γ PATHWAY

Interferon-γ (IFN-γ) is essential for cellular immunity activation and, in turn, for stimulating the immune response against tumors [45]. Cytotoxic immune cells produce INF-γ which increases the cell immunity by increasing the number of Inducible nitric oxide synthase (iNOS) macrophages and reduces the tumor growth. [46]. IFN-γ can activate *signal transducer and activator of transcription (*STAT1) in pancreatic cells, female reproductive carcinoma cell lines, and endometrial cancer cells, which in turn can induce MUC4 transcription [47]. Thus, it affects the programmed death receptor -1 (PD1) gene in endometrial carcinoma [33], [46], [47].

K. TLR PATHWAY

Many clinical trials have shown significant abnormalities in the Toll-Like Receptor (TLR) pathway in endometrial cancer [48]. It interlinks with the NF-kB pathway through TLR *Toll/interleukin-1 receptor* (TRIF) and inhibitor of nuclear factor-κB (IκB) kinase (IKK) genes [33] thus affecting cMyc, MMP9, Bcl2 reporter genes [14]. It affects Mitogen-activated protein kinase (MEK) in MAPK pathway [33] and thus influences cFos and CCND1 genes too [14].

IV. INTERVENTION NODES OF DRUGS AND SUPPLEMENTS

In this paper, we consider dietary supplements, immunotherapies, and targeted therapies. Different drugs and supplements are found to have different intervention nodes in cancer pathways. Table 2 shows a summary of the intervention nodes of each drug and supplement.

A. PEMBROLIZUMAB

Pembrolizumab is a *Food and Drug Administration* (FDA) -approved immunotherapy drug that has shown significant benefit in treating endometrial cancer [49], [50]. Pembrolizumab is a monoclonal antibody that targets the programmed death receptor-1 (PD-1). It is approved broadly (i.e., not specific to any particular tissue) for solid tumors that are mismatch repair-deficient (dMMR) or have microsatellite instability-high (MSI-H) that have progressed after the first-line of therapy [49], [51]. Compared to 38% of participants in the placebo group, 74% of those treated with pembrolizumab in the dMMR group were still alive and their cancer had not progressed 12 months after therapy began. These figures were 50% and 30%, respectively, in the proficient mismatch repair (pMMR) group [52].

B. LENVATININB

Lenvatinib is one of the commonly used FDA-approved targeted therapy drugs employed in combination therapy for endometrial cancer. For patients with advanced endometrial cancer, Lenvatinib, and pembrolizumab significantly extended overall survival and progression-free survival compared to other treatments [50], [53]. This tyrosine kinase inhibitor affects multiple targets such as vascular endothelial growth factor receptors (VEGFR), Fibroblast growth factor receptors (FGFR), KIT, and rearranged during transfection (RET) [54], [55]. Thus, it could affect the mechanisms of MAPK and PI3K pathways, targeting cFos, Bcl2, MMP9, CCND1, and cMyc.

C. AFINITOR

The mTOR inhibitor Afinitor (Everolimus) has been demonstrated in many clinical trials to enhance patient outcomes in a variety of subtypes of breast cancer [56]. Being an mTOR inhibitor, Afinitor can be used to treat mutations in PI3K/AKT/mTOR pathways [33]. Thus it can influence the reporter genes Bcl2, CCND1 and cMyc in suppressing cancer progression [14], [33].

D. EGCG

Epigallocatechin gallate (EGCG) reduces colonic inflammation, TNF-alpha, and NF-kB [57]. It blocks AhR activity and prompts the expression of Nrf2-controlled genes [58]. EGCG shows inhibitory effects on Beta-catenin in the Wnt pathway,

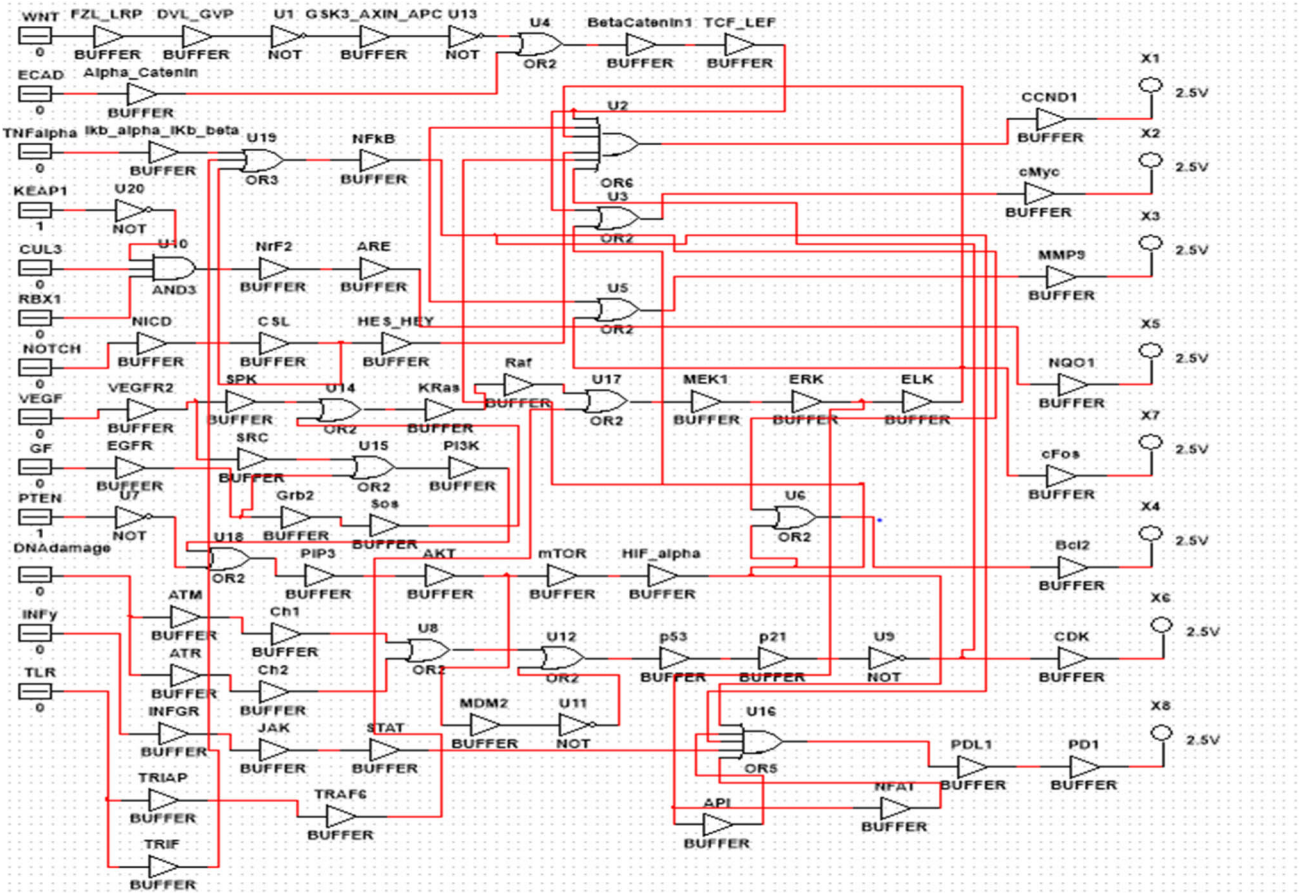

FIGURE 3. Boolean equivalent of endometrial cancer type 1 pathways.

prevents *the murine double minute 2 (* MDM2) mediated p53 ubiquitination, and modifies the membrane lipid arrangement in the MAPK pathway [59].

E. MELATONIN

Melatonin suppresses Akt activation, akin to the specific PI3K, effectively obstructing the PI3K/Akt signaling pathway [56]. Melatonin inhibits KRas and thus affects MAPK and mTOR pathways. It impacts the generation of NOTCH1 intracellular domain (NICD) and the transcriptional effectiveness of Notch effector genes [60], [61].

F. ASPIRIN

A few of the previous works shows that aspirin is linked to a halting endometrial cancer. It inhibits adenomatous polyposis coli (APC) from binding beta-catenin [62], [63]. It helps to restrain NF-kB activation, fostering apoptosis in neoplastic epithelial cells rather than normal ones. Additional in vitro evidence suggests aspirin potentially affects PI3K/mTOR, MAPK, and p53 pathways [64], [65].

G. CURCUMIN

Previous works have shown that curcumin GSK-3β activity, leads to elevated expression of c-Myc, and cyclin-D1. Curcumin impedes the differentiation-induced expression of GSK-3β and Axin [66], [67]. It downregulates NF-kB protein (TNF, IL6) [60]. Curcumin affects the MAPK pathway by influencing transforming growth factor (TGF), EGFR, ERK1/2 [68]. Curcumin reduces the activity of the PI3K–AKT–mTOR pathway [69].

H. BAICALEIN

Western blot analysis shows that baicalein influences the expression of B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), and cyclin D1 in endometrial stromal cells [70]. In vitro studies show it affects the NF-kB, ERK/MAPK, Wnt, Notch, PI3K pathways [71], [72], [73].

V. RESULTS

A. SIMULATION

Utilizing the established Boolean model, we are now able to assess and contrast various drug and supplements combinations. For each potential mutation or fault combination the goal is to identify the optimal combination therapy capable of mitigating the harmful effects as quantified by the downstream reporter outputs. We have 13 inputs and 8 outputs in our Boolean circuit in the MULTISIM and MATLAB models. We considered the effect of 3 drugs and 5 supplements on 45 mutations (faults). The inputs and outputs are fed in the form of binary vectors. In binary vectors, the 1s represents the

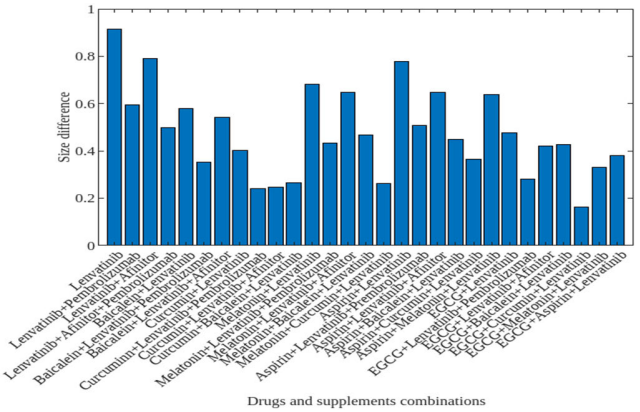

FIGURE 4. SD of two and three agent therapy of Lenvatinib of two faults.

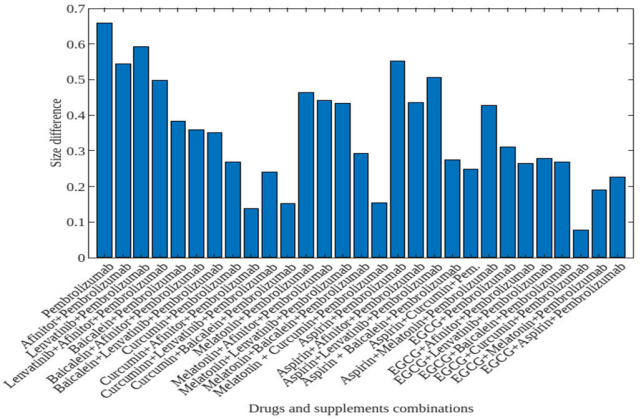

FIGURE 5. SD of two and three agent therapy of Pembrolizumab in case of two faults.

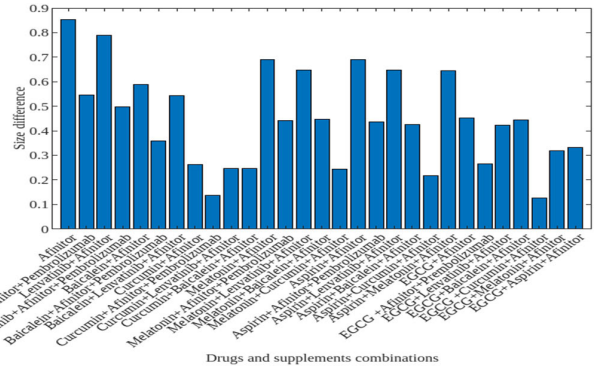

FIGURE 6. SD of two and three agent therapy of Afinitor of two faults.

active gene state and the 0s represent the inactive gene state. The vectors along with the different components are given below:

Input==[WNT; ECAD; TNFalpha; PTEN; KEAP1; CUL3; RBX1; NOTCH;GF;DNAdamage, INF- γ;TLR;VEGF]

Output=[CCND1,BCL2,cMyc,MMP9,NQO1,CDK, cFos, PD1].

Drugs: Pembrolizumab, Lenvatinib, Afinitor

Supplements: EGCG, Melatonin, Aspirin, Curcumin, Baicalein.

The initial states of the inputs and outputs are based on the ideal state i.e., the non-carcinogenic state. The initial input vector is [0001000000] and the corresponding output vector is [00000000]. A zero vector of outputs, with the input vector components set to 0 for growth factors and 1 for tumor suppressors, means a healthy or normal. Different components of the output vector may be in state 1 when there exist mutations in any of the pathways connecting to the reporter genes. In our analysis, our objective is to identify the drug-supplement combination in a mutated (fault-containing) network that drives the output vector close to a zero vector which signifies the healthy state.

When no supplement/drug is given to the cells, the supplements or drugs are kept at 0. If one supplement is introduced in the cells, it is represented by a 1. If a supplement or a drug inhibits a mutation, it is attached with a not gate to the gene and if it exerts an enhancing effect, then it is attached directly to the gene. As previously mentioned, our focus lies in guiding the output vector of a network containing faults toward the healthy output state (all zero vector). To quantify the divergence between two output vectors, we introduce a metric termed the Size Difference (SD). This parameter gauges the divergence between the two vectors.

Consider two binary vectors $a = (a_1, a_2, \ldots, a_n)$ and $b = (b_1, b_2, \ldots, b_n)$. We can then tally the number of agreements and disparities at each bit position, leading to the creation of a confusion matrix, as illustrated in Table 3. In this matrix, entries B and C collectively record the occurrences of the two potential types of discrepancies across all positions, whereas entries A and D collectively account for the occurrences of the two possible types of agreements across all the positions. Using Table 3 the SD can be defined as,

$$d_s(a, b) = \left(\frac{B + C}{A + B + C + D}\right)^2$$

A larger size difference is associated with increased deviation from the healthy outcome, implying potentially heightened cell proliferation, reduced apoptosis, and a greater cancer risk. In this paper, we implement a Boolean network model to explore the effects of different combinations of therapeutic agents on various genetic mutations (faults) in endometrial cancer cells. We simulated the network under 45 distinct genetic faults in one, two, and three combinations, alongside one, two, and three therapeutic agents. In other words, we computationally evaluate the efficacy of individual and combinations of therapeutic agents under the presence of multiple mutations (faults). This dual approach of considering both therapeutic agents and fault combinations enables us to identify efficient strategies for restoring healthy cellular function. The simulation is conducted in MATLAB and seeks to predict optimal therapy combinations that counteract the effects of specific mutations. Since we worked with 45 faults and took one, two, and three combinations of faults, the total

TABLE 3. Confusion matrix.

	$a_i = 1$	$a_i = 0$
$b_i = 1$	A	B
$b_i = 0$	C	D

TABLE 4. SD of Pembrolizumab and its 6 best three-combination therapy.

Combination Therapy	SD in One fault	SD in Two faults	SD in three faults
Pembrolizumab+ Lenvatinib	0.5702	0.5933	0.6173
Pembrolizumab+ Lenvatinib+Afinitor	0.4759	0.4978	0.5282
Pembrolizulam+ Lenvatinib+Aspirin	0.4885	0.5063	0.5322
Pembrolizulab+ Lenvatinib+Melatonin	0.4109	0.4334	0.4647
Pembrolizumab+ Lanvatinib+Baicalein	0.3291	0.3516	0.3804
Pembrolizumab+ Lenvatinib+Curcumin	0.2516	0.2394	0.2381
Pembrolizumab+ Lenvatinib+EGCG	0.2495	0.2791	0.3125

number of possible combinations considered was $C_1^{45}+C_2^{45}+C_3^{45} = 16470$.

B. ANALYSIS AND LIMITATIONS

Using the Boolean network, we found that the most effective (lowest size difference) single FDA-approved drug treatment is Pembrolizumab for one, two, and three mutation combinations. This theoretical result aligns with the existing literature in endometrial cancer and with traditional targeted therapy, which regards Pembrolizumab as a highly effective treatment for endometrial cancer [49], [50]. Next, we extended our analysis further with different drug-supplement combinations of Pembrolizumab. Fig. 4 graphically shows the predicted efficacy, using the size difference metric total of 29 two and three therapeutic agent combinations involving Pembrolizumab over two faults.

To limit the toxic side effects of the combination therapy, this paper considers a maximum of three therapeutic agents in any combination. The bar plots represent the relative performance of these combinations. as measured by the size difference of all two and three drug-supplement combination treatments that contain Pembrolizumab. Table 4 summarizes the efficacies of Pembrolizumab and Lenvatinib in combination with drug-dietary supplements under one, two, and three mutations at a time. Conventional combination therapy for endometrial cancer consists of Pembrolizumab and Lenvatinib. Our theoretical study suggests that incorporating dietary supplements in the regimen of conventional combination therapy increases the predicted efficacy. This is especially true for dietary supplements such as EGCG and curcumin that have shown promising results. Next, we focused on the analysis of Pembrolizumab in combination with two repurposed

TABLE 5. The size difference between Pembrolizumab and its 5 best three-combination therapy.

Drugs and supplements combination	SD	Reduction of SD from solo drug
Pembrolizumab	0.6584	-
Pembrolizumab+EGCG+ Melatonin	0.1895	71.22%
Pembrolizumab+Melatonin+ Curcumin	0.1535	76.68%
Pembrolizumab+Curcumin+ Baicalein	0.1521	76.89%
Pembrolizumab+Curcumin+ Afinitor	0.1370	79.19%
Pembrolizumab+EGCG+ Curcumin	0.0780	99.99%

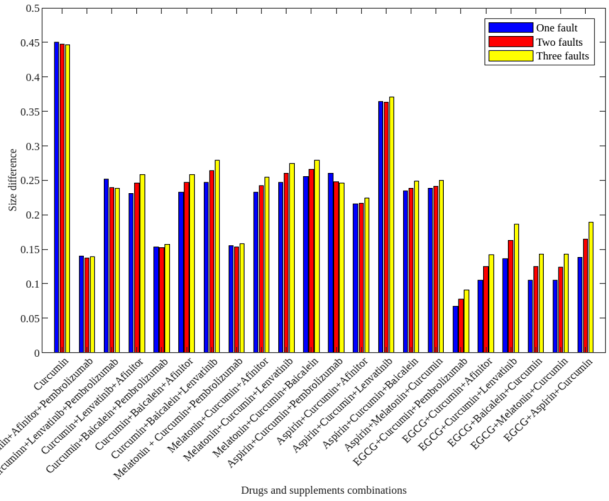

FIGURE 7. SD of three-agent therapy of Curcumin averaged across all faults.

therapeutic agents. Table 5 summarizes the size difference of the top 5 two supplement combinations of Pembrolizumab over two faults. We documented the increase in efficacy as a percentage reduction in size difference. The greater the percentage reduction in size difference, the higher the increase in efficacy. From Table 4 and Table 5, we can deduce that, though Pembrolizumab and Lenvatinib (which has a size difference of 0.5933 for two faults), is a conventional combination therapy, the top 5 two supplements combined with Pembrolizumab (given in Table 5) have a higher predicted efficacy. We also analyzed the efficacies of various combination therapies of Lenvatinib and Afinitor, which are two other FDA-approved drugs. Fig. 5 and Fig. 6 depict the comparative bar plots for two and three-agent combination therapy including Lenvatinib and Afinitor, respectively. For two faults, the best three-agent combination therapy that includes Lenvatinib, EGCG, and Curcumin, while that includes Afinitor, EGCG, and Curcumin.

Next, we analyzed the efficacies of the dietary supplements in combination with various agents over various faults.

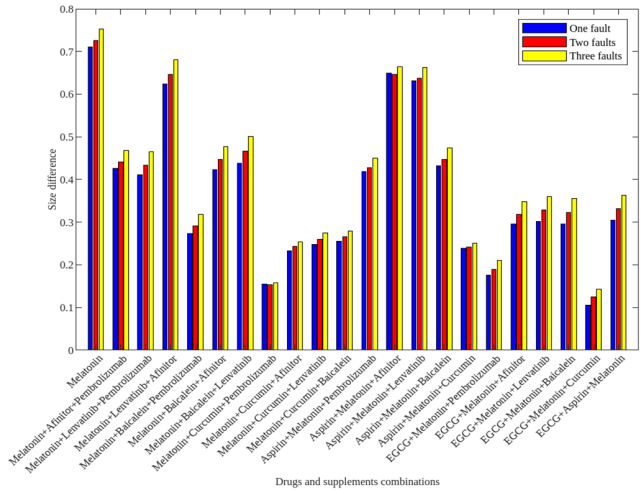

FIGURE 8. SD of three-agent therapy of Melatonin averaged across all faults.

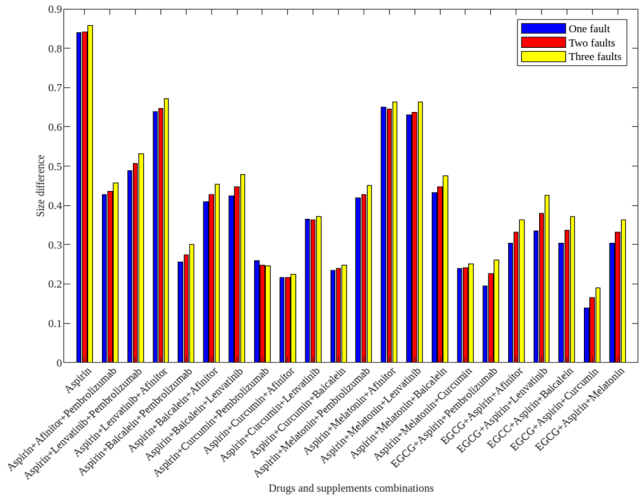

FIGURE 9. SD of three-agent therapy of Aspirin averaged across all faults.

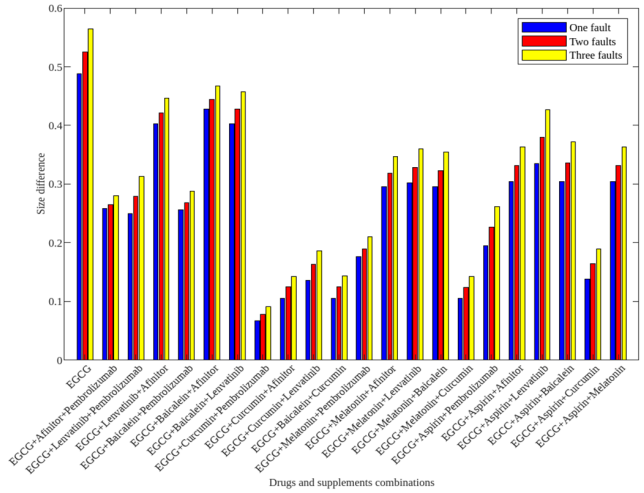

FIGURE 10. SD of three-agent therapy of EGCG averaged across all faults.

Here also we restricted the maximum number of agents to be three to keep toxicity limited. We restricted the number of simultaneously occurring faults to three in each case. Fig. 7 to Fig. 11 represent the bar plots of the efficacies

TABLE 6. SD of Pembrolizumab and its 5 best three-combination therapy.

Number of faults	Size difference of Pembrolizumab+EGCG+ Curcumin
1	0.0671
2	0.0780
3	0.0910

of the three-agent combination therapy of Curcumin, Melatonin, Aspirin, EGCG, and Baicalein respectively. The plots show that the size difference of the combination increases i.e. the efficacies reduce as the number of faults increases. This means that if a patient has more genetic mutations (faults) present in their cancer, the disease becomes more difficult to treat or control. However, this is not the case for every combination. In Fig. 7, for the combination of Curcumin and Pembrolizumab with Lenvatinib and Melatonin, the size difference decreases with an increase in the number of faults. Also, for Curcumin and Curcumin with Afinitor and Pembrolizumab, the size difference does not change much with an increase in the number of faults. This can be due to the compensatory effects of different faults in the pathway, where the presence of two faults may initiate a compensatory mechanism that partially restores the normal functioning of the reporter genes. Also, Curcumin may be more effective in the presence of multiple faults compared to a single fault, which can be a result of the crosstalk of the signaling pathways. However, these verifications are beyond the scope of the current paper, and we leave them as items for future research. The most effective combination among single, double, and triple agent therapies is Pembrolizumab along with EGCG, and Curcumin. As mentioned in [12] the dietary supplements combination - EGCG and Curcumin show promising results in treating endometrial cancer. Earlier this paper has established that Pembrolizumab stands out as the most effective single-agent therapy among chosen FDA-approved drugs. These two facts combined underscore the validity of the three agents' best combination to be Pembrolizumab, EGCG, and Curcumin. Additionally, patients who are unable to consume immunotherapy can also be treated with less toxic ECGC and Curcumin. Notably, the combination of Pembrolizumab, EGCG, and Curcumin tops consistently over one, two, and three faults cases. Table 6 collects the size difference of these combinations. Also, we see that, for this combination, with the an increase in the number of faults, the size difference increases. Therefore, though we conclude this combination to be promising, its efficiency might diminish with an increase in the number of faults.

VI. DISCUSSION AND FUTURE WORK

Our paper implements a BN-based approach to predict and compare the efficacy of combination targeted therapy for endometrial cancer. The BN-based method is based on prior biological pathway knowledge from literature and is not data-driven; thus, it is deterministic, and the simulation results

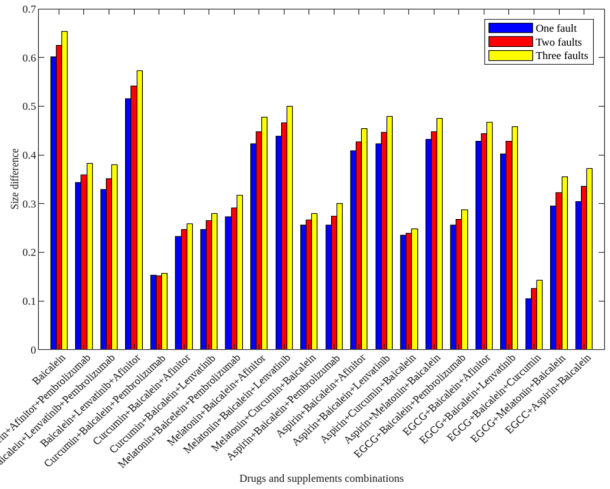

FIGURE 11. SD of three-agent therapy of Baicalein averaged across all faults.

are reproducible. In recent years, with the advent of machine and deep learning, there have been many data-driven methods developed for drug discovery. However, these methods require extensive training data and incur substantial computational costs for their prediction. Publicly available data for endometrial cancer is scarce; thus, these data-driven methods will not produce reliable predictions. Compared to these methods, the BN-based method presented in this paper is designed to work without data and has a comparatively lower computational cost. Various commercially available technologies predict therapies based on gene mutations. Few of them rely on specific tissue samples to make predictions, whereas others work with specific genomic markers to predict treatments based on their curated knowledge base. In contrast, the BN-based approach discussed in this paper does not rely on specific genomic markers or mutations in a particular tissue sample to predict treatment strategies. It can accommodate multiple genomic mutations at a time to predict therapies that will robustly target the malignant effects brought about by the gene mutations. Furthermore, with advancements in cancer biology, pathways can be added or removed from the BN to reflect the current understanding of cancer progression and genesis.

Adjuvant pelvic radiation therapy and chemotherapy, solo or combined, are common treatments in endometrial cancer. Though these treatments can increase the survival periods the potential survival benefits should be weighed against the health-related quality of life (HRQL) after the treatments, the cost of longer duration treatments, and increased toxicity [74]. Though minimal invasive surgery is a cornerstone in treating endometrial cancer, it may be fatal for elderly people. Also, preserving fertility, post-surgical management, cost, and availability are some of the challenges associated with endometrial cancer surgeries. Also, surgery may not be possible in cases where the cancer spreads beyond the endometrium [75], [76], [77]. Therefore, immunotherapy and targeted therapy are emerging as mandatory treatments for patients.

Physiologically, the endometrium immune system is unique. Thus, targeting programmed death ligands is one of the popular choices in immunotherapy to treat EC. Pembrolizumab along with Lenvatinib has shown promising results in clinical trials [78]. In individuals with advanced or metastatic endometrial cancer that was not responding to treatment, Afinitor showed effectiveness and tolerable side effects [79]. Further clinical studies of phosphatidylinositol 3-kinase-targeted therapies for endometrial cancer treatment are gaining popularity [80]. Dietary supplements may be necessary when certain nutrient levels are low. Nutrient absorption challenges due to cancer may warrant a multivitamin and mineral supplement. Many individuals integrate supplements with cancer treatments like radiotherapy or chemotherapy. Previous studies have shown EGCG as a powerful anti-cancer agent [81]. Since curcumin has interactions with several intracellular and extracellular molecules that are involved in various cancers, it is a potential supplement for suppressing cancer progression [82]. Low-dose aspirin use improved the survival outcomes of women with endometrial cancer [83]. Many results suggested that baicalein may suppress the viability of human endometrial stromal cells [70]. Prior evidence indicates that women with endometrial cancer have lower melatonin levels, so infusing melatonin can help in preventing endometrial cancer [84]. The addition of natural or low-dose supplements adds very few side effects compared to popular chemotherapy drugs, such as carboplatin/paclitaxel and cisplatin/doxorubicin [62]. However, taking random supplements can add nausea, headache, and other complications. Our paper provides a theoretical analysis to understand the efficacies of different drug and supplement combinations and attempts to find an optimal one.

Future work may consist of validating our findings with wet lab experiments such as xenograft models or clinical trials. In this paper, we limited our analysis to endometrial type I pathways. Extending the analysis to endometrial type I and type II combined study could be interesting as well as providing a better understanding of the efficacies of medication combinations. Patients who reach the metastatic stage also have a shorter survival period [80]. Therefore, understanding the mechanism and efficacies of combined therapy of drugs and supplements in endometrial cancer metastatic sites and pathways could be an interesting next step. We can also extend the study by including other antioxidants in the studied combinations [81].

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