Combination Supplements for Endometrial Cancer

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***Abstract*— This paper suggests an optimal supplement combination (EGCG, Curcumin, Melatonin, Aspirin, and Baicalein) for treating endometrial cancer using a Boolean model. Endometrial cancer affects the uterine lining, with a high incidence in 2023. Surgery, chemotherapy, or radiation may not be options for some patients, leading to increased interest in dietary supplements. However, using ineffective supplements can cause health problems. Our study focuses on safer, less toxic supplements, offering the most efficient combination.**

Keywords—Boolean Network, EGCG, Curcumin, Melatonin, Aspirin, Baicalein, Endometrial Cancer

I. Introduction

Endometrial cancer arises in the uterine lining (endometrium) and is the most prevalent gynecological cancer in developed nations. It ranks as the fourth most common cancer in postmenopausal women overall, with factors such as extended lifespan, diet, and living conditions playing a role in its increasing incidence [1]. In 2023, approximately 66,200 uterine corpus cancer cases are expected in the USA, with 90% occurring in the endometrium, leading to 13,030 deaths [2]. In this paper, we will specifically address Type I endometrial cancer, which is one of the two types [3].

Compared to other common women's cancers, endometrial cancer diagnosis is more invasive. In the USA, the primary treatment involves removing the uterus, cervix, fallopian tubes, and ovaries [4]. Surgery patients in the right stage may receive additional treatments based on risk factors, but women with metastatic endometrial cancer often have a grim prognosis and survival of less than a year [5]. Targeted therapy offers a novel approach to treating endometrial cancer, representing an intriguing area of pharmacological research in this field [6]. Dietary supplements are an appealing area of complementary and alternative medicine research due to their potential to complement traditional cancer therapies and provide a cost-effective, user-friendly, and less harmful treatment option [7]. Therefore, finding the best combination of natural supplements in endometrial cancer becomes an interesting area of research. Next Generation Sequencing and multispectral analyses provide a deeper understanding of complex intracellular signaling pathways, aiding in the development of precise targeted therapies [8]. Although marginal, such information can provide useful therapeutic pointers for diseases that result from a simple breakdown of such signaling. In computational biology, the discovery of potential breakdown points has led to modified network behavior in a genetic regulatory network [9].

Multiple approaches have emerged to discover cancer therapies by understanding gene interactions within cancer pathways, including using established public databases, and network-based techniques, and developing new cancer pathways from scratch [10]. In this paper, we have used one of those approaches, Boolean Network (BN), which is described in section 2. Section 3 discusses the pathways and the gene interactions in Type I endometrial cancer. Section 4 describes the results obtained. Section 5 assesses the results in the context of the relevant existing literature and outlines some topics for future work.

II. Methods

Our paper explores the hypothesis that cancer develops through sequential gene interactions and signaling pathway crosstalk, making, Boolean Networks (BNs), a commonly employed model to design gene regulatory networks, providing a simple yet effective way to study gene mutations and their dynamic behavior. Boolean models have been extensively used as a method for theoretical computations in the Pancreatic cancer pathway [11], Prostate cancer pathway [12], and Triple-negative breast cancer pathway [13]. However, discussing key concepts of Boolean Networks becomes necessary before we go into its application.

1. Boolean Network (BN): Boolean networks, like binary logic, represent genes as '0' or '1' based on their actual states in gene regulatory networks (GRNs), reflecting whether they are upregulated (1) or downregulated (0), and these networks can

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interpret various gene interactions, including external factors and other genes, through Boolean logic functions [14]. The Boolean model simplifies complex signaling pathways into binary states, aiding in understanding genetic pathways.

2. Modelling abnormalities: Genetic signaling logic in cells can change due to external or internal factors, creating abnormal cells. These mutated cells can lead to cancer, producing more abnormal cells, causing mutations in other genes, disrupting normal signaling, and resulting in uncontrolled growth, tumor spread, organ damage, and immune system changes in Boolean networks, where '1' and '0' represent gene expressions, and mutations are termed as faults with assigned states based on the fault type.

3. Modeling drug interventions: Unlike chemotherapy, targeted therapies bind to cancer cell targets with fewer side effects, sometimes selectively targeting only cancer cells. This inhibits abnormal cancer cell behavior, inducing apoptosis. In a Boolean network, when a gene is mutated to '1' (overexpressed), its output gene product becomes '0' after interacting with the supplements [11].

Figures 1(a) and 1(b) show a gene regulatory network and its corresponding Boolean model. Here A and B are independent Signaling Pathways in endometrial cancer genes that work as inputs to the model and activate the gene C. Similarly, C and D together activate E which then activates gene F. Now we consider D is mutated and the drug interacts with F [11].

III. Signaling Pathways

Signaling pathways are marginal cause-effect relationships that transmit signals from the cell surface to the cytoplasm and nucleus [15]. Table 1 and Fig 2 show a summary of the reporter genes and pathways of interest in endometrial cancer.

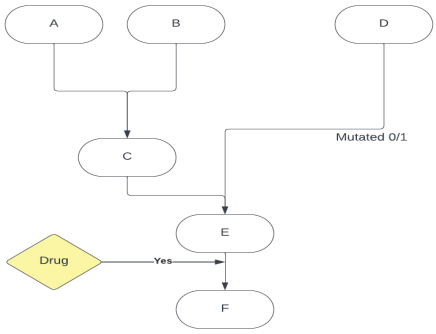

Figure 1(a). Example of gene regulatory network

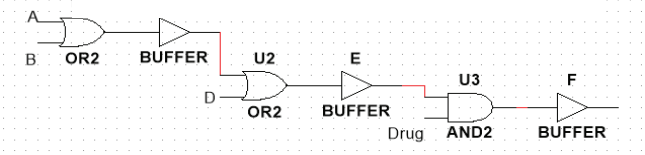

Figure 1(b). Boolean equivalent of the example gene regulatory network of Figure 1(a).

Table 1. Pathways and reporter genes in endometrial cancer

Pathway	Reporter gene	
Wnt/beta-catenin	CCND1, cMyc	[16]
NFkB	CCND1, MMP9, BCL2	[18-19]
PI3k/AKT/mTOR	BCL2, CCND1, cMyc	[19-20]
Notch	CCND1	[21]
NrF2	NQO1	[24]
MAPK	cFos, CCND1, MMP9	[19,25-26]
P53	CCND1, CDK	[27]

The Wnt/Beta-catenin Pathway is responsible for almost 40% of endometrial cancer by affecting beta-catenin levels [16]. The reporter genes of this pathway are CCND1 and cMyc [16]. E-cadherins are responsible for maintaining cell-to-cell junctions which can influence β-catenin substrate levels available downstream for the Wnt pathway [16-17]. Upregulation of NFkB is associated with endometrial cancer and affects CCND1, MMP9, and BCL2, serving as reporter genes for this pathway [18-19]. An understudied aspect in endometrial cancer research is understanding the influence of PI3K/AKT/mTOR signaling [20] on its key downstream mechanisms, including CCND1, BCL2, and cMyc, as reported by the KEGG database. FOAX1 enhances cell proliferation via androgen receptor, activating the Notch pathway in endometrial cancer with overexpressed NOTCH1 and HES1, featuring CCND1 as the reporter gene [21-22]. NrF2, a key regulator of cellular oxidative stress, activates transcription in the nucleus by inhibiting ubiquitination and binding to ARE. Its pathway features NQO1, MMP9, and BCL2 as reporter genes [23-24]. The MAPK pathway's cytosolic mediators, including the RAS GTPases [25]. The reporter genes for this pathway include CCND1, cFos, and MMP9 [19,25-26]. TP53 gene mutations are found in a significant percentage of endometrial cancers in the p53 pathway, with CCND1 and CDK serving as reporter genes in this pathway [27].

IV. Interventions of Supplements

In this paper, supplements target different nodes in pathways. See Table 2 for a summary of the supplements and their corresponding intervention points. The compound (–)-epigallocatechin-3-gallate (EGCG) reduces colonic zand prompts the expression of NrF2-controlled genes [29]. EGCG inhibits Beta-catenin in the Wnt pathway, prevents MDM2-mediated p53 ubiquitination, and modifies the membrane lipid arrangement in the MAPK pathway [30]. Melatonin inhibits Akt activation, resembling PI3K, hindering the PI3K/Akt pathway [31], and impacting KRas in MAPK/mTOR. It affects the Notch intracellular domain (NICD) and Notch effector gene transcription [32-33]. Aspirin has a protective effect against endometrial cancer by inhibiting APC's binding to, MAPK, and Wnt pathway [34-35].

Curcumin affects Wnt -beta-catenin pathway [36]. It potentially influences the PI3K/mTOR and Axin activity and elevates cMyc, and CCND1 levels [36-37]. It downregulates NF-kB protein and affects the MAPK pathway by influencing

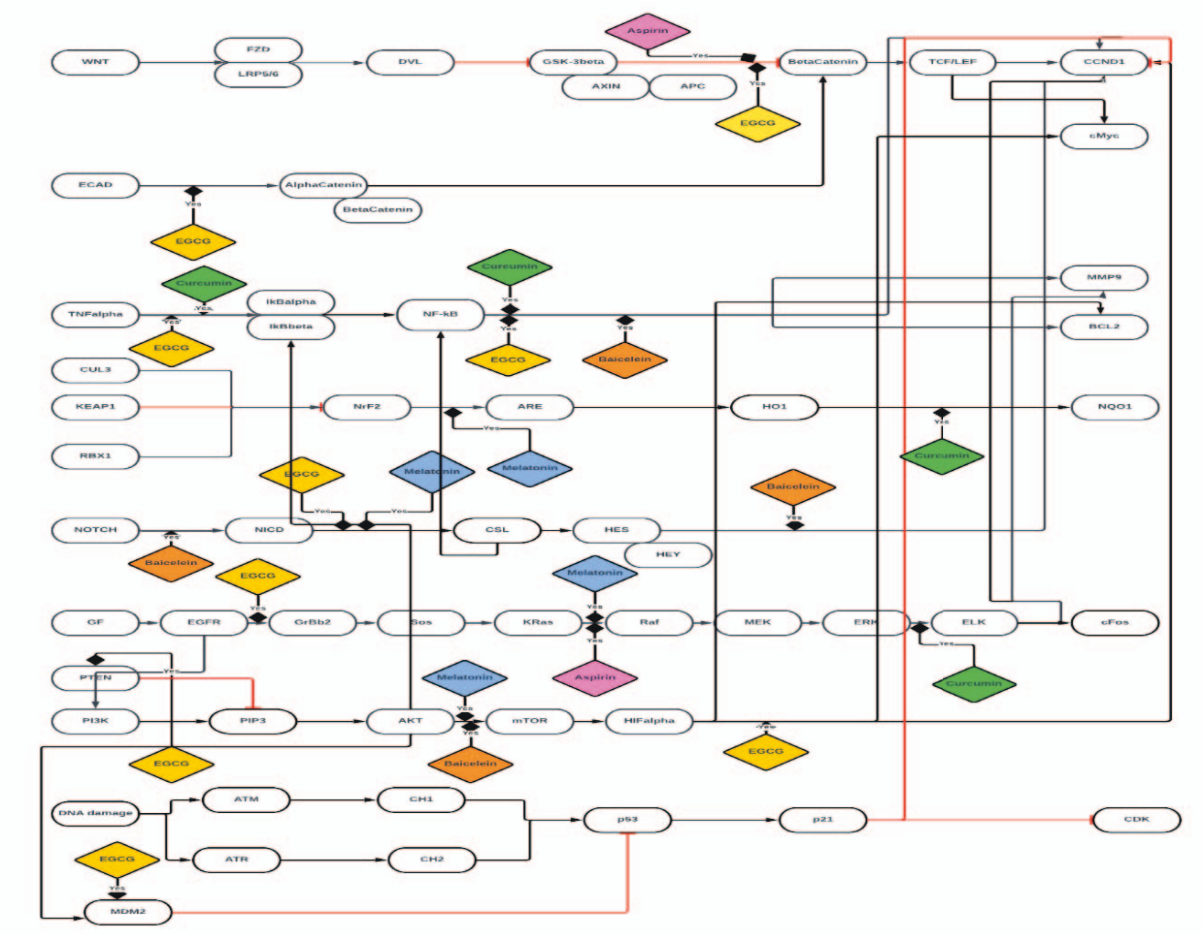

Figure 2. Signaling Pathway in Endometrial Cancer Type I

ERK and KRas [36]. In vitro studies show that Baicalein affects the NF-kB, MAPK, Wnt, Notch and PI3K pathways [38-40].

V. RESULTS

Simulation: We employ a Boolean model with 10 inputs and 7 Boolean outputs, evaluating 5 supplements on 33 faults to mitigate mutation-induced harm using binary data representing active gene states as '1s' and inactivity as '0s'. The vectors are given below:

Input=[WNT; ECAD; TNFalpha; PTEN; KEAP1; CUL3; RBX1; NOTCH;GF;DNAdamage]
Output=[CCND1,BCL2,cMyc,MMP9,NQO1,CDK, cFos].
Supplements: EGCG,Melatonin, Aspirin, Curcumin, Baicalein.

Table 2. Intervention nodes of supplements

Supplement	Intervention nodes
EGCG	GSK3-Axin, ECAD, TNFalpha, NFkB, NICD, EGFR, PTEN, HIF alpha, MDM2 [28-30]
Melatonin	NICD, KRAS, AKT, NrF2 [31-33]
Aspirin	GSK3-Axin-APC, KRAS [34-35]
Curcumin	TNFalpha, NFkB, ERK,HO1 [36-37]
Baicalein	NFkB, AKT, NOTCH, HES [38-40]

The initial states of the inputs and outputs are based on the ideal stage i.e., the non-carcinogenic state. The initial input vector is [0001000000] and the initial output vector is [00000000]. Output vectors indicate positive values with mutated pathways. We seek supplement combos that minimize these values, reducing gene impact. '0' means no supplement, '1' means supplement introduction. Supplements connect through NOT gate for inhibition or directly for activation.

Our main goal is to guide a network's fault-containing output vector toward a more favorable state. We introduce the Size Difference (SD) metric to measure the difference between two output vectors, with its magnitude reflecting the extent of dissimilarity. Consider, two binary vectors, $a = (a_1, a_2, \dots, a_n)$ and $b = (b_1, b_2, \dots, b_n)$. We count agreements and disparities at each bit position, creating a confusion matrix (Table 3).

Larger size differences indicate a stronger deviation, possibly increasing cell proliferation and cancer risk. We used network simulation to assess 33 faults with various supplements, obtaining a mean standard deviation matrix to

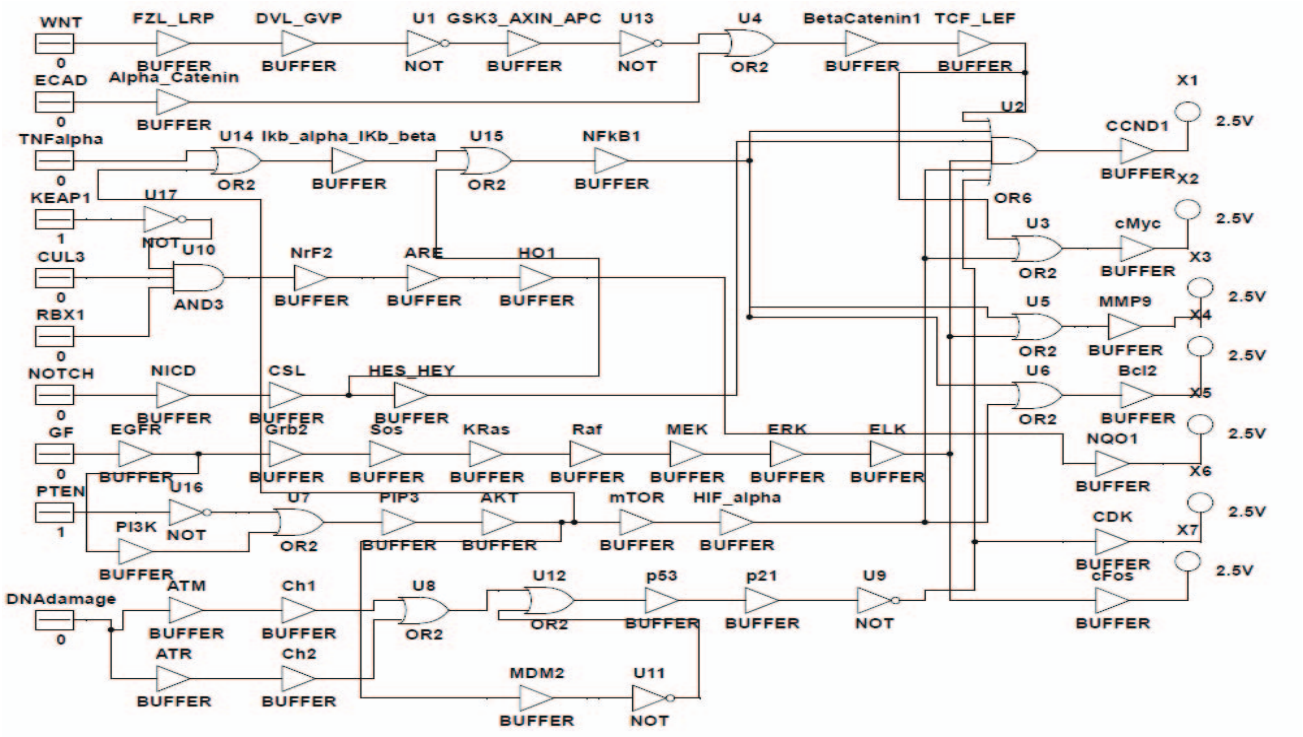

Figure 3. Boolean diagram of endometrial cancer pathway type 1

measure output differences. In MATLAB, we simulated the Boolean network, considering one, two, and three fault combinations, resulting in a total of $C_1^{33} + C_2^{33} + C_3^{33} = 6017$ combinations. In Table 3 entries B and C represent two potential discrepancies, while entries A and D account for possible agreements. The SD can be defined as,

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

Analysis: We tried all three combination faults with up to three combinations of supplements. Table 4 shows output gene vector size differences when one supplement is used with three faults.

Algorithm for finding the size difference.

$Step1 \rightarrow construct\ a\ flowchart\ of\ signaling\ pathways$
$Step2 \rightarrow implement\ boolean\ network$
$Step3 \rightarrow simulate\ the\ boolean\ network$
  $for\ each\ fault\ i\ do \leftarrow$
    $for\ each\ supplement\ s\ do \leftarrow$
      $calculate\ SD(i,s)$
    end
  end

Table 3. Confusion Matrix of Size Difference

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

The size difference of two supplement combinations on two faults is given in Fig 4. For two supplements combined with

Table 4. SD of three faults with one combination of supplement

Supplement	SD
Untreated	1
Baicalein	0.6359
Curcumin	0.4038
Melatonin	0.7716
Aspirin	0.8672
EGCG	0.5129

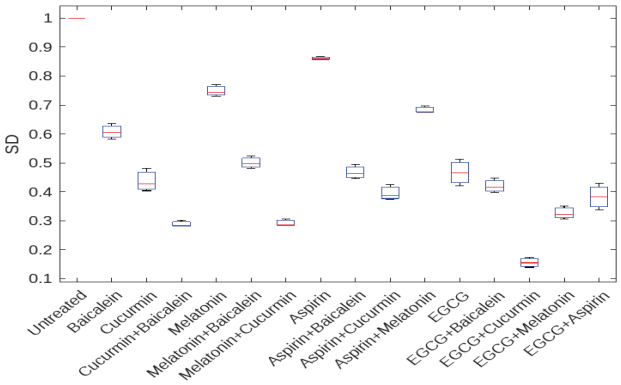

Figure 4. Boxplot of SD of two combination supplements along all faults (Lower values represent more efficient treatment)

two faults, we see the best combination is EGCG and Curcumin with the lowest size difference of 0.1546 in Table 5. Table 5 shows the effectiveness of two combined supplements for two faults. In Table 5, combining supplements reduces the output gene vector size differences, proving their superiority. Using more than two supplements, as shown in Table 6, further reduces the output gene vector size differences.

Table 5. SD vs two combination supplements for two faults

Combination Supplements	SD
Untreated	1
Baicalein	0.6044
Curcumin	0.4273
Baicalein+Curcumin	0.2837
Melatonin	0.7439
Melatonin+Baicalein	0.4965
Melatonin+Curcumin	0.2863
Aspirin	0.8561
Aspirin+Baicalein	0.4626
Aspirin+Curcumin	0.3875
Aspirin+Melatonin	0.6749
EGCG	0.4658
EGCG+Baicelain	0.4161
EGCG+Curcumin	0.1546
EGCG+Melatonin	0.3229
EGCG+Aspirin	0.3815

Table 6. Lowest SD vs its combination supplements and faults

No of faults	Supplements	SD
1	EGCG	0.4213
2	Curcumin	0.4273
3	Curcumin	0.4038
1	EGCG+Curcumin	0.1389
2	EGCG+Curcumin	0.1546
3	EGCG+Curcumin	0.1735
1	EGCG+Baicalein+Curcumin	0.1204
2	EGCG+Baicalein+Curcumin	0.1219
3	EGCG+Baicalein+Curcumin	0.1333

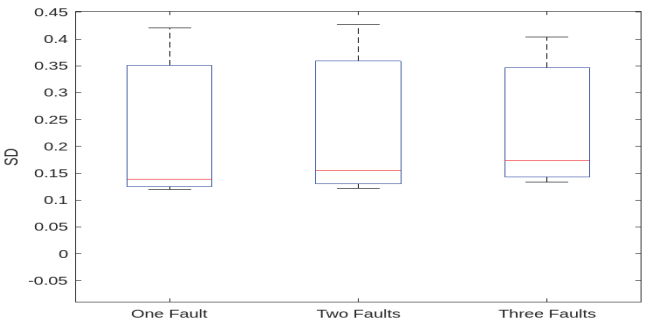

Figure 5. Boxplot of lowest size difference combinations along all faults

VI. Discussion

Low nutrient levels might need dietary supplements, especially with cancer-related absorption problems. Using supplements alone, not conventional treatments, can harm health and hinder cancer control. In our paper, we focused on only 5 supplements and their interventions with endometrial cancer pathways. These supplements show much fewer side effects than ongoing popular chemotherapy drugs in endometrial cancer such as carboplatin/paclitaxel and cisplatin/doxorubicin [34]. Therefore, taking multiple supplements in combination could constitute a good anti-cancer strategy. In addition, combining standard-of-care drugs along with supplements could be an interesting direction for future work.

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