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Review Article

Synergistic Combination of Phytochemical a Multi-Target Strategy Against Cancer

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ABSTRACT

Cancer remains a major global health issue despite advancements in conventional treatments like surgery, chemotherapy, immunotherapy and radiation. While increasing knowledge of the molecular mechanisms underlying cancer progression has led to the development of a vast number of anticancer drugs. Chemotherapy is offered as a treatment for cancer however due to its low specificity, high rates of resistance, toxicity and hypersensitivity reactions, therapy alternatives that improve treatment selectivity, minimize side effects and boost antitumor potential must be sought. To improve efficiency of current cancer therapies new strategies and novel chemoprevention agents are needed to complement. Naturally occurring compounds from plants known as phytochemicals, serve as vital resources for novel drugs and are also sources for cancer therapy. These phytochemicals often act via regulating molecular pathways which are implicated in growth and progression of cancer. Recent studies have increasingly focused on the synergistic effects of combining phytochemicals in cancer therapy, hypothesizing that these combinations may offer enhanced therapeutic benefits compared to single-agent treatments. This review aims to summarize the synergetics anticancer effect of phytochemical combinations from plant focusing on their mechanisms of action, bioactive components, potential clinical applications, challenges and future perspective.

Graphical Abstract

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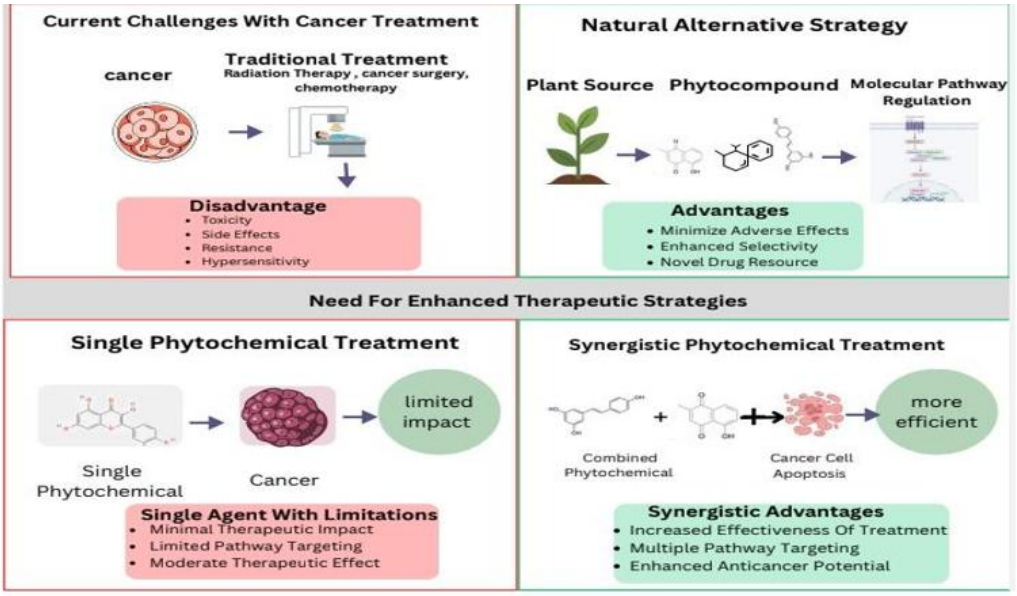

INTRODUCTION

Cancer ranks as one of the most prevalent diseases with 19.3 million new cases worldwide each year due to its rising death rate. It has emerged as the second most common cause of death in recent years, and by 2030, it is predicted that the number of cancer cases will have doubled [1]. Chemotherapy, radiation, immunotherapy, and surgery are common cancer treatment techniques, but each has significant disadvantages. The major limitations of chemotherapy include cancer recurrence, the development of drug resistance, and unfavorable effects on non-targeted tissues, which can make it challenging to use anticancer medications and have a negative impact on patients' quality of life. Research continues to be done to identify novel and promising anticancer drugs that show improved efficacy and less adverse effects in order to resolve the problems associated with current treatments. Phytochemicals, commonly known as plants and their biologically active molecules, provide a promising cancer treatment option with a couple side effects while also enhancing human health [2]. By offering antioxidant, anti-inflammatory and immunomodulatory effects, as well as potential anticancer benefits and symptom relief, phytochemicals enhance the quality of life for cancer patients and promote general well-being during treatment and recovery [3]. The plant contains phytochemicals, which are vital to its growth and development. By removing free radicals, these phytochemicals have biological activity in humans, which is beneficial for the treatment of cancer. Removing free radicals and preventing the proliferation of cancer cells, bioactive substances derived from plants have shown potent anticancer effects in both in vitro and in vivo experiments [1]. Through a variety of interrelated processes, including autophagy and apoptosis induction the activation of both intrinsic and extrinsic pathways that result in the death of cancer cells—phytochemicals contribute to the fight against cancer. Suppression of Vascular Endothelial Growth Factor (VEGF) and Hypoxia-Inducible Factor-1 Alpha (HIF-1α) signaling, which prevents tumor vascularization, inhibits angiogenesis [4]. Reactive oxygen species (ROS) reduction and nuclear factor kappa B (NF-κB)-mediated chronic inflammation are the two main targets of oxidative stress and inflammation [5]. Epithelial-to-Mesenchymal Transition (EMT) regulation, matrix metalloproteinase (MMP)

reduction, and metastasis inhibition [6]. Phytochemicals are effective candidates for chemoprevention and therapeutic intervention due to their varied activities. Potential Synergy and Clinical Applicability Combining phytochemicals may improve anticancer potential and therapeutic efficacy. The review paper highlights anticancerous mechanisms of phytochemicals, their synergistic effect, challenges and future perspective.

1. MECHANISMS OF PHYTOCHEMICAL ACTION ON CANCER CELLS

Phytochemicals are bioactive substances obtained from plants that are beneficial to health, they are primarily secondary metabolites. Table 1 lists the structure, plant source, and anti-cancer efficacy of phytochemicals. Through a variety of processes such as altering signaling pathways and the initiation of apoptosis, the phytochemicals negatively impact cancer cells [7]. By suppressing the production of carcinogenic species and inhibiting the interaction between carcinogens and cells, the anti-cancer drugs show their actions by delaying the growth of tumors [8]. The rat sarcoma (RAS)/mitogen-activated protein kinase (MAPK) pathway, NF-κB, phosphatidylinositol-3-kinase (PI3K)/mammalian target of rapamycin (mTOR) pathway, signal transducer and activator of transcription (STAT) pathway, and Wnt/β-catenin signaling pathway are the main signaling pathways associated with cancer (Fig. 1). In the therapeutic treatment of cancer, the signaling pathways, coupled with the altered enzymes and factors, constitute an important target for activation or inhibition [9]. The RAS pathway is a target for preventing the treatment of related cancers and is associated with the development of tumors as melanomas. By focusing on angiogenesis, metastasis, resistance, and proliferation, phytochemicals are exhibiting strong anticancer effects.

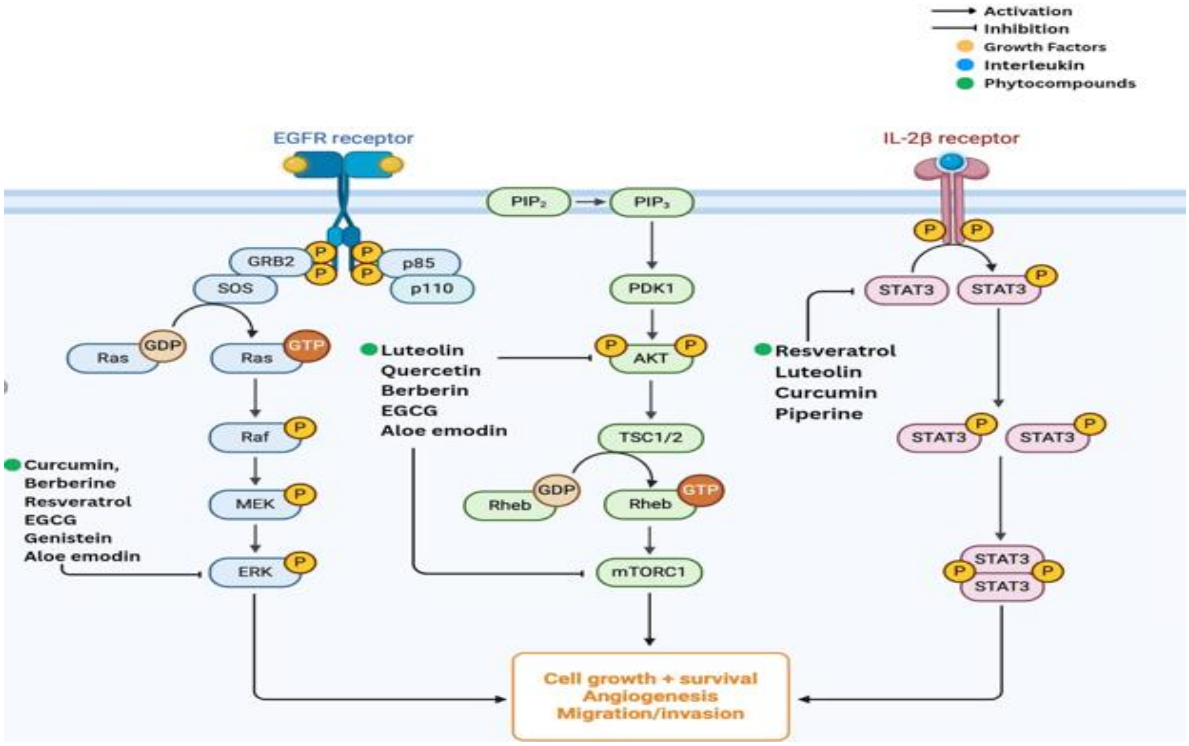

Fig1: Phytochemicals targeted signalling pathway (Template adapted from Biorender and finalized in Canva).

Turmeric contains a polyphenolic chemical called curcumin, which is extracted from the roots of the *Curcuma longa* plant. Curcumin arrests cell cycles in the G2/M phase and inhibits the activity of topoisomerase enzymes [10]. By raising the levels of p53, p21, and p27 and suppressing Sp-1 activation and the expression of its downstream genes, such as ADEM10, EPHB2, HDAC4, and calmodulin, in colorectal cancer cell lines, it inhibits the development of cancer [11]. Curcumin suppresses the NF-κB, STAT3, and Wnt/β-catenin signaling pathways, all of which are critical for the development of cancer [12]. By affecting specific biomarkers associated to the development of cancer, such as cyclooxygenase-2 (COX-2), NF-kB, tumor necrosis factor alpha (TNF-α), cyclin D1, cyclin E, and mouse double minute 2 homolog (MDM2), it inhibits the growth of tumor cells and promotes programmed cell death [13].

The roots of *Tinospora cordifolia* (giloy), *Berberis vulgaris* (barberry), *Berberis aquifolium,* and *Rhizoma coptidis* are the primary sources of berberine, an alkaloid. Berberine inhibits NF-κB and Akt signaling, causing cancer cells to experience cell cycle arrest and death [14]. By binding to nuclear receptor retinoid X receptor alpha (RXRα), repressing β-catenin, upregulating miR-214-3p, and decreasing secretin, berberine may prevent the growth of cancer cells [15]. Additionally, it can slow down the cell cycle by raising p21, p27, and p38 levels while decreasing Cyclin-Dependent-Kinase (CDK) and cyclin, notably CDK1, CDK4, cyclin A, and cyclin D1 levels [16]. Berberine causes cell cycle arrest and inhibits metastasis by blocking the Ras/Raf/ERK pathway. To further prevent metastasis, it also lowers u-PA transcriptional activity and MMP-2 [17], increases E-cadherin, and lowers N-cadherin and snail-1 levels [18]. By inhibiting the PI3K/AKT/mTOR pathway and upregulating miR-203, it causes apoptosis. It also stimulates autophagy through Beclin1 and increases the expression of microtubule-associated Protein 1 Light Chain 3B-II (LC3B-II) [19].

Onions, apples, buckwheat, tea, cherries, tomatoes, citrus, and plums all contain the flavonoid quercetin [20]. Because cancer cells have large quantities of ROS, quercetin possesses antioxidant properties that can be used in targeted cancer therapy to trigger cell death. Through ROS-mediated signaling pathways, specifically the p38/COX2 axis, it causes apoptosis [21]. By activating caspase-3, controlling Akt and mTOR pathways, lowering β-catenin expression, and stabilizing HIF-α, quercetin also promotes autophagy and cancer cell death [22]. According to research on Hela cells, quercetin induces cell cycle arrest, especially in the G2 and M phases, raising intracellular ROS levels and triggering mitochondrial cytochrome C release, which leads to apoptosis [23]. In melanoma cell line A375, it controls Wnt/β-catenin signaling pathways, influencing important proteins including cyclin D1 and β-catenin to prevent cell growth [24]. By decreasing vascular growth and blocking Akt protein production through the VEGFR-2 angiogenesis pathway, quercetin also affects angiogenesis, which is essential for tumor survival and spread. By interfering with many cells signaling pathways and regulating angiogenesis, it considerably inhibits the growth of tumors overall.

Dried white and green tea leaves contain epigallocatechin gallate (EGCG). Human breast cancer cells go through apoptosis when EGCG suppresses telomerase and PI3K/AKT [25]. According to a study conducted on human hepatoma HepG2 cells, EGCG can prevent doxorubicin-induced P-glycoprotein overexpression through the MEK/ERK and PI3K/AKT signaling pathways [26]. According to Gupta et al. (2000), EGCG inhibited cyclin-

dependent kinases in human breast cancer cells, which hindered the progression of the cell cycle [27]. In contrast, it caused apoptosis in prostate cancer cells in a dose-dependent manner. In a variety of cell types, including PC12 cells exposed to oxidative stress, EGCG has been shown to activate crucial apoptotic pathways, such as caspase-3 activation, cytochrome c release, and Poly (ADP-ribose) polymerases (PARP) cleavage [28]. In addition to apoptosis, EGCG's suppression of NF-κB prevents invasion by lowering the production of MMP-9 in lung cancer cells [29].

Aloe vera is the primary source of aloe emodin. Aloe emodin's ability to inhibit Protein kinase C (PKC) isozymes, extracellular signal-regulated kinases (ERKs), and p38 suggests that it may be crucial to the development of cancer metastasis [30]. The HO-8910PM ovarian cancer cell line was used to explore the effects of aloe emodin on migration, invasion, adhesion, and FAK (focal adhesion kinase) expression [31]. According to a study, aloe emodin therapy inhibits the invasion of nasopharyngeal cancer cells (NPC), which lowers MMP-2 production through the p38 MAPK-NF-κB signaling pathway [32]. According to Liu et al., aloe emodin inhibited the proliferation of PC3 cells by disrupting anchorage-independent colony formation and knocking Rictor, a unique binding partner of mTORC2 that is crucial for cell proliferation and tumor metastasis [33]. Hep 3B and Hep G2 liver cancer cell lines showed antiproliferative effects from aloe emodin. Hep G2 cells showed increased production of p53 (tumor protein p53) and p21 (inhibitor of cyclin-dependent kinase), while Hep 3B cells showed p21-dependent inhibition of cell proliferation [34].

Mulberries, blueberries, raspberries, and grapes all contain resveratrol, a non-flavonoid polyphenol. Resveratrol activated the Nrf2 signaling pathway in cancer, which led to the separation of the Nrf2–Keap1 complex [35] and increased transcription of antioxidant enzymes like glutathione peroxidase-2 and heme-oxygenase (HO-1) [36]. According to recent research, resveratrol activated the Nerve Growth Factor Receptor (NGFR)-AMPK-mTOR pathway and increased mRNA expression in non-small-cell lung cancer A549 cells, causing autophagy and death [37]. Resveratrol has been shown to suppress the JAK/STAT3 pathway, which reduces osteosarcoma cell proliferation both in vitro and in vivo [38]. It has been demonstrated that resveratrol inhibits the expression of β-catenins and targets the genes c-Myc, MMP-7, and survivin in multiple myeloma cells, hence decreasing the invasion, migration, and proliferation of cancer cells [39]. Because resveratrol inhibits the activity of the PI3K/AKT signaling pathway and increases the expression of PTEN (the phosphatase and tensin homolog deleted on chromosome ten), it can suppress leukemia cell proliferation and induce apoptosis. This can lead to decreased tumor cell proliferation, division, activated apoptosis, reduced angiogenesis, and formation of metastases [40]. Resveratrol's effects on angiogenesis are linked to its suppression of the production of hypoxia-inducible factor (HIF)-1 and vascular endothelial growth factor (VEGF), which results in a reduction in VEGF secretion [41].

Piperine, a bioactive alkaloid derived from Piper species, has two functions: it inhibits the growth of tumors and increases the bioavailability of phytochemicals and chemotherapy medications. According to a study, piperine inhibited melanoma cell proliferation via inducing apoptosis. In melanoma tumors, piperine decreased ERK and enhanced apoptotic protein expression [42]. Piperine suppressed the growth of prostate cancer cell lines by decreasing the levels of NF-kB and phosphorylated STAT-3 transcription factors [43].

Soybeans contain a bioactive substance called genistein. In a variety of cancer cell lines, the compound increases G2/M and G0/G1 arrest and inhibits the NF-kB and Akt signaling pathways. Pro-apoptotic Bax, Bak and Bad proteins are upregulated by genistein, while BcL-XL and BcL-2 proteins are downregulated. According to a study, genistein increased the activities of caspase-9 and caspase-3, which caused apoptosis in human cervical cancer cells [44]. Genistein downregulates Cdk1, cyclin B1, and Cdc25C in human breast cancer (MDA-MB-231) cells via arresting the cell cycle in G2/M via Ras/MAPK/activator protein-1 [45]. When compared to chemotherapeutic treatments alone, pre-treatment with genistein decreased cell proliferation and increased apoptosis in both in-vitro and in-vivo experiments.

As previously mentioned, each phytochemical interacts with cancer cells and signaling pathways differently, but two or more phytochemicals may also target the same pathways. A combination of two or more phytochemicals approaches the threshold level of activating the common route whereas a single phytochemical cannot reach this level. This is the key point of the shared targets by distinct phytochemicals. This approach demonstrates the potential of integrating natural products to generate better therapeutic outcomes and improve patient quality of life. The function and mechanisms of phytochemical interactions in the prevention of various cancers have been covered in a number of thorough reviews. Section 3 highlights various phytochemical combinations that exhibit synergy in preventing the development of cancer and discusses some new findings.

Table 1: Potential anti-cancer effect of phytochemicals

Phytochemical and Class	Plant Sources	Anticancerous effect	References
Aloe emodin (Anthraquinones)	*Aloe barbadensis* (Aloe vera)	Aloe emodin inhibits p38 MAPK-NF-κB, Akt/mTOR signaling pathway.	[46]
Berberine (Alkaloids)	*Tinospora cordifolia* (Giloy), *Berberis vulgaris* (barberry), *Berberis aquifolium* and *Rhizoma coptidis*	Arrest cell cycle by downregulating NF-κB, Ras/Raf/ERK and Akt signaling.	[47]
Curcumin (Polyphenol)	*Curcuma longa* (Turmeric)	Inhibit JAK/STAT, MAPK, Wnt/β-catenin, NF-κB pathway and modulate apoptosis by increasing the level of p53, p21 and p27.	[48]
Citral (Terpenoids)	*Cymbopogon citratus*	Induce apoptosis by promoting the phosphorylation of p53 protein and upregulating expression of Bax, downregulating Bcl-2 and Bcl-xL expression which promoted the cleavage of caspase-3.	[49]
Chrysin (Flavonoid)	*Passiflora caerulea*	Induced apoptosis in association with the activation of caspase 3 and suppressed Akt signal pathway.	[50]

Daidzein (Flavanoid)	*Trifolium pratense, Glycine max, Medicago sativa, Pueraria radix,Lens esculenta*	Daidzein downregulated the FGFR3, Akt and Erk signalling pathways.	[51]
Emodin (Anthraquinones)	*Rheum palmatum L.*	Downregulate PI3K/AKT and MAPK signaling pathways.	[52]
Epigallocatechin gallate (Flavonoids)	*Camellia sinensis*	EGCG promotes inhibition of carcinogen activity by inhibiting AKT, NF-κB and MAPK signalling pathways.	[53]
Gingerol (polyphenol)	*Zingiber officinale*	Gingerol inhibits NF-κB, STAT3, MAPK signalling pathway and arrest cell cycle.	[54]
Genistein (isoflavonoids)	*Genista tinctoria L.*	Inhibit cell metastasis by consequently downregulating Ras/MAPK/activator protein-1, Cdk1, cyclin B1 and Cdc25C. Modulate apoptosis by upregulating expression of proapoptotic proteins Bax, Bad, Bak.	[55]
Ginsenosides (Terpenoid)	*Panax ginseng*	Regulate the proliferation and induce apoptosis via suppressing the IL-6/JAK2/STAT3 pathway.	[56]
Luteolin (Flavanoid)	*Apium graveolens, Capsicum annuum, Petroselinum crispum*	Luteolin inhibits cell proliferation by downregulating the MAPK, AKT and PI3K signalling pathway. Induced apoptosis through the intrinsic pathway by increasing the levels of caspase-3, caspase-9 and cytochrome c, Bax and Bcl-2.	[57]
Piperine (Alkaloid)	*Piper longum, Piper nigrum*	Piperine reduces cell proliferation by inhibiting expression of STAT-3, NF-kB and ERK.	[58]
Puerarin (isoflavone)	*Pueraria lobata, Pueraria thomsonii Benth, and Pueraria tuberosa*	Modulating cancer cell death via targeting NF-kB, PI3K/AKT/mTOR, AMPK,Raf-MEK-ERK signalling pathway	[59]
Quercetin (Flavanoid)	*Vitis vinifera L., Citrullus colocynthis (L.) Schrad.,*	Induces apoptosis via ROS mediated signaling pathways via increasing levels of p38, ASK1,	[60]

	Cupressus sempervirens L.	AMPKα1, COX2 axis and inhibits cell proliferation by downregulating β-catenin, cyclin D1 and AKT protein expression.	
Resveratrol (phenol)	*Polygonum cuspidatum*	Arrest cell by inhibiting JAK/STAT, PI3K/AKT signalling pathway.	[61]
Vinblastine and vincristine (vinca alkaloids)	*Catharanthus roseus (L.)*	Arrest the cell cycle in the G2/M phase via destabilizing microtubule fibers.	[62]

2. SYNERGISTIC EFFECT OF PHYTOCHEMICAL AGAINST CANCER

According to in vitro and in vivo research, synergistic phytochemicals reduce tumor development, trigger apoptosis, and target several signaling pathways in cancer (see Table 2 & 3). Turmeric's main active ingredient curcumin has strong anti-proliferative properties [63]. By increasing the induction of apoptosis and autophagic cell death and by altering several pathways (JNK, Beclin1, and Bcl-2), curcumin and berberine work in together to suppress the growth of MCF-7 and MDA-MB-231 breast cancer cell lines [64]. By modifying the signaling pathways involved in cancer development and survival, curcumin and berberine operate in concert to prevent cancer cell proliferation and trigger apoptosis, according to a study on colorectal cancer [65]. Combinations of genistein and curcumin have demonstrated synergistic benefits by lowering the proliferation of cancer cells, boosting the induction of apoptosis, and suppressing the growth of breast cancer cells more successfully than when taken independently [66]. According to a study, resveratrol and genistein worked in concert to cause apoptosis in human cervical cancer cells at lower dosages by activating caspases and lowering HDM2 gene expression [44]. In colorectal cancer, a combination of curcumin and resveratrol results in G0/G1 phase arrest, membrane integrity loss, and mitochondrial instability [67]. The combination of resveratrol, curcumin, and quercetin has potent anti-inflammatory and antioxidant qualities; it inhibits the growth of cancer cells and encourages their death [68]. Epigallocatechin gallate (ECGC) and curcumin have a chemopreventive synergy [69]. Gastric cancer cell growths are suppressed in vitro by various combinations of ECGC with the other tea polyphenols epicatechin (EC), epigallocatechin (EGC), or epicatechin gallate (ECG), or by combining all four substances [70]. Soy phytochemicals and green or black tea extract work in concert to prevent the growth of human breast and prostate cancers in mice [71]. Additional dietary phytochemical combinations that demonstrated synergy in in vitro anti-proliferation of cancer cell lines included quercetin-resveratrol and quercetin-resveratrol-ellagic acid on human leukemia cells [72], daidzein-genistein on LNCaP and C4-2B prostate cells [73], and resveratrol-chrysin-curcumin on Caco-2 colon carcinogenic cells [74]. Resveratrol-Curcumin-Quercetin on BALBc mice injected with 2×105 4T1 cells [68], Piperine-Curcumin on lymphoma-bearing mice [75], and

Epigallocatechin gallate-resveratrol on xenograft tumors in nude mice [76] are some of dietary phytochemical combinations that have anti-cancer effects on mice. Research demonstrates stronger anti-tumor and anti-proliferative activities, boosting bioavailability compared to individual extracts. Phytochemical interactions in various biological activities such as anti-oxidation, apoptosis induction, cell cycle arrest, enzyme modification, or gene transcription regulation may be the cause of these combinations' anti-carcinogenic synergy [72]. Combinations of phytochemicals offer the potential for developing more effective and efficient cancer treatments. This tactic emphasizes how combining natural products can improve patient quality of life and lead to improved therapeutic outcomes.

Table 2: In-vitro studies on synergetic effect of Phytochemicals against cancer

Synergistic effect	Concentration/dosages	Cell line	Reference
Combination inhibited cell cycle at G1 and G2/M phase	Indole-3 Carbinol: 40, 50 and 100 µg/ml Resveratrol: 50 and 100 µg/ml	SK-OV-3 ovarian cancer cells	[77]
Combination of luteolin and EGCG induced mitochondria-dependent apoptosis in some cell lines and mitochondria-independent apoptosis in others.	Luteolin 10 µm and Epigallocatechin gallate 30 µm	Tu212, Tu686, 686LN,886LN	[78]
Combination of daidzein and genistein was more effective in inducing apoptosis and inhibiting proliferation in both prostate cancer cells.	Daidzein: 25-50 µM Genistein: 25-50 µM	Early-stage androgen-dependent PCa cells (LNCaP) and bone metastatic LNCaP-derivative PCa cells (C4-2B)	[73]

Combination inhibited cyclin D1, cyclin B1 and arrested cell cycle at G1 and S/G2 phases.	EGCG: 10 µM Curcumin: 10 µM	A549 and NCI-H460 (lung cancer)	[79]
Phytochemical combination significantly suppressed breast cancer cell proliferation (>80%), inhibited migration and invasion caused cell cycle arrest and induced apoptosis resulting in 100% cell death	Indol-3-Carbinol 4 µg/ml; Resveratrol: 0.5 µg/ml; Genistein: 3 µg/ml; Curcumin: 2.25 µg/ml; C-phycocyanin: 50 µg/ml and Quercetin :1.5 µg/ml	MDA-MB-231 and MCF-7 BC cell lines	[80]
The combination of Artemisinin and Resveratrol reduced the ability of cell migration. The combination significantly increased the apoptosis and necrosis rather than use singly.	Artemisinin: 40µM Resveratrol: 80µM	HeLa and HepG2 cells	[81]
Combination of curcumin and citral treatment induced apoptosis cell cycle arrest at G0/G1 phase in breast cancer cells. It formulated ROS and activated p53 and poly (ADP-ribose) polymerase-1 mediated apoptotic pathways.	Curcumin :40 µM Citral: 80 µM	MCF 7 and MDA MB 231 cells.	[82]
Quercetin and curcumin combination modulated the BRCA1 level and inhibited the cell survival and migration of Triple negative breast cancer cell lines.	-	Triple-negative breast cancer	[83]

The Combination of quercetin and Sulforaphane significantly decreased cell viability of Hela cell.	Quercetin: 10, 25, 35 µM Sulforaphane: 1, 2, 5 µM	HeLa Cell	[84]
Berberine and emodin abrogated breast cancer growth and facilitated Apoptosis. The Combination attenuated Akt signaling, thereby inducing G0/G1 phase cell cycle arrest and apoptosis of breast cancer cells in a SIK3-dependent manner.	Emodin 10 µM and Berberine: 5 µM	OVCAR3 cells	[85]
Inhibition of AKT-mTOR signaling by the combination of EGCG and resveratrol	Epigallocatechin gallate 30–80 µM and resveratrol 10–20 µM	SqCCy1, MDA686Tu, Tu212 cells	[76]
The combination significantly impaired the CD44+/CD24- population, clonogenic potential, inherent cisplatin resistance and owing anti-proliferative, EMT inhibitory, and antagonistic cancer stemness functions in Triple negative breast cancer cells.	MDA-MB-468 Cell: Quercetin 5 µM, Curcumin 1.5 µM and Berberine 0.5 µM MDA-MB-231cell: Quercetin 4 µM, Curcumin 1.5 µM and Berberine 3 µM	Triple-negative breast cancer (MDA-MB-468 and MDA-MB-231)	[86]

Combination of curcumin, ellagic acid, quercetin and resveratrol arrested the cells at the S phase.	Curcumin, ellagic acid, quercetin and resveratrol: 5–80 µM	Hela Cervical Cancer Cell line	[87]
Jacalin lectin potentiates and facilitates the cytotoxic effect of curcumin.	Jacalin lectin 2µM and Curcumin: 50 µM	Triple-negative breast cancer MDA-MB-231 cells	[88]
Combination of resveratrol and equol induces apoptosis	Resveratrol 2.8 µM and Equol 25 µM	DU145 cells	[89]
Combination of Resveratrol, Curcumin and Quercetin enhanced oxidative stress response to promote the loss of mitochondrial membrane potential and increase apoptotic signals.	Resveratrol,Curcumin and Quercetin in ratio 1:1:0.5	4T1 cells	[68]
The combination of Daidzein and Puerarin effectively inhibits the	Daidzein: 10, 20, and 30 µM	Human gastric cancer BGC-823	[90]

proliferation of gastric cancer cells by suppressing the STAT3/FAK signaling pathway and downregulating expression cyclin-D1, Bcl-2, and MMP-2.	Puerarin: 10, 20, and 30 μM	cell line and human gastric epithelial cell lines (GES-1).	

Table 3. In vivo studies on synergetic effect on Phytochemicals against cancer

Synergistic effect	Concentration/dosages	Model	References
The combination of curcumin and quercetin appears to reduce the number and size of ileal and rectal adenomas in patients with FAP without appreciable toxicity.	Curcumin 480 mg and Quercetin 200 mg orally 3 times a day	Five Familialadenoma tous polyposis patients	[91]
Combination of luteolin and EGCG was more effective in inhibiting tumor growth than either single agent and may have synergistic/additive effects without inducing any notable toxicity in general.	Epigallocatechin gallate 125 mg/kg and luteolin 10 mg/kg for 7 days	Xenografted mice bearing Tu212 and A549 cells	[78]
Curcumin combined with ginsenosides regulates total ginsenoside immune escape through the PD-L1 pathway and inhibits liver cancer growth through NF-κB-mediated inflammation and angiogenesis.	Curcumin: 200 mg/kg per day and Ginsenosides:520 mg/kg per day	Liver cancer model was established in BALB/c mice by a subcutaneous injection of hepatoma cell line	[92]
Combination of the ECGC and resveratrol significantly inhibited tumor growth.	Epigallocatechin gallate 125 mg/kg and resveratrol 30 mg/kg 5 days a week.	Xenograft tumors in nude mice	[76]

Curcumin and piperine combination significantly improves repairing of the tissue damage due to inoculation of lymphoma.	Piperine 10 mg/kg and Curcumin 50 and 100mg/kg	DAL (Dalton Ascites Lymphoma) lymphoma-bearing mice	[75]
Combination reversed the predominance of immunosuppressive infiltrating cells in the tumor microenvironment and tipped the immune balance toward an immune activation state.	Resveratrol 24 mg/ kg, Curcumin 24 mg/kg and Quercetin 12 mg/kg	BALBc mice injected 2 × 105 4T1 cells	[68]

3. CLINICAL STUDY

The effectiveness and safety of phytochemical supplementation in cancer patients receiving treatment have been assessed in randomized controlled trials with encouraging but varying results. In an effort to improve therapeutic results and lessen the negative effects of traditional cancer treatments, these trials have looked into phytochemical combinations including curcumin, resveratrol, piperine, quercetin, genistein and green tea catechins. In the clinical trials, the 79 prostate cancer patients were randomly assigned by a control diet or tomato products plus selenium, omega-3 fatty acids, soy isoflavones, grape/pomegranate juice, and green/black tea (tomato-plus) for three weeks. The ingestion decreased prostate-specific antigen in patients with prostate cancer [93]. The overall effect on tumor growth and survival rates is still unclear, despite the fact that some phytochemicals may enhance patient quality of life and lessen treatment-related toxicity. Although safety profiles have typically been positive, more study is required to determine uniform dosages and long-term effects so that these phytochemical combinations can be consistently incorporated into cancer treatment (Table 4).

Table 4: List of phytochemical Combination in Clinical Trials

Phytochemical Combination	Cancer	Status	References
Curcumin and Piperine	Cervical cancer	Recruiting	NCT06080841
Green tea and quercetin	Prostate Cancer	Recruiting	NCT06615752
Curcumin and Ursolic Acid	Prostate Cancer	Withdrawn	NCT04403568
Grape juice, pomegranate juice, tomato, green tea,	Prostate Cancer	Completed	NCT00433797 [93]

black tea, soy, selenium and PUFAs			
Sulforaphane and Allin	Prostate Cancer	Completed	NCT04046653
Genistein and Quercetin	Prostate cancer	Unknown	NCT01538316
Genistein, daidzein and glycitein	Breast Cancer	Withdrawn	NCT04880369

4. METHOD FOR ASSESSING SYNERGY OF PHYTOCHEMICALS

Phytochemical combinations leverage the susceptibility of different molecular pathways involved in the genesis of a cancer to the unique mechanisms of action of each individual phytochemical to improve treatment efficacy, reduce cytotoxicity to healthy cells and prevent the emergence of drug resistance [94]. The primary goal of combining two or more phytochemicals is to achieve positive interaction effects by proving that the combination of two or more phytochemicals is more helpful than either one alone [95]. Developing an effective method to demonstrate that the phytochemical combination offers greater advantages than either phytochemical alone is crucial to maximizing the benefits of the combination of bioactive substances. Phytochemical interactions can have potentiation, addition, synergy or antagonistic effects. Potentiation is the process by which the presence of an inactive ingredient increases the strength of an active one in a phytochemical combination that contains two chemicals, one of which is active and the other is inactive [96].The combination may have an antagonistic, synergistic or additive effect if each of the constituents is active. The total effect of additive phytochemical interactions is equal to the sum of the potencies of the mixture's constituent parts. An isobologram or combination index that displays more or less than addition is used to examine the combined effect on synergistic or antagonistic interactions [96]. Effect-based and dose-effect-based approaches are the most often used reference models for assessing synergy in phytochemical combinations.

5.1 Effect-based approach

To evaluate a favorable interaction impact, these techniques rely on the effects of each individual phytochemical in a combination [94]. Combination Subthresholding, Highest Single Agent, Response Additivity, and Bliss Independence model are the four primary techniques used in effect-based approach [94]. Cell death, viability, growth rate, and other indicators of the measurable or phenotypic effect are commonly used to assess the response.

The Combination Subthresholding is the simplest approach based on the concept that the combination of ineffective doses of drugs generates significant effects. The significant effect is defined based on P-values obtained from statistical tests by comparison with control referred to as untreated groups [94]. The observed effect is usually considered statistically significant when $p < 0.05$. Although this approach is sometimes still used, the observed effects may not be accurate and do not necessarily be representative of significant differences if the difference between what is significant or not, is not necessarily significant [94].

Since the Highest Single Agent reference model assesses whether differences are significant rather than the significance of the difference, it is more beneficial. However, this approach does not consider the expected additive effect of both phytochemicals in the combination; instead, it simply compares the phytochemical combination effect to the most effective individual phytochemical (highest single agent) [94] assumes that two phytochemicals, X and Y, are administered at dosages x and y, and that their effects are E_X and E_Y. According to Foucquier and Guedj (2015), E_{XY} is the result of combining phytochemicals X and Y. When the phytochemical combination (E_{XY}) evokes a higher response than the highest single agent (E_{XY} > max (E_X, E_Y)), there is a positive combination interaction. Since it enables the computation of a combination index (CI) using the equation, CI = max (E_X, E_Y)/ (E_{XY}). The p value of the statistical test is used to compare the effects of phytochemical combinations with the single phytochemical that is more effective in order to determine statistical significance if the CI value is positive [94].

Considering that phytochemicals effects are additive, the Response additivity technique is an improvement over Combination subthresholding and Highest single agent techniques as it compares the effects from the combination with the anticipated effects from the single phytochemical. Let's assume that a positive interaction happens when the phytochemical combination (E_{XY}) produces a stronger effect than the total of the effects of the separate medications (E_{XY} > E_X, + E_Y). The CI can be computed as CI = (E_X + E_Y)/E_{XY} In factorial analysis of variance of the individual and combined effects, the P-value indicates the importance of the interaction effect [97]. According to the bliss independence hypothesis, which assumes that phytochemicals act on distinct sites of action, each phytochemical utilized in phytochemical combinations acts independently and does not interact with the other [98]. However, this model presupposes that the observed impact is a result of both phytochemicals. The expected combined effect is defined as $E_{XY} = E_X + E_Y (1- E_X)$, where E_X and E_Y stand for the observed effects of phytochemical X and Y, respectively, and E_{XY} is the effect of phytochemical X combined with phytochemical Y. The phytochemical effects from single and combination treatments are expressed as a probability ($0 \leq E \leq 1$).

Bliss independence model assumes that both phytochemicals used in phytochemical combinations act independently and do not interfere with the other, assuming that phytochemicals act on different sites of action [98]. Nevertheless, this model assumes both phytochemicals contribute to the observed effect. The phytochemical effects from single and combination treatments are expressed in the form of a probability ($0 \leq E \leq 1$) and the expected combined effect can be defined as $E_{XY} = E_X + E_Y (1- E_X)$, where E_X and E_Y represent the observed effects of phytochemical X and Y, respectively, and E_{XY} the effect of phytochemical X combined with phytochemical Y. When using this method, the calculation index is determined as CI = $(E_X+E_Y-E_XE_Y)/E_{XY}$. When CI is less than, greater than, or equal to 1, respectively, it indicates synergy, antagonism, or additivity [94].

5.2. Dose-effect-based approach

Dose-effect-based techniques are superior to effect-based approaches because they take into account the dosage of each phytochemical that has the same quantitative impact [99]. This reference model offers important and clear definitions of antagonism, additivity and synergy while taking into account the dose-effect curves of each phytochemical [94]. The two main methods

employed in the dose effect-based approach are zero interaction potency and Loewe additivity model [94].

The most popular dose-effect-based method is the Loewe additivity model, a null reference model [99]. The isobole representation is the foundation of this concept, which defines the additive effect. This reference model is predicated on the dose equivalency principle, which states that, for any given effect, the dose an of phytochemical X is equal to the dose y_x of phytochemical Y and vice versa. Additionally it is predicated on the sham combination concept, which is different from other null reference models in that dosage y_x can be added to any dose y of phytochemical Y to provide an additive effect [100]. A hybrid method between the Bliss Independence and Loewe Additivity models, zero interaction potency is one of the most current reference models put forth for the assessment of anticipated reactions in phytochemical combinations [101]. This method, which is unaffected by the pharmacodynamics of the compounds in combination, assesses the interactions between the medications by comparing changes in the potency of the dose-response curves between individual and combined phytochemicals. It is predicated on the idea that medications are independent and do not interact with one another when combined, leading to negligible changes in their response curves [101]. This means that determining characteristics like the slope and the relative half-maximal effect concentration (EC50) depends on accurately fitting the dose-response curves which can be challenging if the data is of low quality [102].

5. CHALLENGES AND FUTURE PERSPECTIVE

Combining phytochemicals signify a new era of innovation in healthcare, providing unique therapeutic approaches that can fulfill unmet medical requirements. They possess the capability to transform treatment results and enhance patient care by integrating drugs, devices, and biologics in synergistic manners [103]. The safety of patients remains the highest priority in healthcare. Synergating phytochemicals present distinct challenges due to their varied components, possible interactions and the necessity for thorough risk assessment and mitigation strategies. Ensuring safety is vital for fostering trust between patients and healthcare professionals [104]. Assessing the efficacy of combination products is crucial for validating their clinical usefulness and therapeutic advantages. Comprehensive efficacy evaluations which include clinical trials and post-market monitoring are essential to confirm that these combinations achieve their intended results.

Synergetic effect of phytochemicals despite promising in vitro and in vivo while human clinical trials remain limited as it affects the acceptance of phytochemicals as therapeutic agents. Because many phytochemicals degrade when they are exposed to heat, light and oxygen which result in reducing their long-term stability. Phytochemicals are required in sufficient concentrations to reach target sites, the effectiveness of anticancer agents hinges on phytochemical bioavailability, pharmacokinetics and stability. Many phytochemicals have low bioavailability and stability which complicates their formulation and delivery at target site [105]. Encapsulation, nanoemulsion and liposome complexation are employed to improve solubility and oral bioavailability. While understanding absorption, distribution, metabolism and excretion of drugs is essential in pharmacokinetic research yet a lack of data complicates dosage optimization and therapeutic efficacy prediction. To tackle these issues, researchers are developing physiologically based pharmacokinetic models aimed at predicting phytochemical behavior in the

body and improving formulation strategies [106]. Leveraging synergistic strategies for cancer treatment by integrating natural products, drug repurposing, and precise molecular targeting offers a promising approach to enhancing therapeutic efficacy and minimizing adverse effects. Synergizing phytochemicals can target multiple pathways involved in cancer progression, potentially overcome resistance mechanisms, improve patient outcomes, pave the way for more personalized and effective cancer treatments. To unlock the full potential of phytochemicals synergistic effect on cancer continued research in this multidisciplinary field is essential, ultimately leading to more holistic and successful cancer therapies.

6. CONCLUSION

Combining phytochemicals may have synergistic anti-cancer effects by regulating several pathways and tumor markers. Combinations of bioactive substances may alter the compounds' biological characteristics and bioavailability. Several phytochemical combinations work in concert to prevent oxidation, inflammation, and the growth of cancer cells. In order to fully understand the mechanism of bioavailability interferences and the relationship between bioavailability and bioactivity as a result of interactions between bioactive chemicals, more research should be conducted. The ability of a combination of phytochemicals to concurrently modify different signaling pathways that promote cell death, impede cell growth and invasion, increase the sensitivity of cancer cells, and bolster the immune response may be the reason for their efficacy in cancer treatment.

ABBREVIATIONS

- VEGF : Vascular Endothelial Growth Factor
- HIF-1α : Hypoxia-Inducible Factor-1 Alpha
- ROS : Reactive oxygen species
- NF-κB : nuclear factor kappa B
- EMT : Epithelial-to-Mesenchymal Transition
- MMP : matrix metalloproteinase
- RAS: rat sarcoma
- MAPK : mitogen-activated protein kinase
- PI3K : phosphatidylinositol-3-kinase
- mTOR : mammalian target of rapamycin
- STAT : signal transducer and activator of transcription
- COX-2 : cyclooxygenase-2
- TNF-α : tumor necrosis factor alpha
- MDM2 : mouse double minute 2 homolog
- RXRα : retinoid X receptor alpha
- CDK : Cyclin-Dependent-Kinase
- LC3B-II : Light Chain 3B-II
- EGCG : epigallocatechin gallate
- PARP : Poly (ADP-ribose) polymerases
- PKC: Protein kinase C
- ERK : extracellular signal-regulated kinases
- FAK : focal adhesion kinase
- NPC: nasopharyngeal cancer
- HO : heme-oxygenase
- NGFR: Nerve Growth Factor Receptor
- EC : epicatechin
- EGC : epigallocatechin
- ECG : epicatechin gallate

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CD reviewed the literature, analysed and drafted the manuscript. PC, SM, and ZM assisted in the analysis of the articles.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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