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Review

Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents

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ABSTRACT

Cancer is one of the leading causes of death and significantly burdens the healthcare system. Due to its prevalence, there is undoubtedly an unmet need to discover novel anticancer drugs. The use of natural products as anticancer agents is an acceptable therapeutic approach due to accessibility, applicability, and reduced cytotoxicity. Natural products have been an incomparable source of anticancer drugs in the modern era of drug discovery. Along with their derivatives and analogs, natural products play a major role in cancer treatment by modulating the cancer microenvironment and different signaling pathways. These compounds are effective against several signaling pathways, mainly cell death pathways (apoptosis and autophagy) and embryonic developmental pathways (Notch pathway, Wnt pathway, and Hedgehog pathway). The historical record of natural products is strong, but there is a need to investigate the current role of natural products in the discovery and development of cancer drugs and determine the possibility of natural products being an important source of future therapeutic agents. Many target-specific anticancer drugs failed to provide successful results, which accounts for a need to investigate natural products with multi-target characteristics to achieve better outcomes. The potential of natural products to be promising novel compounds for cancer treatment makes them an important area of research. This review explores the significance of natural products in inhibiting the various signaling pathways that serve as drivers of carcinogenesis and thus pave the way for developing and discovering anticancer drugs.

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1. Introduction

Despite the development of various treatment strategies, cancer remains a major cause of death worldwide [1,2]. Cancer is generally described as a pathological condition characterized by uncontrolled growth and proliferation of cells due to the accumulation of genetic mutations [3,4]. Cancer's incidence and mortality rate rise exponentially, with 19.3 million new cancer cases and approximately 10 million deaths in 2020 [5]. Cancer is commonly treated using conventional treatments such as radiotherapy, chemotherapy, and surgical removal; however, cells' resistance to these therapies reduces their effectiveness [1]. The increasing incidence of deaths due to cancer requires efficient the development of therapeutic approaches that pose lower cytotoxic side effects and resistance. Natural compounds exhibit various beneficial activities that include improving health and treatment of cancer.

Natural products are naturally occurring compounds that possess biological activities derived from abundant natural resources such as plants. Many currently used therapeutic drugs are derived from natural resources such as alkaloids, taxanes, and flavonoids [6]. Recently, chemotherapy using natural compounds has gained increased attention to improve the therapeutic index of specific anti-neoplastic drugs [7]. Moreover, cancer treatment by natural compounds, including phytochemicals, minerals, and vitamins, has shown promising results against various malignant tumors [8,9]. In this regard, natural compounds with potent antitumor activity and minimum toxicity in healthy tissues have been suggested to study their synergistic efficacy with traditional anticancer drugs [10,11]. Natural products have displayed selective benefits against cancer cells compared to normal cells, but their chemical structures also act as models for developing novel drugs. These models formulate drugs with similar or better benefits than existing natural products with lower side effects and resistance [12]. One such interesting option is chemoenzymatic biotransformation which uses common natural products as substrates to generate chemically diverse and well-characterized libraries of natural product derivatives[13]. There have been several modifications to this tool, and one among them is using the secretome (blend of enzymes) of specific fungi instead of using an intact microorganism or a pure enzyme to obtain chemically diverse natural product derivatives [14]. The utilization of secretome takes the use of diverse enzymes' catalytic promiscuity [15]. This technology has been successfully used to generate specific libraries of stilbene dimers [16,17] and phenylpropanoids [14]. Phenylpropanoids as secondary metabolites have been shown to possess anticancer properties by virtue of their potential antioxidant activities [14,18,19]. Phenylpropanoid derivatives such as caffeic and ferulic acids represent important substrates as relevant building blocks in drug discovery [20,21]. Previous research has shown that using these molecules as the starting material for the biotransformation of more complicated compounds using a purified enzyme has been successful. Previous studies have demonstrated the successful use of these compounds as the starting material for the generation of more complex compounds through a biotransformation process using a purified enzyme [22,23]. Therefore, natural products and their derivatives could be better chemotherapeutic agents due to their high selectivity, reduced cost, and low toxicity [24].

Various cell signaling pathways are altered in different tumor types. Cellular signaling pathways are complex and interconnected communication networks of interacting molecules that regulate the biological activities of the cells [25]. Cells receive information from different growth factor receptors and integrate this information to regulate different cellular processes such as cell proliferation, cell death, protein synthesis, cell motility, differentiation, cell architecture, and polarity [26]. Signaling pathways regulate cellular development and bring about different changes in different cell types. Multiple signaling pathways regulate cell survival, proliferation, and motility. Therefore, cancer cells can proliferate through an alternative signaling pathway when a mutationally activated pathway is blocked by an inhibitor [26].

Thus, an advanced treatment for cancer requires effective combination therapies such as signaling inhibitors or a combination of signaling inhibitors with DNA damaging chemotherapeutic agents [27]. Therefore, understanding the intricacy of these pathways is essential for studying tumor cell behavior. Several pathways have been identified to be frequently altered in cancer, such as the cell cycle pathway, PI3K/Akt, and Ras/MAP-Kinase pathways [28]. In addition, aberrations in the Wnt/β-catenin signaling have also been observed across different tumor types [29–31]. Despite having vast knowledge of the molecular mechanism of these cancer-associated cellular signaling pathways, the chemotherapeutic approaches targeting the oncogenic biomarkers are limited [28]. Therefore, a thorough understanding of the changes in cell signaling pathways is essential to identify potential therapeutic targets. Many natural compounds have shown numerous anticancer activities in different cancer types. Therefore, this review will discuss the comprehensive function of some major natural compounds in various cancers. Additionally, (Table 1) discusses additional natural compounds with their role in cancer prevention besides the important ones that have been reviewed extensively here.

2. Targeting signaling pathways by natural products

Natural compounds can target various signaling pathways, thus impacting the molecular activity of cells. Consequently, they can be used as potential adjuvants in cancer therapy. Significant advancements have been made in treating malignant tumors through surgery, chemotherapy, and radiotherapy. However, the development of invasive or diffuse cancers is often associated with poor patient diagnosis and remains a major obstacle in cancer treatment [32]. Latest studies show that cancer stem cells (CSCs), capable of initiating tumor and self-renewal, are responsible for tumor relapse and resistance to chemotherapeutic treatment [33–35]. Thus an elevated CSCs population leads to poor patient prognosis and ineffectiveness of multiple anticancer treatments (Fig. 1). The following sections highlight the importance of various natural compounds in targeting aberrated cell signaling pathways in cancer (Fig. 2).

2.1. Honokiol

Honokiol is a natural phenolic cytotoxic compound produced by *Magnolia grandiflora* L. [Magnoliaceae] and is used in traditional medicines in most Asian countries [36]. Honokiol exhibits anti-inflammatory, anti-angiogenic, anti-oxidative and anti-tumor activities [37,38]. It has been reported to suppress the expression of cyclooxygenase-2, prostaglandin E2, proliferating cell nuclear antigen and tumor necrosis factor-alpha, interleukin (IL)− 1β, and IL-6 in skin cancer [39]. Moreover, honokiol treatment induced apoptosis in SKH-1 mice in which skin tumor was induced through UVB. The apoptosis in skin cancer was facilitated through the activation of p53, DNA fragmentation, caspase activation, and poly (adenosine 5′-diphosphate-ribose) polymerase (PARP) cleavage [39].

Honokiol has also been reported to exhibit anticancer properties in breast cancer [37,40]. In triple-negative breast cancer cell line, MDA-MB-231, honokiol inhibited phospholipase D and Ras activation [37,40]. It also inhibited nuclear factor-kappa B (NF-kB), COX-2, Prostaglandin E2, and cellular signaling mediated by Src/epidermal growth factor receptor [37]. Recently, Honokiol has been found to sensitize breast cancer cells to doxorubicin by downregulating the expression of miR-188–5p via FBXW7/c-Myc signaling [41]. In addition to breast cancer, Honokiol has also displayed anticancer activities in ovarian cancer as it was found to induce apoptosis in ovarian cancer cells through the activation of caspases and cleavage of PARP. Moreover, treatment with honokiol resulted in the accumulation of ovarian cancer cells in the sub-G_0/G_1 phase [37,42]. It has also been reported that Honokiol exerts its anticancer properties in ovarian cancer through the AMP-activated protein kinase/mechanistic target of rapamycin (AMPK/mTOR) signaling pathway as it activates AMPK and reduces the

Table 1
Comprehensive list of natural compounds with their associated anti-cancer activities.

Natural compound	Source	Type of cancer	Outcome	Reference (s)
Formononetin	Red clover	Gastric cancer	• Inhibition of cell proliferation in MGC803 cells • Inhibition of the migration in SGC7901 tumor cells via Wnt/β-Catenin and Akt/ mTOR pathway	[166,167]
Honokiol	*Magnolia officinalis* [Magnoliaceae]	Colon cancer, Oral cancer, Thyroid cancer	• Recruitment of Jagged-1 and Hes-1 towards downstream gene target • Downregulation of CSC marker DCLK1 • Downregulation of CD44 and Wnt / β-catenin (SP) receptor inhibitor	[168,169]
Curcumin	Turmeric	Colon cancer, Gastric cancer, AML, Breast cancer, Head and neck cancer, Lung cancer	• Reduction of CD44 and CD166 expression in chemoresistant colon cancer • Inhibition of tumor growth of ALDH+ /CD133 + cells • Downregulation of Gli-1, Notch-1, and cyclin D1 • Downregulation of the mRNA and the protein expression of cyclin D1	[170–172]
Ursolic acid and Koetjapic acid	Apples, pears, and prunes	Colon cancer	• Inhibition of STAT3 phosphorylation and induction of caspase-3 cleavage in ALDH(+)/CD133(+) colon cancer-initiating cells	[173]
Hesperidin	Citrus fruits	Non-small-cell lung carcinoma	• Modulation of NF-κB signal transduction thereby mediating growth inhibition through apoptosis	[174]
Isobutyrophenone and Arnicolide	*Centipeda minima* (L.) A. Braun & Asch. [Compositae]	Colon cancer	• Promotion of intracellular ROS production • Downregulation of NF-κB protein	[175]
Epigallocatechin gallate	Green tea	Skin cancer	• Inhibition of PKD1 activation	[176,177]
Gossypol	Cotton plants	Prostate cancer	• DNA damage induction, activation of p53, and induction of apoptosis	[178,179]
Ethoxy Mansonone G	*Mansonia gagei* J.R.Drumm. [Malvaceae]	Breast cancer	• Inhibition of estrogen-induced cell proliferation	[180]
Genistein	Soybeans and Soy products	Prostate cancer, Cervical cancer, Colorectal cancer, Non-small-cell lung carcinoma	• Inhibition of Hedgehog-Gli signaling and expression of CSC markers CD44 • p53 stabilization through APE1 pathway • Inhibition of Akt pathway	[181,182]
Sulforaphane	Cruciferous vegetables	Prostate and Pancreatic cancer	• Induction of apoptosis and inhibition of self-renewing potential, ALDH1 activity, clonogenicity, xenograft growth in pancreatic CSCs. Enhanced drug cytotoxicity when combined with other conventional drugs in prostate CSCs. • Inhibited relapse of gemcitabine-treated tumor cells in nude mice	[183]
Proanthocyanidins	Grape seeds	Pancreatic adenocarcinoma	• Reduction of NF-κB expression and reversal of the epithelial-mesenchymal transition process	[184,185]
Methyl antcinate A	Antrodia camphorate	Breast cancer	• Downregulation of heat shock protein 27 • Upregulation of IkBα and p53 expression	[186,187]
Oridonin	*Rabdosia rubescens* [Lamiaceae]	Breast cancer	• Downregulation of Jagged2 expression and Notch1 activity • Activation of the PI3K/PTEN/ Akt/mTORC1 and WNT/ β-catenin pathways	[188,189]
Resveratrol	Grapes	Head and neck cancer, Gastric cancer, Thyroid cancer, Lung cancer	• Downregulation of ALDH1 and CD44 in HNC-TICs in a dose-dependent manner	[190–192]
Guggulsterone	*Commiphora mukul* (Hook. Ex Stocks) Engl. [Burseraceae]	Colon cancer, Prostate cancer, Head and neck cancer	• Activation of caspase-9, caspase-8, and caspase-3 • Induction of cell death in PC-3 cells • Induction of apoptosis in HT-29 cells by activating caspases-3 and − 8 • Downregulation of cIAP1, cIAP2, and Bcl-2 levels and upregulation of truncated Bid, Fas, p-JNK, and p-c-Jun	[193–195]
Emodin	Rhubarb	Prostate cancer	• Activation of Notch signaling pathway	[196]
Artesunate	*Artemisia annua* [Compositae]	Chronic myeloid leukemia	• Inhibition of VEGF expression	[197]
Allicin	Garlic	Ovarian cancer	• Activation of JNK pathway	[198]
Caffeic acid phenethyl ester (CAPE)	Propolis of honeybee hives	Prostate cancer	• Induction of cell G1 or G2/M cell cycle arrest	[199]
Erinacine A (ditherpenoid)	*Hericium erinaceum*	Gastrointestinal cancer, Colorectal cancer	• ROS-mediated cell cycle arrest • Attenuation of NF-κB activity in cancer stem cells	[200,201]
Morusin	*Morus alba L.* [Moraceae]	Cervical cancer	• Downregulation of the PI3K/Akt/mTOR pathway	[202]
Deoxyshikonin	*Arnebia euchroma* [Boraginaceae]	Colorectal cancer, Glioma	• Growth inhibition and apoptosis inductionby modulating Bcl-2, Bax, and STAT3 proteins	[203,204]
Apigenin	*Scutellaria spp*	Colorectal cancer, Lung Cancer, Osteocarcinoma, Liver Cancer, Melanoma, Prostate cancer	• Induction of cell cycle arrest at G2/M phase • Promotion of different anti-inflammatory pathways, including p38/MAPK and PI3K/Akt • Alteration of Raf-1 kinase mediating apoptosis	[205–208]
Paclitaxel	Pacific yew tree	Endometrial cancer, Sarcoma, Cervical cancer, Gastroesophageal cancer, Prostate cancer, Head and neck cancer	• Activation of MEK-independent signaling pathway	[209,210]
Tannins/ Tannic acid	Syzygium guineense,Gall nuts	Triple-negative Breast cancer, Colon cancer, Lung cancer, Liver cancer,	• Inhibits cell proliferation via Wnt3a-induced β-catenin • Downregulate JAK/STAT pathway	[211–213]

(*continued on next page*)

Table 1 (*continued*)

Natural compound	Source	Type of cancer	Outcome	Reference (s)
		Ovarian cancer, Prostate cancer, Pancreatic cancer, Embryonic carcinoma	• Inhibit cell cycle progression by G1/S phase arrest • Decrease TGF-β induced EMT and NF-κB activation • Act synergistic with cisplatin and oxaliplatin • Promotes TRAIL-induced extrinsic apoptosis	
Calotropin	Asclepiadoideae family	Colon cancer	• Inhibits β-catenin	[214]
Quercetin	Nuts, tea, onions, apple and in plant sources	Colorectal cancer, Triple-negative Breast cancer	• Inhibits phosphorylation of GSK-3β • Upregulate E-cadherin	[215]
Lycopene	Red fruits and vegetables	Prostate cancer	• Decrease cyclin E expression • Inhibits β-catenin • Inhibits phosphorylation of GSK-3β	[215]

Abbreviations: Wnt: wingless-related integration site; β-catenin: beta-catenin; Akt: protein kinase B; mTOR: mechanistic target of rapamycin; CSC: cancer stem cell; DCLK1: doublecortin like kinase 1; cluster of differentiation 44; cluster of differentiation 166; ALDH: aldehyde dehydrogenase; CD133: cluster of differentiation 133; Gli1: GLI family zinc finger 1; Notch-1: notch receptor 1; STAT3: signal transducer and activator of transcription 3; NF-κB: nuclear factor kappa b; ROS: reactive oxygen species; PKD1: polycystin 1; APE1: apurinic/apyrimidinic endonuclease 1; ALDH1: aldehyde dehydrogenase 1; IkBα: I-kappa-B-alpha; PI3K: phosphoinositide 3-kinases; PTEN: phosphatase and tensin homolog; mTORC1: mammalian target of rapamycin complex 1; HNC-TICs: head and neck cancer-derived tumor-initiating cells; cIAP1: cellular inhibitor of apoptosis protein 1; cIAP2: cellular inhibitor of apoptosis protein 2; Bcl-2: B-cell lymphoma-2; Bid: BH3 interacting domain death agonist; Fas: fas cell surface death receptor; p-JNK: phospho- jun nuclear kinase; p-c-Jun: phosphorylated c-Jun; VEGF: vascular endothelial growth factor; JNK: jun nuclear kinase; Bax: Bcl-2 associated X, apoptosis regulator; p38/MAPK: p38 mitogen-activated protein kinase; MEK: mitogen-activated protein kinase kinase; TGF-β: transforming growth factor-β; EMT: epithelial to mesenchymal transition; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; GSK-3β: glycogen synthase kinase-3β.

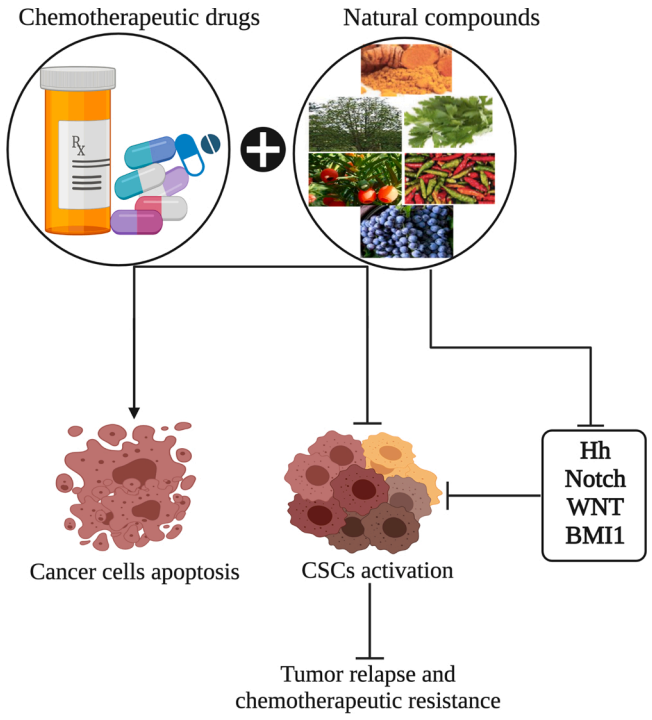

Fig. 1. Role of natural products in cancer prevention. The utilization of natural compounds as adjuvant therapy in targeting the cancer cells apoptotic pathways and as a solo therapy to inhibit cancer cells' self-renewal pathways (Hh, Notch, WNT and BMI1), subsequently inhibiting the tumor relapse and resistance to chemotherapeutic drugs. (Hh: hedgehog; Wnt: wingless-related integration site; BMI1: B lymphoma Mo-MLV insertion region 1 homolog).

phosphorylation of mTOR in ovarian cancer cells [42].

Honokiol has also been implicated in preventing and treating prostate cancer [43]. Honokiol induced DNA fragmentation and apoptosis in prostate cancer cells irrespective of androgen or p53 status [44]. The apoptosis in prostate cancer cells was induced by reducing anti-apoptotic proteins and inducing pro-apoptotic proteins [44]. In addition, honokiol has also been reported to display anti-neoplastic effects in gastric cancer by reducing Cyclooxygenase-2 (COX-2) and peroxisome proliferator-activated receptor-gamma (PPAR-γ), which are found to be involved in tumor growth, and increasing the expression of 15-LOX-1 in gastric cancer cells [37,45]. Honokiol also induced apoptosis in gastric cancer cells by inducing calcium-dependent thiol proteases, caspase-7, 12 activations and reducing glucose-regulated protein (GRP94) expression [46]. Additionally, honokiol has displayed anticancer effects in renal cancer through the downregulation of c-Met and phosphorylated Ras in renal cancer cells. Moreover, honokiol was found to induce apoptosis and reduce blood vasculatures in renal cancer cells [47].

2.2. Paclitaxel

Paclitaxel (Taxol™) is produced in the needles and bark of *Taxus brevifolia* Nutt. [Taxaceae] and has been reported to exhibit anti-neoplastic properties [48,49]. It belongs to a class of taxane drugs and is widely used as a natural anticancer compound [48,49]. Paclitaxel exerts anticancer effects by binding to tubulin and promoting its assembly into microtubules. It prevents the dissociation of microtubules and thus blocks cell progression and eventually prevents the growth of cancer cells [50].

Paclitaxel has been reported to be involved in many signal-transduction pathways that may be associated with its apoptotic-promoting properties. In breast cancer cells, paclitaxel induce apoptosis by activating Erk, p53, and p38 MAP kinase [51]. Moreover, paclitaxel also displayed anticancer effects through various signaling pathways such as toll-like receptor-4 dependent pathway, Janus kinase-(JAK-) signal transducer and activator of transcription factor pathway, and NF-kB in breast cancer [51–54] and through c-Jun N-terminal kinase (c-JNK)/stress-activated protein kinase (SAPK) in ovarian cancer [55]. Paclitaxel has been found to inhibit the cell proliferation of canine mammary carcinoma cell lines and cause cell cycle arrest at G_2/M-phase [56]. Paclitaxel mediated apoptosis through the upregulation of P53, Bax, and cleaved caspase 3 and the downregulation of Bcl-2 in canine mammary carcinoma cell line cells [56]. Moreover, treatment with paclitaxel reduced the expression of p-Akt and p-P70S6K and increased the expression of p-P38 and p-P90RSK in canine mammary carcinoma cell line cells [56]. Upon combination with tanshinone I (a natural compound derived from Chinese herbal medicine), paclitaxel-induced apoptosis in human ovarian cancer cells (A2780) and mouse ID-8 cells through the upregulation of Bax and downregulation of Bcl-2 [57]. Another study showed that the combination of paclitaxel with lobaplatin reduced the expression of p-Akt and phospho-Glycogen synthase kinase 3 beta (p-GSK3β) and inhibited the PI3K/Akt signaling pathway in lung cancer cells (NCI-H446) [58]. In another study, paclitaxel was found to

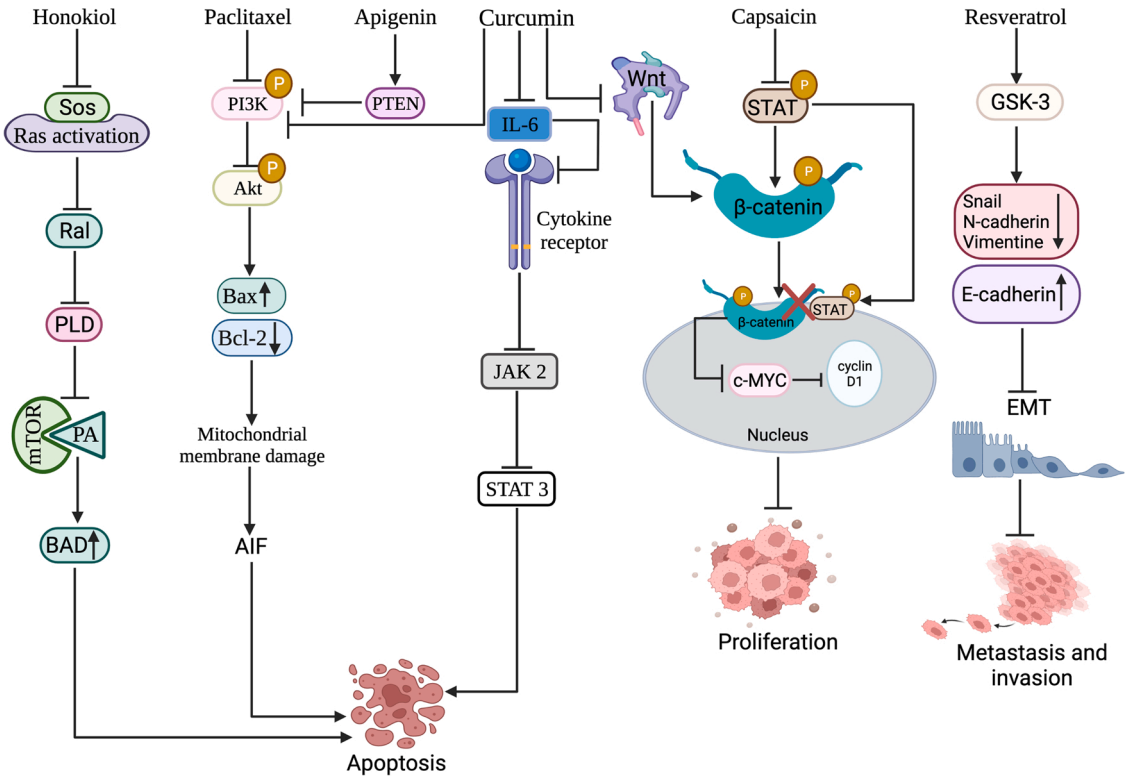

Fig. 2. Schematic representation of natural compounds targeting cancer signaling pathways. Honokiol exerts anticancer properties by inhibiting Sos binding with Ras thus suppressing Ras activation there by inhibiting Ral and PDL. Inhibition of PDL does not allow binding of PA resulting in mTOR suppression while increasing BAD expression. Apigenin increases the PTEN expression and like paclitaxel and curcumin inhibits the activity of phopho-PI3K, which subsequently inhibits the expression of phospho-Akt that upregulates Bax and downregulate Bcl-2 leading to the mitochondrial membrane damage and release of AIF. Curcmin also inhibits the IL-6-induced JAK2/STAT3 pathway. Additionally, curcumin impedes Wnt signaling and capsaicin inhibits STAT activation thus phopsphorylating β-catenin which hinders its entery into the nucleus along with STAT. phosphorylated β-catenin does not allow c-Myc to stimulate cyclin D1. Resveratrol increases the activity of GSK-3 which causes downregulation of snail, N-cadherin and vimentine while upregulates E-cadherin. This results in the inhibition of EMT transition. All of these pathways either cause cancer cells apoptosis or inhibits proliferation and metastasis and invasion. (Sos: son of sevenless (guanosine nucleotide exchange factors); Ras: rat sarcoma virus; Ral: ras-like; PDL: phospholipase D; mTOR:mechanistic target of rapamycin; PA:phosphatidic acid; BAD: BCL2 associated agonist of cell death; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; PTEN: phosphatase and tensin homolog; IL-6: interleukin 6; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; AIF: apoptosis inducing factor; JAK-2: janus kinase 2; STAT signal transducer and activator of transcription; Wnt: wingless-related integration site; c-Myc: cellular myelocytomatosis; GSK-3: glycogen synthase kinase 3; N-cadherin: neural cadherin; E-cadherin:epithelial cadherin; EMT:epithelial–mesenchymal transition).

reduce the proliferation of non-small cell lung carcinoma cell line A549 through the upregulation of p53 and MEG3 [59]. Though paclitaxel has several advantages, whether used alone or in conjunction with anthracyclines [60,61] to treat breast cancer, it does have certain drawbacks, such as being poorly soluble in water due to hydrophobic characteristics, necessitating the use of solvents in clinical formulations. Solvents used as carriers in these formulations cause severe toxicity and can limit the amount of drug delivered to tumors [62]. To address these limitations, the FDA recently approved nanoparticle albumin-bound paclitaxel (nab-paclitaxel, marketed as Abraxane®), a solvent-free version of paclitaxel, for the treatment of metastatic breast cancer, citing greater anticancer efficacy and tolerability over solvent-based paclitaxel [62–66]. The inherent capabilities of albumin are used by nab-Paclitaxel to reversibly bind paclitaxel, transport it through the endothelial cell, and concentrate it in tumor regions. Glycoprotein 60-mediated endothelial cell transcytosis of paclitaxel-bound albumin and accumulation in the tumor by albumin binding to SPARC (secreted protein, acidic and rich in cysteine) is part of the hypothesized drug delivery mechanism [62,67]. Clinical trials have demonstrated that nab-paclitaxel is more effective than paclitaxel manufactured as Cremophor EL (CrEL, Taxol, CrEL-paclitaxel) in second-line patients, with nearly double the response rate, longer time to disease progression, and higher survival [68,69].

2.3. Capsaicin

Capsaicin is an antitumor vanilloid compound derived from the genus capsicum [70]. It has been reported to induce apoptosis via the caspase-independent pathway and through suppression of proto-oncogene, FBI-1 mediated NF-kB in breast cancer cells [70,71]. Moreover, in breast cancer, it reduced expression of Bcl-2, survivin, and Ki-67 in vivo and in vitro, whereas it increased the expression of Bax and activated caspase 3 [72]. In triple-negative breast cancer cell line, MDA-MB-231, capsaicin has been shown to decrease the expression of cyclin-dependent kinase 8 (CDK8), reduce cancer cell viability, and induce cell cycle arrest in the G2/M phase [72]. Moreover, capsaicin has been reported to inhibit breast cancer cell viability by downregulating the CDK8/PI3K/Akt and inhibiting the Wnt/β-catenin signaling pathway [72]. Besides breast cancer, capsaicin also exhibits anticancer properties in esophageal squamous cell carcinoma, where it decreased the expression of matrix metalloproteinase-9 (MMP-9), AMP-activated protein kinase, and nuclear factor-kappaB (NF-κB) [73,74].

In gastric cancer cells, capsaicin-induced apoptosis via the modulation of the mitogen-activated protein kinase (MAPK) signaling pathway [75]. In colon cancer, capsaicin has been reported to elicit anticancer activity through the degradation of cyclin D1 and inactivation of 20 S proteasome [74,76]. Moreover, it has been reported that capsaicin exerts its anticancer effects in prostate cancer through the suppression of

the Wnt/β-catenin pathway [77]. It inhibited p-GSK3β, Wnt-2, β-catenin, cyclin D1, and c-Myc in prostate CSCs [77]. In addition, capsaicin has been reported to suppress pancreatic cancer cell proliferation by inhibiting Hedgehog, extracellular signal-regulated kinase, and c-Jun signaling pathways [78]. Moreover, capsaicin inhibited proliferation and induced autophagy, apoptosis, and cell cycle arrest at the G1 phase in NPC cells. [79]. In addition, treatment with capsaicin was found to inhibit the phosphorylation of Akt, mTOR, Erk, and p-GSK3β and reduce the expression of PI3K in NPC cells, suggesting that capsaicin exerts anticancer effects by downregulating the PI3K/Akt/mTOR signaling pathway. In another study, treatment with capsaicin was found to decrease cell viability and inhibit proliferation in osteosarcoma cells. In addition, the study reported the involvement of the mitochondrial apoptotic pathway in the capsaicin-induced apoptosis in osteosarcoma cells [80]. Moreover, the study reported that the anticancer effects exerted by capsaicin involve the MAPK signaling pathways [80].

2.4. Resveratrol

Resveratrol (RES) (3,4′,5–trihydroxy stilbene) is a non-flavonoid phytoalexin compound derived from plant species, including grapes, peanuts, plums, and berries [81]. However, increased levels of RES exist in the plant *Polygonum cuspidatum* [Polygonaceae] and *Vitis rotundifolia* Michx. [Vitaceae] [82]. RES has been reported to inhibit cell proliferation and induce mitochondrial-mediated and caspase-independent apoptosis in transgenic adenocarcinoma of mouse prostate (TRAMP) cells. It was shown that RES exerted its anticancer effects through changes in the expression of Bax/Bcl-2 and disturbance of the mitochondrial membrane potential in TRAMP cells [82,83]. Although RES is shown to be an effective antitumor agent, its application is limited due to low aqueous solubility and poor bioavailability. To overcome these limitations, various nano-delivery systems such as polymeric nanoparticles, lipid nanoparticles (liposomes, Micelle, Lipid nanoparticles), Gold and silver nanoparticles, and silica nanoparticles for RES loading have been utilized (detailed review in [84–86]). These nanostructures and nanoformulations have distinct physicochemical qualities, such as high loading capacity, cargo protection, and deep tumor penetration, in addition to better safety and biocompatibility. Liposomes are one of the earliest lipid-based drug nano-carriers that have been thoroughly studied, mainly consisting of phospholipids and cholesterol with an inner hydrophilic core and an outer hydrophobic lipid bilayer [87]. This molecular organization of the liposomes enables efficient delivery and enhances the drug's effectiveness. Using the same technique, a study evaluated the efficiency of liposomal encapsulated RES to treat breast tumors in a mouse model. The study found that the encapsulated RES inhibited tumor growth effectively at a reduced dosage with no cytotoxicity to normal tissues. In addition, the encapsulated RES induced apoptosis in breast tumors by upregulating the expression of tumor suppressor p53, downregulating the expression of anti-apoptotic protein Bcl-2, and inducing caspase-3 activation. [88]. It has also been shown that RES exerts anticancer effects through neutralizing reactive oxygen species (ROS), and inhibiting MMP-9 in mouse breast cancer cells in vitro and in vivo [82,89]. Another study showed that RES inhibited the cell proliferation, migration, and invasion of renal carcinoma cells via the inactivation of Akt and Erk1/2 signaling pathways. Moreover, the study found that RES suppressed the mesenchymal markers such as vimentin, N-cadherin, and Snail and increased the expression of epithelial marker E-cadherin, thus demonstrating its role in reversing epithelial to mesenchymal transition (EMT) in renal carcinoma cells [82,90]. A study showed the synergistic effect of RES and docetaxel in prostate cancer cell lines (C4–2B and DU-145). The combination treatment promoted apoptosis in prostate cancer cells by upregulating the pro-apoptotic genes and downregulating the anti-apoptotic genes. Moreover, the combination treatment upregulated the expression of tumor suppressor p53 and cell cycle inhibitors such as p21 and p27, resulting in cell cycle arrest at the G2/M phase [91]. RES has also been shown to exhibit antiproliferative effects in osteosarcoma cells by inhibiting the expression of endothelial growth factor (VEGF) [82,92]. RES induced apoptosis in osteosarcoma cells through caspase 3 activation, cleavage of PARP, upregulation of Bax, and downregulation of Bcl-2 and Bcl-xL. Moreover, it reduced the phosphorylation of Janus kinase 2 (JAK2), signal transducer, and activator of transcription 3 (STAT3) and inhibited the expression of p-PI3K, p-Akt, and NF-κB in osteosarcoma cells [93].

In colorectal cancer-derived cell lines, RES inhibited metastasis and cell invasion through the inhibition of the Wnt/β-catenin signaling pathway [82,94]. RES reversed EMT through the Akt/GSK-3β/Snail signaling pathway in colon cancer cells and tumor tissues of nude mice. Treatment with RES increased the expression of epithelial marker E-cadherin and decreased the expression of mesenchymal markers such as N-cadherin and Snail [95]. In another study, RES inhibited cell proliferation, induced apoptosis, and cell cycle arrest at the G1 phase in colon cancer cells. In addition, the study identified Akt1 and Akt2 as potential targets of RES. Furthermore, the study found that Akt1/2 knockdown inhibited cell proliferation and colony formation in colon cancer cells, effects that were similar to those caused by RES treatment [96].

2.5. Apigenin

Apigenin is a natural trihydroxyflavone found in various fruits, vegetables, and nuts. It exhibits significant physiological and pharmacological properties, including anticancer, antioxidant, antibacterial, and antiviral properties [97]. The anticancer effect of apigenin has been observed in several cancers, including colorectal cancer [98,99], melanoma, prostate cancer, lung cancer, osteosarcoma, liver cancer, and breast cancer [100,101].

Apigenin exerts its anticancer effects by inhibiting several signaling pathways, inducing apoptosis, autophagy, cell cycle arrest [122], and inhibiting cell migration and invasion [102]. Studies demonstrate that apigenin is associated with the modulation of many cell signaling pathways such as Wnt/β–catenin [99,103], JAK/STAT [101], AMPK [104], TGF-β [105], and FAK/ERK1/2 [106]. Apigenin is also found to exert immune-regulatory activities in an organic-specific manner by modulating NF-κB activity in the lungs of transgenic mice [107]. A study showed that co-treatment of apigenin with cisplatin enhanced the cytotoxic effect of cisplatin in multiple cell lines (MCF-7, HeLa, A549, and HCT116). In addition, apigenin was found to induce apoptosis in human lung cancer A549 cells through the Erk/MAPK pathway activation. Moreover, the combination treatment with apigenin and cisplatin-induced caspase-dependent apoptosis in A549 cells elevated the expression of p53 and promoted p53 phosphorylation and accumulation in A549 cells [108].

Previous studies have reported that progestins, a medication that mimics the effects of naturally occurring female sex hormone progesterone, favor breast cancer metastasis or could be a risk factor for developing breast cancer in women who consume progestins [109,110]. Given this, a study demonstrated the effect of apigenin on the growth of BT-474 xenograft tumors in nude mice exposed to progestin (medroxyprogesterone acetate) [111]. The study found that apigenin effectively inhibited the progression of the xenograft tumors by inhibiting proliferation, inducing apoptosis, and reducing the expression of proto-oncogene HER2/neu [111]. Additionally, apigenin was also found to reduce VEGF levels, thereby inhibiting cell survival [111]. Another study showed that apigenin inhibited cell proliferation and induced autophagy by suppressing the PI3K/Akt/mTOR signaling pathway in hepatocellular carcinoma in vitro and in vivo [112]. Furthermore, cervical cancer HeLa cells treatment with apigenin 7-O-glucoside (AGL) inhibited cell proliferation, induced cell cycle arrest at G_0/G_1 phase, reduced mitochondrial membrane potential, and increased the expression of pro-apoptotic proteins and downregulated anti-apoptotic proteins in [113]. Moreover, the study found that AGLpromoted apoptosis

in cervical cancer cells via the PTEN/Akt/PI3K pathway [113].

EMT is an important process in the metastasis of colorectal cancer. Targeting EMT using natural products and dietary compounds has gained much attention during the past few decades. Apigenin has been found to reverse EMT in colon cancer cells by upregulating the expression of E-cadherin and downregulating the expression of Snail. Moreover, apigenin inhibited the expression of NF-kB and reduced the transcriptional activity of Snail, thus demonstrating that apigenin reversed EMT via suppressing the NF-kB/Snail pathway [114]. Another study showed that apigenin induced apoptosis and autophagy in cisplatin-resistant HT-29 colon cancer cells by inhibiting the mTOR/-PI3K/Akt signaling pathway [115].

2.6. Curcumin

Curcumin, also known as diferuloylmethane, is a primary component of turmeric. Curcumin interacts with various cellular targets and, therefore, is regarded as a pleiotropic molecule [116,117]. Many studies have investigated the effectiveness of curcumin in various pathological processes such as inflammation, infection, hepatic diseases, cancer, and diabetes [118].

Several in vivo studies have demonstrated the pro-apoptotic effects of curcumin. Curcumin inhibited tumor growth in nude mice, which was injected with tumorspheres of lung cancer NCI-H460 cells. Curcumin was found to repress NCI-H460 tumorspheres via suppressing the JAK2/STAT3 signaling pathway [119]. JAK2/STAT3 pathway activity is constitutive in cancer cells and is involved in various cancer initiation processes [120]. Thus, JAK2/STAT3 pathway is a great target for curcumin to suppress tumor formation. In another study, curcumin inhibited cell proliferation and induced caspase-dependent apoptosis in a dose-dependent manner via JAK/STAT3 pathway suppression in primary effusion lymphoma cells [121]. Studies suggest that IL-6 promotes proliferation and survival of multiple myeloma cells through STAT3 phosphorylation. Thus, agents that suppress STAT3 phosphorylation, such as curcumin are potential therapeutic targets for treating multiple myeloma. Treatment with curcumin was found to inhibit constitutive STAT3 phosphorylation and proliferation in multiple myeloma cells [122]. Interestingly, curcumin emerged as a much stronger inhibitor of STAT3 phosphorylation than AG490, a selective inhibitor of the Janus kinase 2 (JAK2)/STAT3 signaling pathway [123]. Moreover, in other cancer cell lines such as pancreatic [124,125], ovarian and endometrial [126,127], malignant gliomas [128,129], and hepatocellular [130], curcumin was also reported to inhibit cellular proliferation by down-regulating the JAK-STAT3 signaling pathway.

In cancer, several miRNAs are indicated to be involved in modulating the pathological processes and are considered an important target for anticancer therapies. Curcumin has been shown to exhibit an epigenetic regulatory effect on miRNA [131]. A recent study in lung cancer cells showed that curcumin inhibited the enhancer of zeste homolog 2 (EZH2) coding mRNA expression through the upregulation of miR-let 7c and miR-101 [124]. Interestingly, many studies provide evidence of the EZH2 association with tumor malignancy and poor prognosis [125]. Therefore, inhibiting EZH2 can be a potential target to treat lung cancers.

Additionally, curcumin was found to upregulate the expression of miR-9, with subsequent downregulation of the Wnt/β-catenin expression in oral squamous cell carcinoma cells [132]. Aberrant Wnt/β-catenin pathway activation plays a critical role in tumorigenesis by altering cell cycle progression, cell survival, and invasion [132]. Thus, by regulating the expression of miR-9 and Wnt/β-catenin signaling pathways, curcumin inhibits the proliferation of oral squamous cell carcinoma (SCC-9) cells[132]. Moreover, miR-31 is usually upregulated in oral squamous cell carcinoma, which can be due to the activation of epidermal growth factor (EGF). Surprisingly, treatment with curcumin reduced Akt activation leading to the attenuation of C/EBPβ and suppression of miR-31 upregulation in oral squamous cell carcinoma cells [133]. Likewise, curcumin regulates the expression of miR-7, which has been shown to suppress cell growth and proliferation, promote apoptosis in pancreatic cancer cells, and reduce histone lysine methyltransferase (SET8) expression, a target of miR-7 [134]. Also, miR-146a expression is reduced in pancreatic cancer samples as compared to healthy tissues. One of the miR-146a targets is EGFR, and treating pancreatic cancer cells with difluorinated curcumin (CDF) resulted in the re-expression of miR-146a that led to the inhibition of tumor xenografts growth as well as decreased expression of EGFR, extracellular signal-regulated kinases (Erk1, Erk2) and Kirsten rat sarcoma viral oncogene homolog (KRas). The miR-146a knockdown in the pancreatic AsPC-1 cell line increased EGFR expression and enhanced clonogenic growth. Therefore, the inhibition of EGFR by upregulation of miR-146a through CDF treatment can be used to treat pancreatic cancer [135]. These findings suggest that various miRNAs are great anti-neoplastic targets for curcumin.

Furthermore, curcumin plays an essential role in gastric cancer by suppressing G1 to S phase transition during cell cycle progression [136]. Cyclin D1 activity is crucial for cell proliferation and regulation during the cell cycle, and its degradation at the G1 phase will halt the cells from progressing to the S phase [137]. In gastric cancer cell line (AGS), the synergistic effect of curcumin with doxorubicin, a chemotherapeutic agent, has been reported [138]. This synergism has been shown to significantly reduce tumor spheroid formation, invasion, and migration compared to doxorubicin or curcumin alone [138]. The effect of both compounds together caused caspase-9 and Bax upregulation and the downregulation of Bcl-2 expression [138]. This implies that curcumin can ameliorate the doxorubicin drug resistance in chemotherapy treatment by increasing the doxorubicin efficacy. However, curcumin's limited efficacy in clinical investigations is attributed to its low solubility, high rate of metabolism, and poor bioavailability. The use of nanotechnology strategies may aid in overcoming obstacles and facilitating the translation of curcumin from the bench to the clinic. Advanced drug delivery of curcumin (curcumin nanoformulations or nanomedicine) can leverage therapeutic effects by enhancing bioavailability and pharmacokinetics, increasing tumor binding, internalization, and targeting. The benefits of adopting these innovative drug delivery systems are immense, and they have been well studied [139–142].

3. Natural products as immunomodulators in cancer

The maintenance of immune system homeostasis is a key mechanism essential for the physiological stability of living organisms. Natural products participate in different innate and adaptive immunity processes and are important regulators of immune system function. Natural products and their derivatives with immunomodulatory characteristics are now being used as therapeutic agents against various types of cancer. Natural products are known to stimulate non-specific innate immune responses in which the immune system mediators such as innate leukocytes (NK cells, eosinophils, basophils, mast cells) and phagocytic cells (neutrophils, macrophages, dendritic cells) provide defense against pathogens [143]. The amplification of the innate immunity promotes effector innate immune responses such as immune cell infiltration, phagocytosis, and other cytotoxic mechanisms such as NK cell-mediated cytotoxicity that leads to tumor cell destruction [144] (Fig. 3). Besides activating the innate immune response, some of the natural compounds act as immunomodulatory agents and lead to the subsequent activation of the adaptive immune system. In adaptive immunity, the tumor antigens are recognized by T and B lymphocytes through cell-surface antigen-specific receptors and lead to an enhanced humoral response and elimination of tumor cells by different mechanisms such as T-cell mediated cancer cell death (Fig. 3).

Some of the well-known natural compounds in clinical trials that play an important role in immunomodulation in cancer are curcumin, RES, epigallocatechin-3-gallate (EGCG), quercetin, capsaicin, and genistein [145]. The antioxidant properties of natural immunomodulatory compounds such as curcumin, RES, quercetin, and genistein allow them

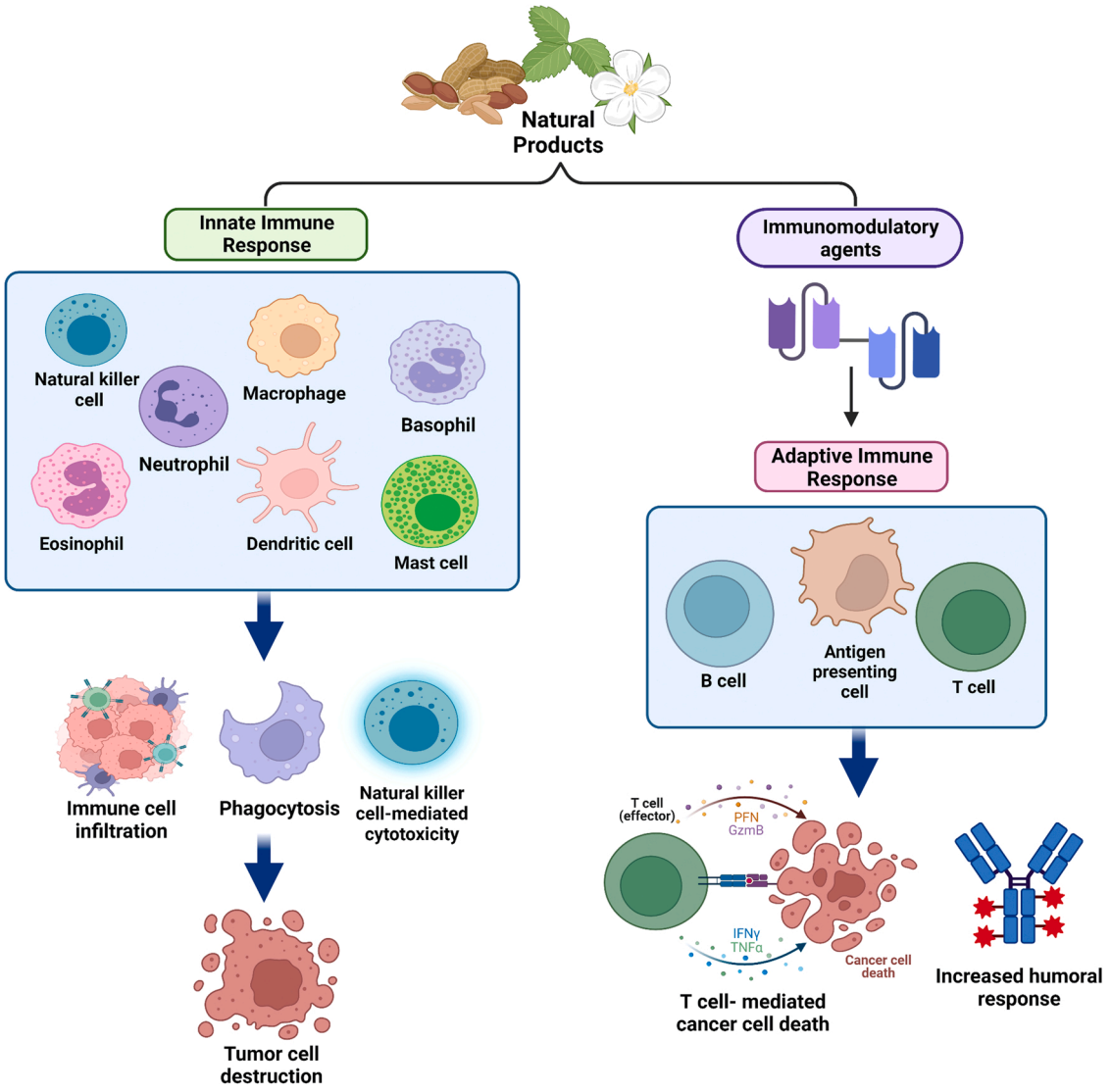

Fig. 3. Role of natural products in innate and adaptive immune responses. Natural products stimulate non-specific innate responses that leads to the elimination of tumor cells by various mechanisms such as immune cell infiltration, phagocytosis and NK-cell mediated cytotoxicity. Natural products also possess immunomodulatory properties that can cause the activation of the adaptive immune system leading to T-cell mediated tumor cell death and enhanced humoral responses. (NK: natural killer).

to be used as a prophylaxis against tumor initiation and development [146–149]. Naturally occurring immunomodulatory agents can prevent tumor propagation through cell cycle arrest and induction of apoptosis [150,151]. Besides the well-known anticancer and anti-inflammatory effects of curcumin, studies have also reported the immunomodulatory effects of curcumin by regulating a diverse range of molecular targets. Curcumin has been reported to inhibit the accumulation of myeloid-derived suppressor cells (MDSCs) in the spleen, blood, and tumor tissues in a human gastric cancer xenograft and mouse colon cancer allograft model [152]. Moreover, in-vivo studies have reported that curcumin enhances the cytotoxicity of CD8(+) T cells towards tumors through the alteration of the tumor microenvironment (TME) when combined with adoptive therapy [153] and also enhance the mitogen and antigen-induced proliferation potential of T cells [154]. On the other hand, RES is reported to exhibit immunomodulatory effects in various cancer models in vitro and in vivo by favoring tumor inhibitory cells in the TME and increasing immunogenicity (check review [155]). In addition, RES and curcumin have also been shown to stimulate natural killer (NK) cell activation in YAC-1 cells [156]. Among the flavonoids, flavones such as apigenin and luteolin are reported to exhibit immunomodulatory properties [157]. A study found flavonoids such as apigenin, luteolin, and quercetin to enhance NK-cell mediated cytotoxicity against lung cancer cells [158]. Moreover, the study reported that treatment with apigenin and luteolin increased the secretion levels of perforin and granulysin (cytolytic proteins stored inside NK cells) from NK cells [158]. Another naturally occurring flavonoid, genistein, has exhibited immunomodulatory effect by increasing lymphocyte proliferation in a cervical cancer mouse model [159]. Another study showed that treatment with genistein enhanced cytotoxic T-cell (CTL) activity and enhanced IL-2-stimulated NK cell activity in B16F10 melanoma tumor cells in vivo and in vitro [160]. In another study, the combination of EGCG, the antioxidant component of the green tea, and DNA vaccination enhanced tumor specific T-cell immune response in murine tumor models [161]. *In vivo* studies have also shown that treatment with EGCG promoted NK cell activity and increased T and B-cell proliferation and enhanced NK-cell mediated cytotoxicity in a murine leukemia and bladder cancer model respectively [162,163]. Alternatively, EGCG, the antioxidant component of green tea, has been reported to suppress the proliferation of peripheral blood mononuclear cells isolated from breast cancer patients and stimulated separately with mitogen, anti-CD3, and

cancer antigen peptides, thus showing an immunosuppressive effect [164]. Treatment with capsaicin, an active component of chili peppers, has also been reported to enhance CTL activity in colon carcinoma cells and elicit a robust T-cell response in a Meth A fibrosarcoma tumor mice model [165].

Thus, the immunomodulatory characteristics of natural products, their extracts, and derivatives can serve as efficient therapeutic targets to develop novel immunomodulatory agents to supplement chemotherapies which can help restore immune surveillance and target the complex immunosuppressive TME, the major obstacles in cancer therapeutics.

4. Conclusion

The frequent occurrence of various cancer-causing genetic mutations leads to the failure of cancer management therapies, thereby making cancer prevention an exciting area of anticancer research. Due to increased research, the mechanisms of cancer's abnormal signal transduction pathways and their effects on carcinogenesis, apoptosis, and metastasis are becoming more clear. The quest for specific molecules that can influence signal transduction has recently become a popular biomedical research topic worldwide. One common theme that has emerged in all the studies comprising natural products is their tendency to target multiple oncogenic signaling pathways simultaneously by modulating the activity or expression, or both, of their molecular targets, affecting apoptotic cell death, cell proliferation, migration/invasion, angiogenesis, metastasis, and other pathways that are unique to certain natural products. The majority of natural products target intrinsic apoptotic signaling pathways, generating several intracellular signals that trigger mitochondrial-initiated events that lead to cancer cell death. Interestingly, natural products can be employed as adjuvants to improve the drug sensitization of chemoresistant cancers. Understanding oncogenes, anti-oncogenes, and their regulatory signaling pathways is required for the prospective use of natural substances combined with conventional treatment therapies. Natural products as chemoadjuvants are an active research area that must be treaded cautiously to produce the best treatment outcome in cancer patients. In the near future, a better knowledge of natural product targets and how they disrupt the oncogenic network in cancer cells in combination with existing therapeutic choices in different tumors by lowering drug-related toxicities will be a hot topic of research.The other research area regarding natural products that needs special attention in future is to improve their solubility, rate of metabolism, and bioavailability and use of advanced drug delivery options such as various nano-delivery systems that include polymeric nanoparticles, lipid nanoparticles (liposomes, Micelle, Lipid nanoparticles), Gold and silver nanoparticles, and silica nanoparticles may aid in overcoming these obstacles and facilitating their translation from the bench to the clinic.

To summarize, the goal of this review is to draw scientists' and researchers' attention to the various beneficial effects of natural products in the development of new and safe drugs for possible cancer therapy, and it could serve as a strong foundation for more extensive research into natural compounds in cancer therapeutics.

Author statement

All the authors meet the criteria for authorship. This manuscript is not under consideration for publication elsewhere. Every author is aware of, has agreed to this paper's content, and is listed as an author on the paper. All the authors declared no potential conflict of interest involved with this work.

Author's contribution

S.H., T.A.A., S.A., S.N., G.S., S.A.M, L.T., R.M., I.E., M.M.M., wrote the manuscript and generated figures. **S.H., M.A.M., A.A.B., M. S.**, and M.H. contributed to the concept and design and critically edited the manuscript. **S.A., F.J., T.M.**, and **S.U.** performed critical revision and editing of the scientific content. All authors read and approved the final manuscript.

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Conflict of interest statement

The authors declare that they have no competing interests.

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References

[1] C.-L. Zhang, et al., Stem cells in cancer therapy: opportunities and challenges, Oncotarget 8 (43) (2017) 75756–75766.
[2] A.Z. Ayob, T.S. Ramasamy, Cancer stem cells as key drivers of tumour progression, J. Biomed. Sci. 25 (1) (2018) 20.
[3] S. Choudhuri, R. Chanderbhan, A. Mattia, Chapter 20 - carcinogenesis: mechanisms and models, in: R.C. Gupta (Ed.), Veterinary Toxicology, third ed., Academic Press, 2018, pp. 339–354.
[4] S.H. Hassanpour, M. Dehghani, Review of cancer from perspective of molecular, J. Cancer Res. Pract. 4 (4) (2017) 127–129.
[5] WHO. Latest global cancer data: Cancer burden rises to 19.3 million new cases and 10.0 million cancer deaths in 2020. 2020. ⟨https://www.iarc.who.int/news-events/latest-global-cancer-data-cancer-burden-rises-to-19–3-million-new-cases-and-10–0-million-cancer-deaths-in-2020/⟩.
[6] M. Hasanpourghadi, et al., Phytometabolites targeting the warburg effect in cancer cells: a mechanistic review, Curr. Drug Targets 18 (9) (2017) 1086–1094.
[7] T. Marika, K. Magdalena, B. Piotr, New hopes in cancer battle - a review of new molecules and treatment strategies, Med. Chem. 12 (8) (2016) 700–719.
[8] M.K. Shanmugam, et al., Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds, Semin Cancer Biol. 40–41 (2016) 35–47.
[9] S. Nobili, et al., Natural compounds for cancer treatment and prevention, Pharmacol. Res 59 (6) (2009) 365–378.
[10] S. Naviglio, F. Della Ragione, Naturally occurring molecules and anticancer combination therapies in the era of personalized medicine and economic crisis, Curr. Pharm. Des. 19 (2013).
[11] M.K. Shanmugam, et al., Cancer prevention and therapy through the modulation of transcription factors by bioactive natural compounds, Semin. Cancer Biol. 40–41 (2016) 35–47.
[12] J.E. Darnell Jr., STATs and gene regulation, Science 277 (5332) (1997) 1630–1635.
[13] G. Li, H.X. Lou, Strategies to diversify natural products for drug discovery, Med. Res. Rev. 38 (4) (2018) 1255–1294.
[14] R. Huber, et al., Chemoenzymatic synthesis of complex phenylpropanoid derivatives by the botrytis cinerea secretome and evaluation of their Wnt inhibition activity, Front Plant Sci. 12 (2021), 805610.
[15] S.D. Copley, Enzymes with extra talents: moonlighting functions and catalytic promiscuity, Curr. Opin. Chem. Biol. 7 (2) (2003) 265–272.
[16] K. Gindro, et al., Generation of antifungal stilbenes using the enzymatic secretome of Botrytis cinerea, J. Nat. Prod. 80 (4) (2017) 887–898.
[17] D. Righi, et al., Generation of stilbene antimicrobials against multiresistant strains of Staphylococcus aureus through biotransformation by the enzymatic secretome of Botrytis cinerea, J. Nat. Prod. 83 (8) (2020) 2347–2356.
[18] M. Hasan, et al., Oxyprenylated phenylpropanoids bind to MT1 melatonin receptors and inhibit breast cancer cell proliferation and migration, J. Nat. Prod. 80 (12) (2017) 3324–3329.
[19] A. Hematpoor, et al., Phenylpropanoids isolated from Piper sarmentosum Roxb. induce apoptosis in breast cancer cells through reactive oxygen species and mitochondrial-dependent pathways, Chem. Biol. Interact. 279 (2018) 210–218.
[20] M. Touaibia, J. Jean-François, J. Doiron, Caffeic Acid, a versatile pharmacophore: an overview, Mini Rev. Med. Chem. 11 (8) (2011) 695–713.
[21] E.K. Davison, M.A. Brimble, Natural product derived privileged scaffolds in drug discovery, Curr. Opin. Chem. Biol. 52 (2019) 1–8.
[22] F. Carunchio, et al., Oxidation of ferulic acid by laccase: identification of the products and inhibitory effects of some dipeptides, Talanta 55 (1) (2001) 189–200.

[23] H.L. Liu, et al., Biotransformation of ferulic acid into two new dihydrotrimers by Momordica charantia peroxidase, Chem. Pharm. Bull. 53 (7) (2005) 816–819.
[24] H.F. Torquato, et al., Anti-cancer phytometabolites targeting cancer stem cells, Curr. Genom. 18 (2) (2017) 156–174.
[25] Y. Li, et al., Induction of cancer cell death by isoflavone: the role of multiple signaling pathways, Nutrients 3 (2011) 10.
[26] R. Sever, J.S. Brugge, Signal transduction in cancer, Cold Spring Harb. Perspect. Med. 5 (4) (2015) a006098.
[27] G.S. Martin, Cell signaling and cancer, Cancer Cell 4 (3) (2003) 167–174.
[28] F. Sanchez-Vega, et al., Oncogenic signaling pathways in the cancer Genome Atlas, Cell 173 (2) (2018) 321–337, e10.
[29] T.N. Martić, et al., Changes of AXIN-1 and beta-catenin in neuroepithelial brain tumors, Pathol. Oncol. Res. 16 (1) (2010) 75–79.
[30] R. Dixit, et al., Genetic mutational analysis of β-catenin geneaffecting GSK-3β phosphorylation plays a role in gall bladder carcinogenesis: results from a case control study, Cancer Treat Res Commun 23 (2020), 100173.
[31] J. Worm, et al., Genetic and epigenetic alterations of the APC gene in malignant melanoma, Oncogene 23 (30) (2004) 5215–5226.
[32] A. Jemal, et al., Cancer statistics, 2009, CA Cancer J. Clin. 59 (4) (2009) 225–249.
[33] J.E. Dick, Stem cell concepts renew cancer research, Blood 112 (13) (2008) 4793–4807.
[34] T. Reya, et al., Stem cells, cancer, and cancer stem cells, Nature 414 (6859) (2001) 105–111.
[35] Y. Li, et al., Implications of cancer stem cell theory for cancer chemoprevention by natural dietary compounds, J. Nutr. Biochem. 22 (9) (2011) 799–806.
[36] A. Woodbury, et al., Neuro-modulating effects of Honokiol: a review 4 (2013) 130.
[37] S. Arora, et al., Honokiol: a novel natural agent for cancer prevention and therapy, Curr. Mol. Med. 12 (10) (2012) 1244–1252.
[38] C.P. Ong, et al., Honokiol: a review of its anticancer potential and mechanisms, Cancers 12 (2019) 1.
[39] S. Chilampalli, et al., Chemopreventive effects of honokiol on UVB-induced skin cancer development, Anticancer Res. 30 (3) (2010) 777–783.
[40] W. Hou, et al., Synergistic antitumor effects of liposomal honokiol combined with adriamycin in breast cancer models, Phytother. Res. 22 (8) (2008) 1125–1132.
[41] X. Yi, et al., Honokiol antagonizes doxorubicin resistance in human breast cancer via miR-188-5p/FBXW7/c-Myc pathway, Cancer Chemother. Pharmacol. 87 (5) (2021) 647–656.
[42] J.S. Lee, et al., Honokiol induces apoptosis and suppresses migration and invasion of ovarian carcinoma cells via AMPK/mTOR signaling pathway, Int J. Mol. Med. 43 (5) (2019) 1969–1978.
[43] E.R. Hahm, et al., Honokiol inhibits androgen receptor activity in prostate cancer cells, Prostate 74 (4) (2014) 408–420.
[44] E.R. Hahm, et al., Honokiol, a constituent of oriental medicinal herb magnolia officinalis, inhibits growth of PC-3 xenografts in vivo in association with apoptosis induction, Clin. Cancer Res. 14 (4) (2008) 1248–1257.
[45] S.H. Liu, et al., Honokiol inhibits gastric tumourigenesis by activation of 15-lip-oxygenase-1 and consequent inhibition of peroxisome proliferator-activated receptor-gamma and COX-2-dependent signals, Br. J. Pharmacol. 160 (8) (2010) 1963–1972.
[46] M.L. Sheu, S.H. Liu, K.H. Lan, Honokiol induces calpain-mediated glucose-regulated protein-94 cleavage and apoptosis in human gastric cancer cells and reduces tumor growth, PLoS One 2 (10) (2007) e1096-e1096.
[47] M. Balan, et al., Honokiol inhibits c-Met-HO-1 tumor-promoting pathway and its cross-talk with calcineurin inhibitor-mediated renal cancer growth, Sci. Rep. 7 (1) (2017) 5900.
[48] N.C. Kampan, et al., Paclitaxel and its evolving role in the management of ovarian cancer, Biomed. Res. Int. 2015 (2015), 413076.
[49] L. Zhu, L. Chen, Progress in research on paclitaxel and tumor immunotherapy, Cell. Mol. Biol. Lett. 24 (2019) 40.
[50] B.A. Weaver, How Taxol/paclitaxel kills cancer cells, Mol. Biol. Cell 25 (18) (2014) 2677–2681.
[51] S.S. Bacus, et al., Taxol-induced apoptosis depends on MAP kinase pathways (ERK and p38) and is independent of p53, Oncogene 20 (2) (2001) 147–155.
[52] N.M. Patel, et al., Paclitaxel sensitivity of breast cancer cells with constitutively active NF-kappaB is enhanced by IkappaBalpha super-repressor and parthenolide, Oncogene 19 (36) (2000) 4159–4169.
[53] S.R. Walker, M. Chaudhury, D.A. Frank, STAT3 inhibition by microtubule-targeted drugs: dual molecular effects of chemotherapeutic agents, Mol. Cell Pharmacol. 3 (1) (2011) 13–19.
[54] S.R. Walker, et al., Microtubule-targeted chemotherapeutic agents inhibit signal transducer and activator of transcription 3 (STAT3) signaling, Mol. Pharmacol. 78 (5) (2010) 903–908.
[55] T.H. Wang, et al., Microtubule dysfunction induced by paclitaxel initiates apoptosis through both c-Jun N-terminal kinase (JNK)-dependent and -independent pathways in ovarian cancer cells, J. Biol. Chem. 274 (12) (1999) 8208–8216.
[56] X. Ren, et al., Paclitaxel suppresses proliferation and induces apoptosis through regulation of ROS and the AKT/MAPK signaling pathway in canine mammary gland tumor cells, Mol. Med. Rep. 17 (6) (2018) 8289–8299.
[57] J. Zhou, et al., Natural compound Tan-I enhances the efficacy of Paclitaxel chemotherapy in ovarian cancer, Ann. Transl. Med. 8 (12) (2020) 752.
[58] D. Ma, et al., Paclitaxel increases the sensitivity of lung cancer cells to lobaplatin via PI3K/Akt pathway retraction in /10.3892/ol.2021.12480, Oncol. Lett. 15 (5) (2018) 6211–6216.
[59] J. Xu, et al., Paclitaxel promotes lung cancer cell apoptosis via MEG3-P53 pathway activation, Biochem. Biophys. Res. Commun. 504 (1) (2018) 123–128.
[60] M. De Laurentiis, et al., Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials, J. Clin. Oncol. 26 (1) (2008) 44–53.
[61] M.J. Piccart-Gebhart, et al., Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer, J. Clin. Oncol. 26 (12) (2008) 1980–1986.
[62] W.J. Gradishar, Albumin-bound paclitaxel: a next-generation taxane, Expert Opin. Pharmcother. 7 (8) (2006) 1041–1053.
[63] W.J. Gradishar, et al., Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer, J. Clin. Oncol. 23 (31) (2005) 7794–7803.
[64] Y. Yamamoto, I. Kawano, H. Iwase, Nab-paclitaxel for the treatment of breast cancer: efficacy, safety, and approval, Oncol. Targets Ther. 4 (2011) 123–136.
[65] A. Rehman, et al., Integrated core proteomics, subtractive proteomics, and immunoinformatics investigation to unveil a potential multi-epitope vaccine against schistosomiasis, Vaccines 9 (2021) 6.
[66] D.A. Yardley, nab-Paclitaxel mechanisms of action and delivery, J. Control Release 170 (3) (2013) 365–372.
[67] A. Neesse, et al., SPARC independent drug delivery and antitumour effects of nab-paclitaxel in genetically engineered mice, Gut 63 (6) (2014) 974–983.
[68] N. Chen, et al., Albumin-bound nanoparticle (nab) paclitaxel exhibits enhanced paclitaxel tissue distribution and tumor penetration, Cancer Chemother. Pharmacol. 76 (4) (2015) 699–712.
[69] D.M. Robinson, G.M. Keating, Albumin-bound Paclitaxel: in metastatic breast cancer, Drugs 66 (7) (2006) 941–948.
[70] C.-C. Chou, et al., Capsaicin-induced apoptosis in human breast cancer MCF-7 cells through caspase-independent pathway, Oncol. Rep. 21 (2009) 665–671.
[71] M. Chen, et al., Capsaicin inhibits proliferation and induces apoptosis in breast cancer by down-regulating FBI-1-mediated NF-kappaB pathway, Drug Des. Dev, Ther. 15 (2021) 125–140.
[72] D. Wu, et al., Capsaicin suppresses breast cancer cell viability by regulating the CDK8/PI3K/Akt/Wnt/β-catenin signaling pathway, Mol. Med. Rep. 22 (6) (2020) 4868–4876.
[73] G.R. Lee, et al., Capsaicin suppresses the migration of cholangiocarcinoma cells by down-regulating matrix metalloproteinase-9 expression via the AMPK-NF-kappaB signaling pathway, Clin. Exp. Metastasis 31 (8) (2014) 897–907.
[74] G.D.A. Popescu, et al., The effects of capsaicin on gastrointestinal cancers, Molecules 26 (2020) 1.
[75] S.Y. Park, et al., Capsaicin induces apoptosis and modulates MAPK signaling in human gastric cancer cells, Mol. Med. Rep. 9 (2) (2014) 499–502.
[76] R. Clark, S.H. Lee, Anticancer properties of capsaicin against human cancer, Anticancer Res. 36 (3) (2016) 837–843.
[77] M. Zhu, et al., Capsaicin suppressed activity of prostate cancer stem cells by inhibition of Wnt/beta-catenin pathway, Phytother. Res. 34 (4) (2020) 817–824.
[78] H. Bai, et al., Inhibition of chronic pancreatitis and pancreatic intraepithelial neoplasia (PanIN) by capsaicin in LSL-KrasG12D/Pdx1-Cre mice, Carcinogenesis 32 (11) (2011) 1689–1696.
[79] Y.-T. Lin, et al., Capsaicin induces autophagy and apoptosis in human nasopharyngeal carcinoma cells by downregulating the PI3K/AKT/mTOR pathway, Int. J. Mol. Sci. 18 (2017) 7.
[80] Y. Zhang, et al., Capsaicin inhibits proliferation and induces apoptosis in osteosarcoma cell lines via the mitogen-activated protein kinase pathway, Oncol. Rep. 38 (5) (2017) 2685–2696.
[81] M. Koushki, et al., Resveratrol: a miraculous natural compound for diseases treatment, Food Sci. Nutr. 6 (8) (2018) 2473–2490.
[82] V.K. Bhaskara, et al., Resveratrol, cancer and cancer stem cells: a review on past to future. Curr. Res. Food Sci. 3 (2020) 284–295.
[83] S. Kumar, et al., Resveratrol induces mitochondria-mediated, caspase-independent apoptosis in murine prostate cancer cells, Oncotarget 8 (13) (2017) 20895–20908.
[84] J. Sharifi-Rad, et al., Resveratrol-based nanoformulations as an emerging therapeutic strategy for cancer, Front. Mol. Biosci. 8 (2021), 649395.
[85] I.-M. Chung, et al., Resveratrol nanoparticles: a promising therapeutic advancement over native resveratrol, Processes 8 (4) (2020) 458.
[86] Z. Ahmadi, R. Mohammadinejad, M. Ashrafizadeh, Drug delivery systems for resveratrol, a non-flavonoid polyphenol: emerging evidence in last decades, J. Drug Deliv. Sci. Technol. 51 (2019) 591–604.
[87] P. Yingchoncharoen, D.S. Kalinowski, D.R. Richardson, Lipid-based drug delivery systems in cancer therapy: what is available and what is yet to come, Pharmacol. Rev. 68 (3) (2016) 701–787.
[88] Y.N. Zhao, et al., Anti-breast cancer activity of resveratrol encapsulated in liposomes, J. Mater. Chem. B 8 (1) (2020) 27–37.
[89] H.S. Lee, A.W. Ha, W.K. Kim, Effect of resveratrol on the metastasis of 4T1 mouse breast cancer cells in vitro and in vivo, Nutr. Res. Pract. 6 (4) (2012) 294–300.
[90] Y. Zhao, et al., Resveratrol inhibits proliferation, migration and invasion via Akt and ERK1/2 signaling pathways in renal cell carcinoma cells, Biomed. Pharmcother. 98 (2018) 36–44.
[91] S.K. Singh, et al., Resveratrol induces cell cycle arrest and apoptosis with docetaxel in prostate cancer cells via a p53/ p21WAF1/CIP1 and p27KIP1 pathway, Oncotarget 8 (10) (2017) 17216–17228.
[92] Z. Liu, Y. Li, R. Yang, Effects of resveratrol on vascular endothelial growth factor expression in osteosarcoma cells and cell proliferation, Oncol. Lett. 4 (4) (2012) 837–839.

[93] L. Peng, D. Jiang, Resveratrol eliminates cancer stem cells of osteosarcoma by STAT3 pathway inhibition, PLoS One 13 (10) (2018), e0205918.
[94] Q. Ji, et al., Resveratrol inhibits invasion and metastasis of colorectal cancer cells via MALAT1 mediated Wnt/beta-catenin signal pathway, PLoS One 8 (11) (2013), e78700.
[95] L. Yuan, et al., Resveratrol inhibits the invasion and metastasis of colon cancer through reversal of epithelial- mesenchymal transition via the AKT/GSK-3β/Snail signaling pathway, Mol. Med. Rep. 20 (3) (2019) 2783–2795.
[96] D. Li, et al., Resveratrol suppresses colon cancer growth by targeting the AKT/STAT3 signaling pathway, Int. J. Mol. Med. 43 (1) (2019) 630–640.
[97] M. Xu, et al., Apigenin suppresses colorectal cancer cell proliferation, migration and invasion via inhibition of the Wnt/beta-catenin signaling pathway, Oncol. Lett. 11 (5) (2016) 3075–3080.
[98] P. Angulo, et al., Natural compounds targeting major cell signaling pathways: a novel paradigm for osteosarcoma therapy, J. Hematol. Oncol. 10 (1) (2017) 10.
[99] Y. Zhong, et al., Molecular targets of apigenin in colorectal cancer cells: involvement of p21, NAG-1 and p53, Eur. J. Cancer 46 (18) (2010) 3365–3374.
[100] C. Huang, et al., Chrysin, abundant in morinda citrifolia fruit water-EtOAc extracts, combined with apigenin synergistically induced apoptosis and inhibited migration in human breast and liver cancer cells, J. Agric. Food Chem. 64 (21) (2016) 4235–4245.
[101] B. Sung, H.Y. Chung, N.D. Kim, Role of apigenin in cancer prevention via the induction of apoptosis and autophagy, J. Cancer Prev. 21 (4) (2016) 216–226.
[102] X. Yan, et al., Apigenin in cancer therapy: anti-cancer effects and mechanisms of action, Cell Biosci. 7 (2017) 50.
[103] C.M. Lin, et al., Apigenin-induced lysosomal degradation of beta-catenin in Wnt/beta-catenin signaling, Sci. Rep. 7 (1) (2017) 372.
[104] X. Tong, K.A. Smith, J.C. Pelling, Apigenin, a chemopreventive bioflavonoid, induces AMP-activated protein kinase activation in human keratinocytes, Mol. Carcinog. 51 (3) (2012) 268–279.
[105] S. Mirzoeva, C.A. Franzen, J.C. Pelling, Apigenin inhibits TGF-beta-induced VEGF expression in human prostate carcinoma cells via a Smad2/3- and Src-dependent mechanism, Mol. Carcinog. 53 (8) (2014) 598–609.
[106] M.A. Hasnat, et al., Apigenin attenuates melanoma cell migration by inducing anoikis through integrin and focal adhesion kinase inhibition, Molecules 20 (12) (2015) 21157–21166.
[107] H. Cardenas, et al., Dietary apigenin exerts immune-regulatory activity in vivo by reducing NF-kappaB activity, halting leukocyte infiltration and restoring normal metabolic function, Int. J. Mol. Sci. 17 (3) (2016) 323.
[108] R. Liu, et al., Apigenin enhances the cisplatin cytotoxic effect through p53–modulated apoptosis, Oncol. Lett. 13 (2) (2017) 1024–1030.
[109] R.P. Carnevale, et al., Progestin effects on breast cancer cell proliferation, proteases activation, and in vivo development of metastatic phenotype all depend on progesterone receptor capacity to activate cytoplasmic signaling pathways, Mol. Endocrinol. 21 (6) (2007) 1335–1358.
[110] Y. Liang, et al., Synthetic progestins induce growth and metastasis of BT-474 human breast cancer xenografts in nude mice, Menopause 17 (5) (2010) 1040–1047.
[111] B. Mafuvadze, et al., Apigenin induces apoptosis and blocks growth of medroxyprogesterone acetate-dependent BT-474 xenograft tumors, Horm. Cancer 3 (4) (2012) 160–171.
[112] J. Yang, C. Pi, G. Wang, Inhibition of PI3K/Akt/mTOR pathway by apigenin induces apoptosis and autophagy in hepatocellular carcinoma cells, Biomed. Pharmacother. 103 (2018) 699–707.
[113] M.-M. Liu, et al., Apigenin 7-O-glucoside promotes cell apoptosis through the PTEN/PI3K/AKT pathway and inhibits cell migration in cervical cancer HeLa cells, Food Chem. Toxicol. 146 (2020), 111843.
[114] J. Tong, et al., Apigenin inhibits epithelial-mesenchymal transition of human colon cancer cells through NF-κB/Snail signaling pathway, Biosci. Rep. 39 (2019) 5.
[115] X. Chen, et al., Apigenin inhibits in vitro and in vivo tumorigenesis in cisplatin-resistant colon cancer cells by inducing autophagy, programmed cell death and targeting m-TOR/PI3K/Akt signalling pathway, J. buon 24 (2) (2019) 488–493.
[116] M.K. Shanmugam, et al., The multifaceted role of curcumin in cancer prevention and treatment, Molecules 20 (2) (2015) 2728–2769.
[117] J.S. Jurenka, Anti-inflammatory properties of curcumin, a major constituent of Curcuma longa: a review of preclinical and clinical research, Alter. Med Rev. 14 (2) (2009) 141–153.
[118] X.Y. Xu, et al., Bioactivity, health benefits, and related molecular mechanisms of curcumin: current progress, challenges, and perspectives, Nutrients 10 (2018) 10.
[119] L. Wu, et al., Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway, Oncol. Rep. 34 (6) (2015) 3311–3317.
[120] L.L. Marotta, et al., The JAK2/STAT3 signaling pathway is required for growth of CD44+CD24− stem cell-like breast cancer cells in human tumors, J. Clin. Investig. 121 (7) (2011) 2723–2735.
[121] L. Ricci-Vitiani, et al., Identification and expansion of human colon-cancer-initiating cells, Nature 445 (7123) (2007) 111–115.
[122] A.C. Bharti, N. Donato, B.B. Aggarwal, Curcumin (Diferuloylmethane) inhibits constitutive and IL-6-inducible STAT3 Phosphorylation in human multiple myeloma cells, J. Immunol. 171 (7) (2003) 3863–3871.
[123] Y. Zhou, et al., The JAK2/STAT3 pathway inhibitor, AG490, suppresses the abnormal behavior of keloid fibroblasts in vitro, Int. J. Mol. Med. 46 (1) (2020) 191–200.
[124] Y. Liu, et al., The targeting of noncoding RNAs by curcumin: facts and hopes for cancer therapy (Review), Oncol. Rep. 42 (1) (2019) 20–34.
[125] Y. Zhang, et al., EZH2 overexpression is associated with poor prognosis in patients with glioma, Oncotarget 8 (1) (2017) 565–573.
[126] J. Adiwidjaja, A.J. McLachlan, A.V. Boddy, Curcumin as a clinically-promising anti-cancer agent: pharmacokinetics and drug interactions, Expert Opin. Drug Metab. Toxicol. 13 (9) (2017) 953–972.
[127] B. Bao, et al., Hypoxia-induced aggressiveness of pancreatic cancer cells is due to increased expression of VEGF, IL-6 and miR-21, which can be attenuated by CDF treatment, PLoS One 7 (12) (2012), e50165.
[128] A. Pagliuca, et al., Analysis of the combined action of miR-143 and miR-145 on oncogenic pathways in colorectal cancer cells reveals a coordinate program of gene repression, Oncogene 32 (40) (2013) 4806–4813.
[129] C.C. Yu, et al., miR145 targets the SOX9/ADAM17 axis to inhibit tumor-initiating cells and IL-6-mediated paracrine effects in head and neck cancer, Cancer Res. 73 (11) (2013) 3425–3440.
[130] K.S. Ahn, et al., Guggulsterone, a farnesoid X receptor antagonist, inhibits constitutive and inducible STAT3 activation through induction of a protein tyrosine phosphatase SHP-1, Cancer Res. 68 (11) (2008) 4406–4415.
[131] F.-U. Hassan, et al., Curcumin as an alternative epigenetic modulator: mechanism of action and potential effects, Front. Genet. 10 (2019) 514.
[132] C. Xiao, et al., Curcumin inhibits oral squamous cell carcinoma SCC-9 cells proliferation by regulating miR-9 expression, Biochem. Biophys. Res. Commun. 454 (4) (2014) 576–580.
[133] W.C. Lu, et al., EGF up-regulates miR-31 through the C/EBPbeta signal cascade in oral carcinoma, PLoS One 9 (9) (2014), e108049.
[134] J. Ma, et al., Curcumin inhibits cell growth and invasion through up-regulation of miR-7 in pancreatic cancer cells, Toxicol. Lett. 231 (1) (2014) 82–91.
[135] S. Ali, et al., Deregulation of miR-146a expression in a mouse model of pancreatic cancer affecting EGFR signaling, Cancer Lett. 351 (1) (2014) 134–142.
[136] G. Sa, T. Das, Anti cancer effects of curcumin: cycle of life and death, Cell Div. 3 (2008) 14.
[137] C. Bertoli, J.M. Skotheim, R.A.M. de Bruin, Control of cell cycle transcription during G1 and S phases, Nat. Rev. Mol. Cell Biol. 14 (8) (2013) 518–528.
[138] F. Firouzi Amoodizaj, et al., Enhanced anticancer potency of doxorubicin in combination with curcumin in gastric adenocarcinoma, J. Biochem. Mol. Toxicol. 34 (6) (2020), e22486.
[139] S. Bisht, et al., Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy, J. Nanobiotechnol. 5 (2007) 3.
[140] M.M. Yallapu, et al., Anti-cancer activity of curcumin loaded nanoparticles in prostate cancer, Biomaterials 35 (30) (2014) 8635–8648.
[141] M.M. Yallapu, M. Jaggi, S.C. Chauhan, Curcumin nanomedicine: a road to cancer therapeutics, Curr. Pharm. Des. 19 (11) (2013) 1994–2010.
[142] A.S. Ombredane, et al., In vivo efficacy and toxicity of curcumin nanoparticles in breast cancer treatment: a systematic review, Front. Oncol. 11 (2021), 612903.
[143] H.A. Alhazmi, et al., Medicinal plants and isolated molecules demonstrating immunomodulation activity as potential alternative therapies for viral diseases including COVID-19, Front. Immunol. 12 (1721) (2021).
[144] O. Demaria, et al., Harnessing innate immunity in cancer therapy, Nature 574 (7776) (2019) 45–56.
[145] I. Jantan, W. Ahmad, S.N.A. Bukhari, Plant-derived immunomodulators: an insight on their preclinical evaluation and clinical trials, Front. Plant Sci. 6 (2015) 655.
[146] H. Wei, et al., Antioxidant and antipromotional effects of the soybean isoflavone genistein, Proc. Soc. Exp. Biol. Med. 208 (1) (1995) 124–130.
[147] T. Ak, İ. Gülçin, Antioxidant and radical scavenging properties of curcumin, Chem. Biol. Interact. 174 (1) (2008) 27–37.
[148] İ. Gülçin, Antioxidant properties of resveratrol: a structure–activity insight, Innov. Food Sci. Emerg. Technol. 11 (1) (2010) 210–218.
[149] D. Xu, et al., Antioxidant activities of quercetin and its complexes for medicinal application, Molecules 24 (6) (2019) 1123.
[150] E. Safarzadeh, S. Sandoghchian Shotorbani, B. Baradaran, Herbal medicine as inducers of apoptosis in cancer treatment, Adv. Pharm. Bull. 4 (Suppl 1) (2014) 421–427.
[151] N. Bailon-Moscoso, et al., Natural compounds as modulators of cell cycle arrest: application for anticancer chemotherapies, Curr. Genom. 18 (2) (2017) 106–131.
[152] S.P. Tu, et al., Curcumin induces the differentiation of myeloid-derived suppressor cells and inhibits their interaction with cancer cells and related tumor growth, Cancer Prev. Res. 5 (2) (2012) 205–215.
[153] Y.-F. Chang, et al., Immunomodulation of curcumin on adoptive therapy with T cell functional imaging in mice, Cancer Prev. Res. 5 (3) (2012) 444.
[154] C. Varalakshmi, et al., Immunomodulatory effects of curcumin: in-vivo, Int. Immunopharmacol. 8 (5) (2008) 688–700.
[155] G. Chhabra, et al., Recent advancements on immunomodulatory mechanisms of resveratrol in tumor microenvironment, Molecules 26 (5) (2021) 1343.
[156] V. Vetvicka, J. Vetvickova, Natural immunomodulators and their stimulation of immune reaction: true or false? Anticancer Res. 34 (5) (2014) 2275.
[157] S. Kilani-Jaziri, et al., Flavones induce immunomodulatory and anti-inflammatory effects by activating cellular antioxidant activity: a structure-activity relationship study, Tumor Biol. 37 (5) (2016) 6571–6579.
[158] A.M. Oo, et al., Immunomodulatory effects of flavonoids: an experimental study on natural-killer-cell-mediated cytotoxicity against lung cancer and cytotoxic granule secretion profile, Proc. Singap. Healthc. 30 (4) (2020) 279–285.
[159] A. Ghaemi, et al., Genistein induces a protective immunomodulatory effect in a mouse model of cervical cancer, Iran. J. Immunol. 9 (2) (2012) 119–127.
[160] T.L. Guo, et al., Genistein modulates immune responses and increases host resistance to B16F10 tumor in adult female B6C3F1 mice, J. Nutr. 131 (12) (2001) 3251–3258.

[161] T.H. Kang, et al., Epigallocatechin-3-gallate enhances CD8+ T cell-mediated antitumor immunity induced by DNA vaccination, Cancer Res. 67 (2) (2007) 802–811.
[162] A.C. Huang, et al., Epigallocatechin gallate (EGCG), influences a murine WEHI-3 leukemia model in vivo through enhancing phagocytosis of macrophages and populations of T- and B-cells, In Vivo 27 (5) (2013) 627–634.
[163] D.S. Hsieh, et al., The treatment of bladder cancer in a mouse model by epigallocatechin-3-gallate-gold nanoparticles, Biomaterials 32 (30) (2011) 7633–7640.
[164] F. Saleh, et al., Analysis of the effect of the active compound of green tea (EGCG) on the proliferation of peripheral blood mononuclear cells, BMC Complement. Altern. Med. 14 (1) (2014) 322.
[165] J. Beltran, A.K. Ghosh, S. Basu, Immunotherapy of tumors with neuroimmune ligand capsaicin, J. Immunol. 178 (5) (2007) 3260.
[166] J.N. Yao, et al., Discovery and anticancer evaluation of a formononetin derivative against gastric cancer SGC7901 cells, Investig. New Drugs 37 (6) (2019) 1300–1308.
[167] H. Wang, et al., Formononetin inhibits enterovirus 71 replication by regulating COX- 2/PGE_2 expression, Virol. J. 12 (2015) 35.
[168] L.E. Fried, J.L. Arbiser, Honokiol, a multifunctional antiangiogenic and antitumor agent, Antioxid. Redox Signal. 11 (5) (2009) 1139–1148.
[169] S. Ponnurangam, et al., Honokiol in combination with radiation targets notch signaling to inhibit colon cancer stem cells, Mol. Cancer Ther. 11 (4) (2012) 963–972.
[170] S.S. Kanwar, et al., Difluorinated-curcumin (CDF): a novel curcumin analog is a potent inhibitor of colon cancer stem-like cells, Pharm. Res 28 (4) (2011) 827–838.
[171] H. Shibata, et al., Newly synthesized curcumin analog has improved potential to prevent colorectal carcinogenesis in vivo, Cancer Sci. 100 (5) (2009) 956–960.
[172] Y. Li, et al., Evaluation of curcumin, a natural product in turmeric, on Burkitt lymphoma and acute myeloid leukemia cancer stem cell markers, Future Oncol. 14 (23) (2018) 2353–2360.
[173] W. Wang, et al., Ursolic acid inhibits the growth of colon cancer-initiating cells by targeting STAT3, Anticancer Res 33 (10) (2013) 4279–4284.
[174] Z. Birsu Cincin, et al., Anti-proliferative, apoptotic and signal transduction effects of hesperidin in non-small cell lung cancer cells, Cell Oncol. 38 (3) (2015) 195–204.
[175] R.S. Taylor, G.H. Towers, Antibacterial constituents of the Nepalese medicinal herb, Centipeda minima, Phytochemistry 47 (4) (1998) 631–634.
[176] G.J. Du, et al., Epigallocatechin Gallate (EGCG) is the most effective cancer chemopreventive polyphenol in green tea, Nutrients 4 (11) (2012) 1679–1691.
[177] Y.S. Chiou, et al., Peracetylated (-)-epigallocatechin-3-gallate (AcEGCG) potently prevents skin carcinogenesis by suppressing the PKD1-dependent signaling pathway in CD34+ skin stem cells and skin tumors, Carcinogenesis 34 (6) (2013) 1315–1322.
[178] S.Z. Qian, Z.G. Wang, Gossypol: a potential antifertility agent for males, Annu Rev. Pharmacol. Toxicol. 24 (1984) 329–360.
[179] S.R. Volate, et al., Gossypol induces apoptosis by activating p53 in prostate cancer cells and prostate tumor-initiating cells, Mol. Cancer Ther. 9 (2) (2010) 461–470.
[180] P. Chonsut, et al., Ethoxy mansonone G as an anticancer agent in estrogen receptor-positive and endocrine-resistant breast cancer, J. Pharm. Pharmacol. 71 (12) (2019) 1839–1853.
[181] L. Zhang, et al., Genistein inhibits the stemness properties of prostate cancer cells through targeting Hedgehog-Gli1 pathway, Cancer Lett. 323 (1) (2012) 48–57.
[182] J. Zhu, et al., Genistein induces apoptosis by stabilizing intracellular p53 protein through an APE1-mediated pathway, Free Radic. Biol. Med. 86 (2015) 209–218.
[183] G. Kallifatidis, et al., Sulforaphane increases drug-mediated cytotoxicity toward cancer stem-like cells of pancreas and prostate, Mol. Ther. 19 (1) (2011) 188–195.
[184] S.K. Katiyar, Grape seed proanthocyanidines and skin cancer prevention: inhibition of oxidative stress and protection of immune system, Mol. Nutr. Food Res. 52 Suppl 1 (Suppl 1) (2008) S71–S76.
[185] R. Prasad, S.K. Katiyar, Grape seed proanthocyanidins inhibit migration potential of pancreatic cancer cells by promoting mesenchymal-to-epithelial transition and targeting NF-κB, Cancer Lett. 334 (1) (2013) 118–126.
[186] Y.C. Hsieh, et al., Methyl antcinate A from Antrodia camphorata induces apoptosis in human liver cancer cells through oxidant-mediated cofilin- and Bax-triggered mitochondrial pathway, Chem. Res. Toxicol. 23 (7) (2010) 1256–1267.
[187] W.C. Tsai, et al., Methylantcinate A induces tumor specific growth inhibition in oral cancer cells via Bax-mediated mitochondrial apoptotic pathway, Bioorg. Med. Chem. Lett. 20 (20) (2010) 6145–6148.
[188] Y. Dong, et al., Oridonin inhibits tumor growth and metastasis through anti-angiogenesis by blocking the Notch signaling, PLoS One 9 (12) (2014), e113830.
[189] N. Kang, et al., Inhibition of caspase-9 by oridonin, a diterpenoid isolated from Rabdosia rubescens, augments apoptosis in human laryngeal cancer cells, Int. J. Oncol. 47 (6) (2015) 2045–2056.
[190] F.W. Hu, et al., Impairment of tumor-initiating stem-like property and reversal of epithelial-mesenchymal transdifferentiation in head and neck cancer by resveratrol treatment, Mol. Nutr. Food Res. 56 (8) (2012) 1247–1258.
[191] M. Kasdagly, et al., Colon carcinogenesis: influence of Western diet-induced obesity and targeting stem cells using dietary bioactive compounds, Nutrition 30 (11–12) (2014) 1242–1256.
[192] M. Careri, et al., Direct HPLC analysis of quercetin and trans-resveratrol in red wine, grape, and winemaking byproducts, J. Agric. Food Chem. 51 (18) (2003) 5226–5231.
[193] R. Deng, Therapeutic effects of guggul and its constituent guggulsterone: cardiovascular benefits, Cardiovasc. Drug Rev. 25 (4) (2007) 375–390.
[194] S.V. Singh, et al., Caspase-dependent apoptosis induction by guggulsterone, a constituent of Ayurvedic medicinal plant Commiphora mukul, in PC-3 human prostate cancer cells is mediated by Bax and Bak, Mol. Cancer Ther. 4 (11) (2005) 1747–1754.
[195] Z. Peng, J.P. Raufman, G. Xie, Src-mediated cross-talk between farnesoid X and epidermal growth factor receptors inhibits human intestinal cell proliferation and tumorigenesis, PLoS One 7 (10) (2012), e48461.
[196] G. Deng, et al., Emodin inhibits the proliferation of PC3 prostate cancer cells in vitro via the Notch signaling pathway, Mol. Med. Rep. 12 (3) (2015) 4427–4433.
[197] J.H. Du, et al., Artesunate induces oncosis-like cell death in vitro and has antitumor activity against pancreatic cancer xenografts in vivo, Cancer Chemother. Pharmacol. 65 (5) (2010) 895–902.
[198] L. Xu, et al., Role of JNK activation and mitochondrial bax translocation in allicin-induced apoptosis in human ovarian cancer SKOV3 cells, Evid. Based Complement. Altern. Med. 2014 (2014), 378684.
[199] H.P. Lin, et al., Caffeic acid phenethyl ester induced cell cycle arrest and growth inhibition in androgen-independent prostate cancer cells via regulation of Skp2, p53, p21Cip1 and p27Kip1, Oncotarget 6 (9) (2015) 6684–6707.
[200] K.C. Lee, et al., A proteomics approach to identifying novel protein targets involved in erinacine A-mediated inhibition of colorectal cancer cells' aggressiveness, J. Cell Mol. Med. 21 (3) (2017) 588–599.
[201] H.C. Kuo, et al., A comparative proteomic analysis of erinacine a's inhibition of gastric cancer cell viability and invasiveness, Cell Physiol. Biochem. 43 (1) (2017) 195–208.
[202] L. Wang, et al., Morusin inhibits human cervical cancer stem cell growth and migration through attenuation of NF-κB activity and apoptosis induction, Mol. Cell Biochem. 379 (1–2) (2013) 7–18.
[203] Y. Zhu, et al., Deoxyshikonin isolated from Arnebia euchroma inhibits colorectal cancer by down-regulating the PI3K/Akt/mTOR pathway, Pharm. Biol. 57 (1) (2019) 412–423.
[204] F.L. Zhang, et al., Topoisomerase I inhibitors, shikonin and topotecan, inhibit growth and induce apoptosis of glioma cells and glioma stem cells, PLoS One 8 (11) (2013), e81815.
[205] B. Salehi, et al., The therapeutic potential of apigenin, Int. J. Mol. Sci. 20 (2019) 6.
[206] H.S. Seo, et al., Apigenin induces caspase-dependent apoptosis by inhibiting signal transducer and activator of transcription 3 signaling in HER2-overexpressing SKBR3 breast cancer cells, Mol. Med. Rep. 12 (2) (2015) 2977–2984.
[207] W. Wang, et al., Cell-cycle arrest at G2/M and growth inhibition by apigenin in human colon carcinoma cell lines, Mol. Carcinog. 28 (2) (2000) 102–110.
[208] S. Shukla, S. Gupta, Apigenin-induced cell cycle arrest is mediated by modulation of MAPK, PI3K-Akt, and loss of cyclin D1 associated retinoblastoma dephosphorylation in human prostate cancer cells, Cell Cycle 6 (9) (2007) 1102–1114.
[209] M.V. Blagosklonny, et al., Taxol-induced apoptosis and phosphorylation of Bcl-2 protein involves c-Raf-1 and represents a novel c-Raf-1 signal transduction pathway, Cancer Res. 56 (8) (1996) 1851–1854.
[210] J. Okano, A.K. Rustgi, Paclitaxel induces prolonged activation of the Ras/MEK/ERK pathway independently of activating the programmed cell death machinery, J. Biol. Chem. 276 (22) (2001) 19555–19564.
[211] A. Koval, et al., Tannins from Syzygium guineense suppress Wnt signaling and proliferation of Wnt-dependent tumors through a direct effect on secreted Wnts, Cancer Lett. 435 (2018) 110–120.
[212] N. Rajasekar, et al., An overview on the role of plant-derived tannins for the treatment of lung cancer, Phytochemistry 188 (2021), 112799.
[213] R. A.Y, et al., Recent advances in tannic acid (Gallotannin) anticancer activities and drug delivery systems for efficacy improvement; a comprehensive review, Molecules 26 (2021) 5.
[214] H.Y. Park, et al., Calotropin: a cardenolide from Calotropis gigantea that inhibits Wnt signaling by increasing casein kinase 1α in colon cancer cells, ChemBioChem 15 (6) (2014) 872–878.
[215] G. Sferrazza, et al., Nature-derived compounds modulating Wnt/β-catenin pathway: a preventive and therapeutic opportunity in neoplastic diseases, Acta Pharm. Sin. B 10 (10) (2020) 1814–1834.