Review

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Anticancer Activity of Phytochemicals of the Papaya Plant Assessed: A Narrative Review

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Cancer remains to be a pervasive disease as traditional treatments have plateaued in efficacy. Anticancer research continues to grow in an effort to find novel preventive and treatment measures for cancers. The papaya plant produces several biologically active phytochemicals, which exhibit anti-inflammatory, antibacterial, and anti-oxidative properties. This review explores studies examining these phytochemicals derived from the papaya plant as a potential chemopreventive agent and a cancer therapeutic. Further studies must be done to establish the papaya plant and its phytochemicals as an alternative to traditional cancer treatments.

Key Words Papaya plant, Cancer prevention, Anticancer activity, *Carica papaya*, Phytochemicals

INTRODUCTION

Despite significant innovations in the fight against cancer over the past few decades, anticancer research remains a rampant industry [1]. Cancer describes an increasing list of diseases that are caused by an unsystematic disregard for cell cycle checkpoints. Researchers continue examining novel therapeutic methods and management due to the lack of an effective treatment, combined with its increasing pervasiveness [2].

Cancer cases continue to surge while the efficacy of conventional treatments has plateaued. Moreover, conventional treatments such as chemotherapy are riddled with side-effects including toxicity, neutropenia, lymphedema, deep vein thrombosis, hair loss, etc. [3]. Alternative therapy has demonstrated halting growth of cancer cells and a decreased risk of developing cancer [4]. Research has delineated that higher intake of fruits and vegetables in a diet is linked to a lower risk of malignancies in the breast, colon, lung, pancreas, bladder, larynx, stomach, mouth and esophagus [5].

Chemoprevention is an alternative to chemotherapy which uses natural or synthetic agents to inhibit, suppress or reverse the initial stages of carcinogenesis or to prevent the invading potential of premalignant cells [6]. Chemopreventive agents have two modes of action: to prevent carcinogenesis by guarding against DNA damage or to prevent malignancy by blocking division of cells with DNA damage [7]. Using chemopreventive agents as an alternative to traditional cancer treatments is a rational approach in the management of cancer. Dietary components such as capsaicin, cucurbitacin B (CuB), flavonoids, catechins, lycopenes, benzyl isothiocyanate (BITC), phenethyl isothiocyanate (PEITC), resveratrol, and piperlongumine have demonstrated chemopreventive potential [7].

Figure 1 illustrates the chemical structures of several phytochemicals that are associated with cancer prevention. The importance of providing the chemical structure revolves around how these phytochemicals are able to react with receptors and tissues within the body to prevent cancer.

The *Carica papaya* plant, more commonly known as the papaya plant of the *Caricaceae* family, is known to have many medicinal benefits. It is a fast-growing plant commonly found in tropical and subtropical regions of the world [8]. The bark, leaf, and seeds of the plant have been used as home remedies for gastrointestinal ailments, and preventative measures for cancer in different cultures, most notably in Indian and Indigenous Australian tribe populations [1]. Table 1 demonstrates the different phytochemical components found in the *Caricaceae* plant that provide cytotoxic effects when used as a treatment in different cancers that are investigated in this review. This review discusses the chemopreventive mechanisms, and other anticancer effects of *C. papaya* and

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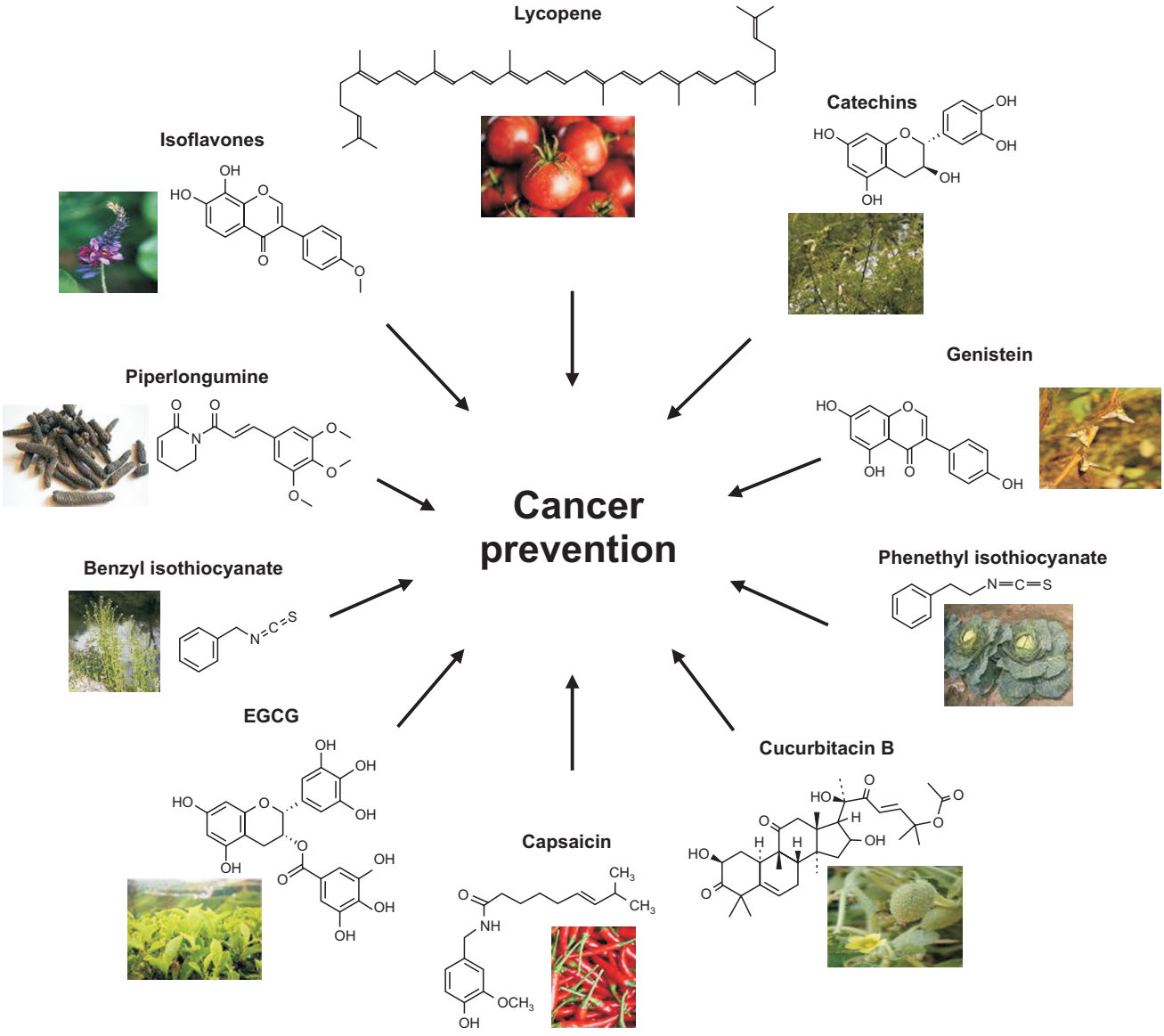

Figure 1. Representative chemopreventive and anticarcinogenic phytochemicals in edible plants. The structures and names of commonly researched phytochemicals in cancer prevention and treatment. EGCG, epigallocatechin-3-gallate. Data from Ranjan et al. (Int J Mol Sci 2019;20:4981) [7].

its ingredients. The plant's primary elements such as the bark, leaf, and seeds contain active components, namely CuB, catechins, lycopenes, BITC, PEITC, resveratrol, piperlongumine, alkaloids, glycosides, tannins, and flavonoids, which are responsible for its medicinal properties (Fig. 1) [9,10].

Figure 2 shows healing properties of the papaya plant. Its notable antiproliferative effects in cancer cells have been examined through observational and experimental studies. Other studies revealed antibacterial, anti-viral, and pro- and anti-inflammatory as well as anti-tumor properties [9,11]. Some laboratory studies have examined capability of some bioactive phytochemicals present in papaya leaves in treating breast, prostate, and colon carcinomas.

This narrative review was operated through the use of literature collected from databases such as PubMed, Embase, Scopus, Google Scholar, Web of Science. A bibliographic search was conducted using keywords 'Papaya plant', 'Cancer therapy', 'Cancer prevention', 'Cancer chemoprevention', 'Anticancer activity', '*Carica papaya*', 'Papaya plant extracts', 'Phytochemicals', etc. Further, the inclusion criteria for the article consist of, (i) a peer-reviewed journal article, (ii) relevant to the article that was published within the last 15 years, and (iii) in vitro cell-culture-based studies.

Table 1. Caricaceae plant constituents with cytotoxic effects on cancer cell growth

Caricaceae plant constituent	Phytochemical	Treatment	References
Papaya juice (0.28–28 mg/mL)	Lycopene	Pure lycopene extracted (3–30 g/mL) Colon cancer: 10 μM Breast cancer: 3.5 μM (48 h) 1 μM (48 h) 5 μM (48 h)	[12,27]
Extract of papaya seed or pulp (0.1–100 g/mL)	BITC	Pure BITC (10 M) Treatment: 6.5–12 μmol	[7,27]
Caricaceae plant	Quercetin	25 μM	[12]
Leaves	α-Tocopherol	2.5 ± 0.4 μg/mL	[1,12]
Caricaceae plant	Resveratrol	10–50 μM	[2]
Caricaceae plant	PEITC	10 μmol	[7]
Shoot	Isoflavone	40,000 μg/day for 3–6 weeks	[1,7]
Caricaceae plant	Piperlongumine	100,000–300,000 μg/kg	[7]

BITC, benzyl isothiocyanate; PEITC, phenethyl isothiocyanate.

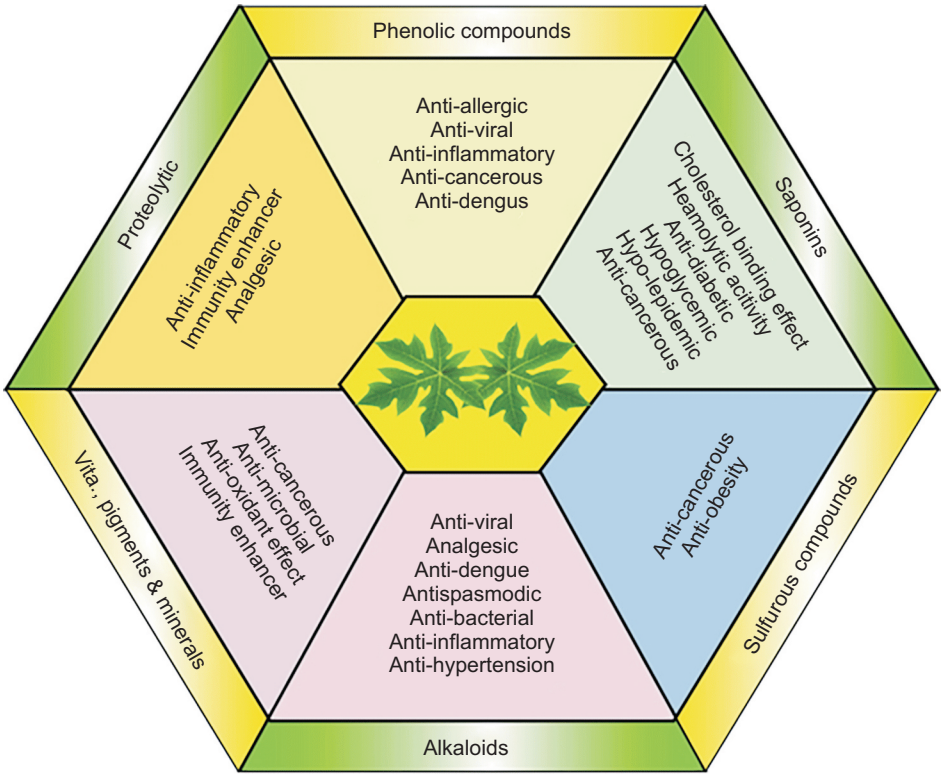

Figure 2. Chemopreventive and other health beneficial effects of phytochemicals derived from *Carica papaya*. Data from Sharma et al. (Oxid Med Cell Longev 2022;2022:2451733) [39].

MAJOR CHEMOPREVENTATIVE AND ANTICARCINOGENIC COMPONENTS OF PAPAYA PLANT

Alkaloids

Alkaloids are compounds that have a nitrogenous group in their chemical structure; they can be found in several plants and fungi [2]. Alkaloids are commonly used in pharmaceutical drugs–including those involved in anti-cancer treatments [2]. Carpaine and capsaicin are two of the main alkaloids found in the papaya plant that possess chemopreventive and tumor suppressing properties [7,12].

Glycosides

Glycosides are commonly described as sugar molecules bonded to another compound [13]. The primary glycosides found in the papaya plant are glucosinolates and cyanogenic glucoside [12]. These molecules are important for increasing the total availability of antioxidants within the blood while also reducing lipid peroxidation levels [12].

Saponins are another class of plant-based glycosides that confer health benefits by interfering with the replication of DNA and thereby preventing the proliferation of cancer cells [2,14]. Saponins are also known to be antimicrobial, anti-malarial, anti-allergenic, anti-diabetic, and anti-inflammatory as

well as anti-carcinogenic in nature [14,15].

Tannins

Tannins (tannic acids) are water-soluble polyphenols; their antioxidant properties protect against carcinogenesis as seen in cultured HL-60 cells [14,16,17]. They act by binding to proteins, basic compounds, pigments, larger-molecular compounds, and some metallic ions to limit the damage caused by reactive oxygen species (ROS) [14,18,19]. ROS can cause cellular damage and spontaneous mutations [18,19].

Flavonoids

Flavonoids are phytochemicals, found naturally in plants and fruits [20-22]. There are numerous flavonoids, which can be classified into the following categories: flavones, flavonols, flavanones, isoflavonoids, flavanols, and anthocyanins [23-25]. The papaya plant is known to produce the following flavonoids: Quercetin 3-*O*-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranoside], Kaempferol 3-*O*-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyl-(1→2)-α-L-rhamnopyranoside] [26], quercetin 3-rutinoside, myricetin 3-rhamnoside, kaempferol 3-rutinoside, quercetin, and kaempferol [24,26]. Numerous studies provide evidence that flavonoids have anti-inflammatory [21] and antioxidant [20] properties [26].

BITC

The papaya pulp and seed contain considerable amounts of BITC, a major group of isothiocyanates (ITCs) [27]. The BITC extract has been evaluated for its effect on cancer cell growth [27]. This phytochemical can suppress growth of proliferating cancer cells and act as an antioxidant through electrophilic reactions [17,27]. Studies have also examined its ability to suppress the formation of chemically induced tumors or the growth of cancer xenografts in vivo [27]. BITC makes tumors more susceptible to chemotherapy and has demonstrated anticancer properties in patients with leukemia, breast cancer, prostate cancer, lung cancer, pancreatic cancer, colon cancer, and hepatocellular carcinoma [27].

Lycopene

Lycopene is an acyclic, non-provitamin subtype of carotene that gives fruits and vegetables, such as tomatoes and papayas, their red and/or orange color [28]. Lycopene is also an antioxidant, and studies have shown that it may play a role in preventing carcinogenesis, particularly that in the prostate.

Table 2. Chemopreventive and anticarcinogenic effects of lycopene and underlying mechanisms of action

Type of cancer explored with phytochemical lycopene	Mechanism of action	Results	References
Breast cancer	Blocks NF-κB, API, STAT3 signaling. Inhibits breast tumor formation by immunological regulation of intra thymic T-cell differentiation. Inhibits β-signaling and cell cycle arrest.	Hinders the growth of breast cancer by blocking the NF-κB signaling. Shows anti-proliferative effects in MCF-7, T47D, HL-60, and HEPG2 cell lines. Prevents hydrogen peroxide (H_2O_2) and N-nitrosodiethylamine induced DNA damage in HepG2 cells.	[7,32]
Prostate cancer	Prevents cell division in the G0-G1 cell cycle phase. Reduces carcinogen induced phosphorylation of regulatory proteins such as p53 and Rb antioncogenes. Inhibits NF-κB signaling cascade.	Papaya seed extract effectively induces apoptosis and cell death in prostate cancer cells and leukemic HL-60 cells. Lycopene's anti-prostate cancer effects as a result that it predominantly accumulates in prostate tissue as compared to others. Decreases serum PSA levels, clinical diagnostic indicators and BPH symptoms in elderly men with BPH who were administered lycopene supplements (at doses of 15 mg/day) for six months. A higher intake of lycopene is linked to a decreased risk of prostate cancer.	[7,17,31]
Colon cancer	Suppresses phosphoinositide 3-kinase/Akt signaling pathway in colon HT-29 cells. Increases phosphorylation of β-catenin genes, and the amount of nuclear cyclin-dependent kinase inhibitor p27. Inhibits activation of retinoblastoma tumor suppressor protein via phosphorylation.	Effectively inhibits the growth of colon cancer cells through suppression of the Akt signaling pathway and modulation of downstream molecules and genes. Aqueous extract of the leaves (1.25-27 mg/mL) displays a concentration-dependent anticancer effect on DLD-1, and MCF-7.	[32,33]

MCF-7, breast cancer cell line; T47D, breast cancer cell line; HL-60, acute promyelocytic leukemia; HepG2, hepatocellular carcinoma; PSA, prostate-specific antigen; BPH, benign prostatic hyperplasia; p53, tumor protein 53; Rb, retinoblastoma protein; HT-29, colon adenocarcinoma; p27, cyclin-dependent kinase inhibitor 1B; Akt, protein kinase B; DLD-1, colon cancer cell line.

The anticarcinogenic efficacy of lycopene was evaluated at 3 to 30 μg/mL [27]. Lycopene has been shown to protect against DNA damage and reduce inflammation. The anticancer activity of lycopene has been studied in a variety of cancer types, including breast, ovarian, and prostate cancer.

CHEMOPREVENTIVE AND ANTICARCINOGENIC EFFECTS OF REPRESENTATIVE INGREDIENTS OF PAPAYA PLANTS AND THEIR UNDERLYING MECHANISMS

The anticarcinogenic and chemopreventive effects of the papaya plants' phytochemicals are outlined in Tables 2–8. Extensive research revealed great promise of these compounds in mitigating prostate, breast and colon cancers. Not all of the phytochemicals mentioned in the introduction were included in the results due to the lack of research in the three cancers specified. Seven of them are discussed below.

Lycopene

Lycopene's anti-carcinogenic properties are explained by two main processes: nonoxidative and oxidative mechanisms. Lycopene also plays a major role in preventing DNA damage. It has been proposed that lycopene prevents carcinogenesis by safeguarding vital cellular molecules such lipids, lipoproteins, proteins, and DNA [29]. Cells interact with one another through crucial processes, which supports the healthy cell and organ function [29]. By preventing aberrant cell proliferation, the use of lycopene looks to be a promising anticancer strategy for controlling the cell cycle. Additionally, it controls cell-cycle progression and prevents cancer cells from growing out of control [30]. By expanding gap-junctions between cells, lycopene improves communication between cells.

Lycopene blocks several signaling pathways such as NF-κB, API, STAT3, 3-kinase/Akt as stated above in Table 2, thereby inhibiting the growth of cancer cells [7,31-33]. The underlying mechanism of defense against preneoplastic lesions caused by carcinogens in the rat liver is mediated through lycopene-induced regulation of cytochrome P450E1 [28]. Additionally, preliminary in vitro studies suggest that lycopene inhibits the ability of insulin-like growth factor to stimulate cellular proliferation in a variety of cancer cell lines [31]. Lycopene treatment to SHN retired mice, which is a high mammary tumor strain, suppressed breast tumor formation through immunological regulation of intra-thymic T-cell differentiation [30].

Based on the evidence presented in Table 2, there is strong evidence that lycopene has significant anticancer activity. This activity is thought to be partly due to the ability of lycopene to scavenge free radicals and protect cells from oxidative damage. Additionally, lycopene has been shown to inhibit the growth of cancer cells and induce apoptosis [6,34].

BITC

Through DNA damage and the induction of apoptosis by the mechanisms summarized in Table 3, BITC was shown to curb migration and proliferation in prostate, breast and colon cancers [24]. It arrested the cell cycle during the G2/M phase in both prostate and breast cancer cells, thereby decreasing their proliferation [7,35]. It also inhibited MMP-2 and MMP-9 pathways in both breast and colon cancers, although in different ways [7].

Breast cancers showed marked reduction in the PKC and mitogen-activated protein kinase (MAPK) pathways but colon

Table 3. Chemopreventive and anticarcinogenic effects of BITC and underlying mechanisms of action

Type of cancer explored with phytochemical BITC	Mechanism of action	Results	References
Breast cancer	Activates the p53-LKB1 and p73-LKB1 axis to intensify p53 signaling and PI3K/AKT/FOXO pathways. Downregulates MMP-2/9 through the signaling pathways PKC and MAPK. Induces apoptosis and G2/M cell cycle arrest.	Sensitizes tumors to chemotherapy. Demonstrates anticancer effects by activating p53 signaling in breast cancer cells. A study reports that BITC oppresses the mammosphere-constituting efficacy of breast cancer cells.	[7,37]
Prostate cancer	Induces apoptosis and G2/M cell cycle arrest. Induces apoptosis in HL-60 cells.	Promotes apoptosis through the inhibition of several key signaling pathways.	[7,17]
Colon cancer	Decreases cholesterol levels which inadvertently inhibits the Akt signaling pathway. Inhibits NF-κB DNA binding activity through suppression of MMP-2, MMP-9 and urokinase-plasminogen activator (u-PA). Reduced phosphorylation of JNK1/2, ERK1/2.	Inhibits human colon cancer cell migration and invasion.	[7,38]

BITC, benzyl isothiocyanate; p53, tumor protein 53; LKB-1, liver kinase B1; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; FOXO, forkhead box O; MMP, matrix metalloproteinase; PKC, protein kinase C; MAPK, mitogen-activated protein kinase; HL-60, acute promyelocytic leukemia; JNK, c-Jun N-terminal kinase; ERK, extracellular signal-regulated kinase.

Table 4. Chemopreventive and anticarcinogenic effects of PEITC and underlying mechanisms of action

Type of cancer explored with phytochemical PEITC	Mechanism of action	Results	References
Breast cancer	Downregulates STAT3 and HER2 signaling pathways.	When combined with paclitaxel, it shows anti-proliferative effects by instigating apoptosis and cell cycle arrest. A study indicates that oral management of 10 μmol of PEITC for 10 days suppresses breast cancer cell metastasis to other organs. In a laboratory experiment, PEITC-modified mice carrying breast tumor xenografts demonstrate immune modulation. MDSCs and T regulatory lymphocytes were greatly decreased by PEITC therapy, which inhibited the growth of breast tumors. Treatment results in a remarkable suppression of the breast tumor growth by depleting T regulatory lymphocytes and myeloid derived tumor suppressor cells.	[7]
Prostate cancer	Regulates cell invasion by microRNA-194. Reactivates RASSF1QA by aiding apoptosis and G2/M cell cycle arrest.	A study by the National Cancer Institute demonstrates that HDAC activity is inhibited by ITC in prostate and colorectal cancer cells.	[7]
Colon cancer	Induces apoptosis and G2/M cell cycle arrest. Inhibits SOS-1, PKC, ERK1/2, and Rho A. Stimulates apoptosis by activating mitochondrial caspases.	Possess antimetastatic properties that reduce the invasion and migration of cancerous cells through alteration of cell signaling pathways.	[38]

PEITC, phenethyl isothiocyanate; MDSC, myeloid-derived tumor suppressor cells; RASSF1A, Ras association domain family member 1A; HDAC, histone deacetylase; ITC, isothiocyanate; SOS-1, son of sevenless homolog 1; PKC, protein kinase C; ERK, extracellular signal-regulated kinase; Ras, rat sarcoma gene; Rho A, Ras homolog family member A.

Table 5. Chemopreventive and anticarcinogenic effects of CuB and underlying mechanisms of action

Type of cancer explored with phytochemical CuB	Mechanism of action	Results	References
Breast cancer	Inhibits JAK-STAT3, VEGF/FAK/MMP-9 MAPK, HER2 integrin signaling pathways. Suppresses HER2-integrin signaling which downregulates α6 and β4 integrins.	Exceptionally displays anti-angiogenic effects in metastatic cancer cells. Limits the growth of breast tumors. Integrins α6 and β4 that are overexpressed in breast cancer cells are downregulated as HER2-integrin signaling is suppressed. Suppresses the growth of breast cancer cells when combined with gemcitabine or docetaxel. Inhibits VEGF/FAK/MMP-9 signaling in highly metastatic breast cancer cells and has anti-angiogenic properties.	[7]
Colon cancer	Decreases phosphorylation of JAK2 and STAT3. Reduces M2 macrophage polarization.	Reduces the metastasis of colorectal cancer.	[7,20]

CuB, cucurbitacin B; JAK, Janus kinase; VEGF, vascular endothelial growth factor; FAK, focal adhesion kinase; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase.

cancers showed inhibition of NF-κB DNA binding activity, decreased urokinase-plasminogen activator and reduced phosphorylation of JNK1/2 and ERK1/2 [7,36,37]. In breast cancer, it activated p53-LKB1 and p73-LKB1 and stimulated p53 signaling, thereby inadvertently increasing susceptibility to chemotherapy [7]. p53 is an important cell cycle regulator positioned to induce apoptosis in aberrant cells. Thus, the increased p53 levels would intensify the reaction to chemotherapy-induced damage and decrease cancerous growth.

PEITC

Both PEITC and BITC have similar effects on cancer cell

Table 6. Chemopreventive and anticarcinogenic effects of flavonoids and underlying mechanisms of action

Type of cancer explored with phytochemical flavonoid	Mechanism of action	Results	References
Breast cancer	Isoflavone inhibits c-erB-2, MMP-2, and MMP-9 signaling pathways. Also affects IGF-1R/p-Akt signaling transduction. Quercetin controls the NF-κB signaling system through modulation of target genes Bcl-2 and Bax.	By controlling the NF-B signaling system and its target genes Bcl-2 and Bax, it causes tumor cell apoptosis. After 4 weeks of tumor inoculation, a study reveals that quercetin and green tea coupled with a diet exert a stronger inhibition of tumor growth in mice with malignancies than green tea alone, and this combination therapy reduces the tumor growth by 47% compared to control. This cotreatment boosts non-methylated EGCG by 1.8 times while also enhancing tissue concentrations of total green tea polyphenols by 1.5 times.	[6,7]
Prostate cancer	Deactivates tumor suppressor gene and oncogene products via cytochrome p450 isozyme inhibition. DNA methylation of CpG islands via DNMT, histone acetylation via HAT and histone deacetylation via HDAC.	Isoflavones improve the effectiveness of current treatments by sensitizing cells to chemotherapy. In 2018, a clinical trial on isoflavones where 40 mg of daily purified isoflavones and placebo were monitored for 2-6 weeks. The results showed a change in levels of Ki-67 in prostate tumor cells.	[7,36]
Colon cancer	Suppresses K-Ras and β-catenin expression.	Flavonoids lutein and zeaxanthin reduce the risk of colon cancer. Beta-Caroteine inhibits the growth of tumors in the skin, lung, liver, and colon.	[6,41]

c-erB-2, humanized epidermal growth factor receptor 2; MMP, matrix metalloproteinase; IGF-1R, insulin-like growth factor 1 receptor; p-Akt, phosphorylated protein kinase B; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; EGCG, epigallocatechin-3-gallate; p450, cytochrome p450 enzyme; CpG, cytosine-phosphate-guanine; DNMT, DNA methyltransferase; HAT, histone acetyltransferase; HDAC, histone deacetylase inhibitors; Ki-67, tumor cell proliferation and growth marker; K-Ras, kirsten rat sarcoma virus.

Table 7. Chemopreventive and anticarcinogenic effects of resveratrol and underlying mechanisms of action

Type of cancer explored with phytochemical resveratrol	Mechanism of action	Results	References
Breast cancer	Inhibits NF-κB and MMP-9 activity in breast cancer cells, blocking their ability to migrate. Decreases DNA methyltransferases.	Numerous intracellular targets of resveratrol were discovered by extensive in vitro research, and these targets include cell proliferation, inflammation, apoptosis, angiogenesis, invasion, and metastasis. The PI-3K/AKT and the MAPK pathways, two important survival cascades that are commonly abnormally activated in human malignancies, have both been found to be inhibited by resveratrol.	[7,25]
Prostate cancer	Induces apoptosis by targeting the Akt/microRNA-21 pathway.	Suppresses prostate cancer by decreasing cell migration and proliferation and promoting apoptosis.	[6]
Colon cancer	Mediates the ratio of T regulatory (Treg) and T helper lymphocytes (Th17), and the cytokines IL-10, TGF-β1, IL-6, and IL-17 plasma levels. Dampens the secretion of IFN-γ and TNF-α.	Suppresses tumor/cancer cell growth and is also a probable chemoprophylaxis agent for colorectal tract.	[6]

MMP, matrix metalloproteinase; PI-3K, phosphoinositide 3-kinase; AKT (Akt), protein kinase B; MAPK, mitogen-activated protein kinase; Treg, regulatory T cell; Th17, T helper 17 cell; IL, interleukin; TGF-β1, transforming growth factor beta 1; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor-alpha.

migration and invasions as shown in Table 4. They achieved cell cycle cessation through the alteration of cell signaling pathways [7]. In colon cancer, PEITC inhibited son of sevenless homolog-1, PKC, ERK1/2 and Ras homolog gene family member A [37,38]. These alterations induced apoptosis and cell cycle arrest in the G2/M phase in both prostatic and colonic cancer cells [38]. A study conducted on anti-metastatic benefits of PEITC in a breast cancer model indicated that oral administration of 10 μmol of PEITC for 10 days resulted in suppression of breast cancer cell metastasis to other organs

Table 8. Chemopreventive and anticarcinogenic effects of piperlongumine and underlying mechanisms of action

Type of cancer explored with phytochemical piperlongumine	Mechanism of action	Results	References
Breast cancer	PIK3/Akt/mTOR inhibits autophagy-mediated apoptosis.	Piperiongumine given to rats and mice at doses ranging from 100 to 3,000 mg/kg did not exhibit any harmful effects. The $t_{1/2}$ was determined to be 1.42 hours and 0.84 hours after oral administration of 5 mg/kg and 10 mg/kg piperlongumine, respectively. The Cmax values were 884.31 g/L and 201.42 g/L.	[7]
Colon cancer	Increases ROS generation by targeting the GSH antioxidant systems. Inhibits various signaling pathways mediated by: Akt and ERK1/2, MAPK/ERK kinase (MEK), and JNK.	Piperlongumine exacerbates apoptosis through extensive ROS generation and inhibition of signaling pathways.	[7,43]

PIK3, phosphoinositide 3-kinase inhibitors; Akt, protein kinase B; mTOR, mammalian target of rapamycin inhibitor; ROS, reactive oxygen species; GSH, glutathione; ERK1/2, extracellular signal-regulated kinase 1/2; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinases; MEK, methyl ethyl ketone; JNK, c-Jun N-terminal kinase.

[7]. When PEITC was combined with paclitaxel, it showed anti-proliferative effects by instigating apoptosis and cell cycle arrest [39]. PEITC treatment resulted in a remarkable suppression of the breast tumor growth by depleting T regulatory lymphocytes and myeloid derived tumor suppressor cells [7].

CuB

Cucurbitacin B is a tetracyclic triterpenoid with chemopreventive and anticarcinogenic activity in breast and colon cancers as shown in Table 5. In both cancers it showed anti-angiogenic effects by inhibiting STAT3 signaling, but, in breast cancer it also inhibited VEGF/FAK/MMP-9 [7,20]. By preventing HER2-integrin signaling and downregulating integrins α6 and β4, it limited the growth of breast tumors [7]. It is likely that the cancer cells are deprived of their proliferative abilities because of the reduction of intracellular signaling pathways. This compound also inhibited colon cancer growth and migration; however, this reduced M2 macrophage polarization [20].

Flavonoid

Table 6 shows the mechanisms by which flavonoids repressed signal transduction pathways and activated apoptosis. Cyclins and cyclin-dependent kinases are responsible for cell cycle adherence [40]. It has been shown that the flavonoids work through the alteration of these molecules to halt cell cycle progression [40]. In prostate cancer, it inhibited cytochrome P450 isozymes to deactivate oncogene products [7]. Their epigenetic modifications induced cell cycle disruption in prostate and breast cancer [25,40]. DNA methylation of CpG islands via DNA methyltransferases, histone acetylation via histone acetyltransferases and histone deacetylation via histone deacetylases halted the propagation of aberrant prostatic cells [40]. Breast cancer cell reduction was achieved by targeting the c-ERB-2, MMP-2, MMP-9, and IGF-1R/p-Akt signaling pathways [7,41].

Other flavonoids lutein and zeaxanthin have suppressed K-Ras and β-catenin expression [41]. The flavonoid quercetin has been shown to inhibit azoxymethane/dextran sodium sulfate induced colon in mice [42]. The mice had initially shown a decline in leukocytes and red blood cells after the induction which was restored upon quercetin administration [42]. It decreased the formation of aberrant crypt foci within the colon cells and inhibited the tumor growth [42].

Resveratrol

Resveratrol is shown to induce apoptosis and suppress cancer cell migration by a variety of mechanisms detailed in Table 7. In both prostate and colon cancers, resveratrol inhibited the Akt signaling pathway [7,32,41]. In breast cancer, it inhibited NF-κB and MMP-9, blocked cancerous migration, and decreased cell proliferation, inflammation, angiogenesis, invasion, and metastasis [32,41]. The phosphatidylinositol-3 kinase/AKT and the MAPK pathways, two important survival cascades that are commonly abnormally activated in human malignancies, have been found to be inhibited by resveratrol [41]. Chromatin modifications in breast cancer arose as a consequence of decreased DNA methyltransferase [25]. By targeting the reduced glutathione (GSH) antioxidant system, it increased ROS production in colon cancer [19,41].

Piperlongumine

Piperlongumine is an alkaloid compound noted for its beneficial roles in colorectal and breast cancer. The mechanisms of action listed in Table 8 showed how this compound works to exacerbate apoptosis [43]. Induced ROS generation is highly damaging to cancerous cells that are often subjected to more oxidative stress than normal cells [43,44].

The ability of piperiongumine to impair various cell cycle pathways allowed this compound to incite cellular damage

[43]. In breast cancer, piperlongumine inhibited the PIK3/Akt/mTOR signaling. The inhibition of these pathways disabled autophagy-mediated apoptosis. Piperlongumine inhibited Akt, ERK1/2, MAPK/ERK, and JNK pathways in colon cancer. These pathways all played a role in cell differentiation, growth, and stress [43,45,46]. This compound was selectively cytotoxic against cancer cells, stimulated genotoxicity as an alternative method for killing cancerous cells, had excellent oral bioavailability in mice, restricted cancer progression in mice, and had only minor overall systemic toxicity [16].

COMMON CHEMOPREVENTIVE AND ANTICARCINOGENIC TARGETS OF PHYTOCHEMICALS DERIVED FROM PAPAYA PLANTS

The phytochemicals comprising the papaya plant affect the three targets (inhibition of cell proliferation, inhibition of angiogenesis, and prevention of metastasis) of tumor progression as depicted in Figure 3. Phytochemicals show chemopreventive effects by inhibiting key events in tumor initiation and progression which reverses the premalignant stage. These agents also inhibited or slowed tumor progression in addition to promoting cell differentiation and preventing tumorigenesis [47]. Of the chemicals listed, the most notable actions invlove ROS generation, and the inhibition of cell signal pathways to induce apoptosis. Inhibiting these signals defied cancerous ambition of cell growth, development, differentiation, migration, and overall survival [48]. These two factors in conjunction were adequate in abetting cancer diminution.

CONCLUSION

The *C. papaya* plant produces several bioactive phytochemicals that have shown cancer chemopreventive and anticarcinogenic potential. These include lycopene, CuB, BITC, PEITC, flavonoids, piperlongumine and resveratrol that act mainly by inhibiting tumor growth signaling pathways and inducing apoptosis or cell cycle arrest. Various observational and experimental studies accompanied with repeatable results bolster the use of bioactive extracts from the papaya plant for anticancer formulations in place of conventional treatments. More studies should be conducted to evaluate the efficacy of these phytochemicals in vivo as well as in vitro. Further studies will provide actionable evidence to assess whether chemopreventive and anti-carcinogenuc components of extracts from the papaya plant can be used as alternatives for conventional cancer treatments.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

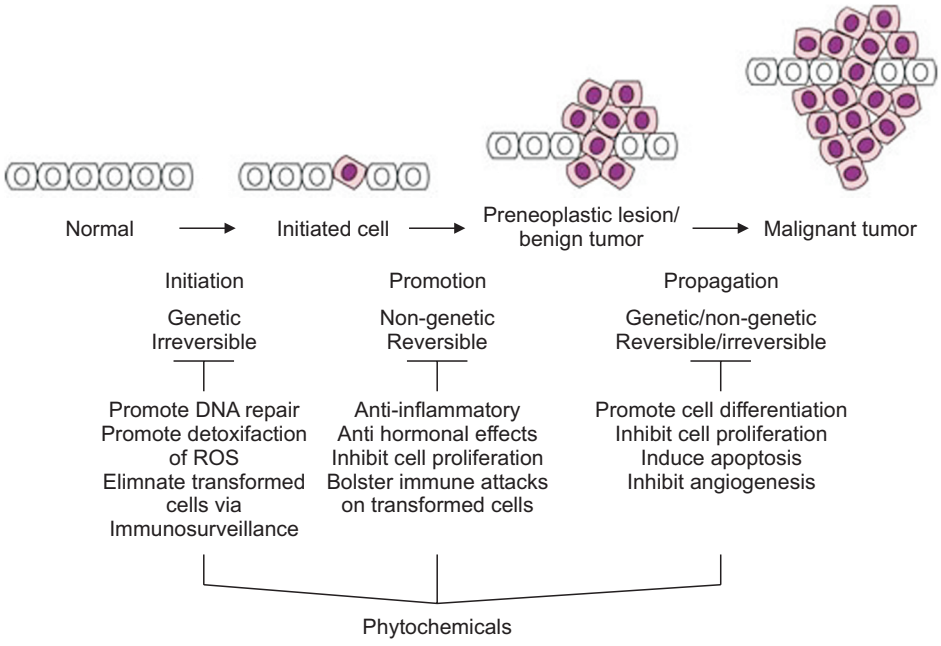

Figure 3. Sites of action of chemopreventive phytochemicals in multistage carcinogenesis. Data from Kotecha et al. (Oncotarget 2016;7:52517-29) [42].

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