Food and Chemical Toxicology 128 (2019) 240–255

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Natural products: An upcoming therapeutic approach to cancer

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ARTICLE INFO

Keywords:
Cancer
Natural compounds
Apoptotic pathway
Autophagy
Wnt
Notch
Hedgehog

ABSTRACT

Cancer is one of the leading causes of death across the world. Different environmental and anthropogenic factors initiate mutations in different functional genes of growth factors and their receptors, anti-apoptotic proteins, self-renewal developmental proteins, tumor suppressors, transcription factors, etc. This phenomenon leads to altered protein homeostasis of the cell which in turn induces cancer initiation, development, progression and survival. From ancient times various natural products have been used as traditional medicine against different diseases. Natural products are readily applicable, inexpensive, accessible and acceptable therapeutic approach with minimum cytotoxicity. As most of the target-specific anticancer drugs failed to achieve the expected result so far, new multi-targeted therapies using natural products have become significant. In this review, we have summarized the efficacy of different natural compounds against cancer. They are capable of modulating cancer microenvironment and diverse cell signaling cascades; thus playing a major role in combating cancer. These compounds are found to be effective against several signaling pathways, mainly cell death pathways (apoptosis and autophagy) and embryonic developmental pathways (Notch pathway, Wnt pathway and Hedgehog pathway). This review article is expected to be helpful in understanding the recent progress of natural product research for the development of anticancer drug.

1. Introduction

Cancer is considered as a major cause of death worldwide (Antoni et al., 2017). Cancer is a group of diseases where uncontrolled cell growth occurs and has the potential to spread to other parts of the body. The tumor suppressing mechanisms present in a normal cell always distinguishes between abnormally growing cancer cells and normal cells but the problem arises when the functions of these tumor suppressing genes get restricted by different environmental factors (like pollution, radiation, certain infections, etc.) or human habits (like tobacco, poor diet, alcohol, etc.) (Aruoma et al., 2014; Bagnardi et al., 2014; Gallagher et al., 2017; Leon et al., 2015; Massarweh and El-Serag, 2017; Raaschou-Nielsen et al., 2016; Taylor et al., 2017). In 2018, about 18.1 million (17.0 million excluding nonmelanoma skin cancer) new cases of cancer and 9.6 million deaths from cancer (9.5 million excluding nonmelanoma skin cancers) were reported. Cancer has become a major cause of mortality all over the world irrespective of human development. Lung cancer is the most identified cancer (11.6% of the total cases), narrowly followed by female breast cancer (11.6%), prostate cancer (7.1%) and colorectal cancer (6.1%). Moreover, lung cancer is also the major reason of cancer death (18.4% of the total cancer deaths), followed by colorectal cancer (9.2%), stomach cancer (8.2%) and liver cancer (8.2%) (Bray et al., 2018).

Natural products isolated from medicinal plants have been used for the treatment of various diseases from ancient times. The first use of natural products as medicine was dated back in 2600 BC in Mesopotamia. The “Ebers Papyrus” records of more than 700 drugs back in 1550 BC are also well preserved (Borchardt, 2002; Cragg and Newman, 2013b). Similarly, traditional Chinese medicine (TCM) is well documented over thousands of years (Unschuld, 1985; Yang et al., 2017c) and the Indian Ayurveda system is practiced since the 1st millennium BC (Parasuraman et al., 2014; Patwardhan and Gautam, 2005).

Abbreviations: BCC, Basal cell carcinoma; c-FLIP, Cellular FLICE inhibitory protein; CSCs, Cancer stems cells; CYPs, cytochromes P450; DHH, Desert HH; DIM, 3,3′-Diindolylmethane; DISC, Death-inducing signaling complex; DMBA, 7,12-dimethyl benz[a]anthracene; EGCG, Epigallocatechin-3-gallate; EMT, Epithelial–mesenchymal transition; FDA, Food and Drug Administration; HH, Hedgehog; HTS, High throughput screening; IAP, Inhibitor of apoptosis; IGFR, Insulin growth factor receptor; IHH, Indian HH; IMS, Inter-membrane space; LC3, Light chain 3; MAP, Mitogen-activated protein, mTOR; MOMP, Mitochondrial outer membrane permeabilization; MPM, Malignant pleural mesothelioma; MT, Melatonin receptor; NDEA, N-Nitrosodiethylamine; NPC, Nasopharyngeal carcinoma; PDAC, Pancreatic ductal adenocarcinoma; PFJ, Pomegranate fruit juice; PI3K, Phosphoinositide 3-kinase; SHH, Sonic HH; TCM, Traditional Chinese medicine; VEGF, Vascular endothelial growth factor; YAP, Yes-associated protein

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https://doi.org/10.1016/j.fct.2019.04.012
Received 21 February 2019; Received in revised form 8 April 2019; Accepted 9 April 2019

0278-6915/

Natural product-based drug discovery is related to some challenges, like availability, identification of bioactive compounds, difficulty in the collection of wild specimen and incompatibility of natural products with high throughput screening (HTS) (Atanasov et al., 2015). Further evaluation of the exact molecular mechanism of action of natural products is a difficult task. Due to these difficulties, pharmaceutical industries shifted their main focus towards synthetic compounds for new drug discoveries. But the results obtained from the newly introduced synthetic drugs in the 1990s did not match the expectations (Scannell et al., 2012). The approval rates of these drugs by the US Food and Drug Administration (FDA) was low. Due to these reasons, the interest in natural product-based drug discovery was revived.

Different natural phytochemicals used for the treatment of various diseases including cancer are becoming important for drug discovery and research (Dutta et al., 2018; Jagtap et al., 2009; Jeong et al., 2006; Manna et al., 2006; Pal et al., 2012, 2015; Sadhukhan et al., 2018a, 2018b; Saha et al., 2018). These phytochemicals are found to be effective against various types of cancer. They show such effectiveness by alternating the cancer initiation, development and progression as well as interrupting several mechanisms like differentiation, cellular proliferation, angiogenesis, apoptosis and metastasis (Amin et al., 2009; Huang et al., 2009; Nobili et al., 2009). Irrespective of cancer specificity, recent research indicates that most of the cancer onsets are caused by mutations in protein coding-genes and alteration in protein production (Davies et al., 2002; Nik-Zainal et al., 2016). Several cell signaling proteins such as growth factors and their receptors, anti-apoptotic proteins, tumor suppressors and transcription factors are altered in cancer and can be treated as therapeutic targets (Gotwals et al., 2017; Topalian et al., 2015). Programmed cell death, especially apoptosis and autophagy, are the natural obstacles that limit cancer cells progression and development. These mechanisms may jointly decide the fate of cancer cells. They play an important role during tissue homeostasis preservation and elimination of cancerous cells (Esteve and Knecht, 2011). However, cancer cells develop different approaches to avoid cell death by producing epigenetic modifications or genetic mutations in the major component of programmed cell death pathways (Coyle et al., 2017). These cells become resistant to programmed cell death and become tumor-relapsing self-renewal cancer stems cells (CSCs). CSCs display many features of embryonic or tissue stem cells (Zhang et al., 2019). They exhibit determined activation of one or more highly conserved tissue developmental pathway, including the Notch, Hedgehog (HH), and Wnt pathways (Takebe et al., 2015a). These pathways are the key modulator of tumorigenicity of cancer stem cells. Increasing evidence indicates that these embryonic pathways can crosstalk with other cellular signaling pathways (Apoptosis, autophagy, NFκB, MAPK, PI3K, and EGF) (Sever and Brugge, 2015). Recent studies indicate that in anticancer therapy, we can use different natural compounds targeting programmed cell death mechanism or embryonic developmental pathways to restored normal tissue homeostasis (Ke et al., 2016; Oren and Smith, 2017; Varoni et al., 2016). Although diverse approaches are accessible for the discovery of novel and potential therapeutic agents modulating cell signaling cascades, natural products from medicinal plants and other sources seems to be the most cost-effective and promising approach (Atanasov et al., 2015; Dutta et al., 2017, 2018).

Therefore, identification of natural compounds which selectively inhibit the initiation, progression, metastasis of carcinogenesis and elimination of the CSCs at the same time, without cytotoxic effects in normal cells, has become important.

2. Cell signaling pathways as therapeutic targets for cancer therapy

Cellular signaling pathways are complex communication network made up of small three-dimensional signaling cascades comprising of many signaling proteins. The actions of these proteins are specific to cell type, cell site and intra-molecular interactions. Alteration in these proteins homeostasis leads to the diverse diseased conditions. In case of cancer, alternation of cell signaling cascades may lead to an elevated immune response, increased cancer cell proliferation and survival (Hanahan and Weinberg, 2011).

2.1. Cell death pathways and cancer

Programmed cell death is referring to apoptosis and autophagy. In any pathophysiological condition, programmed cell death can be initiated by some intracellular program. These forms of cell death pathways may cooperatively regulate the fate of cancer cells (Liu et al., 2009). Apoptosis contributes to cell death, whereas autophagy can play either pro-survival or pro-death roles (Ouyang et al., 2012).

2.1.1. Apoptosis

Apoptotic pathway plays a significant role in the developmental process and regulates tissue homeostasis by destroying harmful cells. Inhibition of apoptosis leads to abnormal cell proliferation and increases the chance of genetic defects that ultimately leads to tumor formation (Sun et al., 2015). Apoptosis can be initiated by intrinsic signals due to genotoxic stress or by extrinsic signals where different ligands bind to cell surface receptor. In recent studies, it has been found that cancer cells protect themselves from apoptosis due to the abnormal action of some major apoptosis regulatory proteins like Bcl-2 family proteins, the inhibitor of apoptosis (IAP) proteins, cellular FLICE-inhibitory protein, etc. (Siddiqui et al., 2015). The Bcl-2 family proteins work as an apoptotic switch by controlling the activation of BAX and BAK that consequently induces the mitochondrial outer membrane permeabilization (MOMP) (Brahmbhatt et al., 2015). MOMP initiates diffusion of various proteins into the cytosol which is normally restricted to mitochondrial inter-membrane space (IMS). Activated MOMP also shifts the binding activities of pro-apoptotic and anti-apoptotic Bcl-2 family proteins in response to diverse stimuli which ultimately determine the fate of the cancer cell, whether a cell will live or die (Brahmbhatt et al., 2015). IAP protein family members are generally over-expressed in cancer and lead to tumor chemo-resistance, cell survival and disease progression. They resist the apoptosis of diverse tumor cell by inhibiting the caspase activation or otherwise they get degraded via different proteasome to allow apoptosis (Obexer and Ausserlechner, 2014). Cellular FLICE inhibitory protein (c-FLIP) blocks apoptosis by preventing the activation of caspase-8 within the death-inducing signaling complex (DISC). In recent studies, elevated expression of c-FLIP was reported in human cancers (like pancreatic cancer, breast cancer, lung cancer, etc.). c-FLIP also plays an important role in modulating different drug-induced apoptosis in human breast cancer and lung cancer cells (Baratchian et al., 2016; Nazim et al., 2016). (Fig. 1)

2.1.2. Autophagy

Autophagy, a ‘‘self-eating’’ phenomenon, is the intracellular process involving lysosomal degradation and recycling of proteins as well as organelles. Various carcinogenic risk factors (e.g., chronic inflammation, aging and obesity) hinder the process of autophagy. The role of autophagy in cancer is context-dependent due to its diverse cellular activities (Maiuri et al., 2007). In epithelial cells, altered autophagic signaling increases the chance of genomic instability, oxidative stress and activates Nrf2 which ultimately promotes tumor initiation, induces the expression of several antioxidant genes and drug-metabolizing enzymes (Moscat et al., 2016). Altered autophagy inhibits tumor suppressing gene-mediated cell senescence and thus directs the proliferation of cancer progenitor cells (Dou et al., 2015). In fast-growing cancer cells, autophagy provides nutrition for better survival of cancer cell (Perera et al., 2015). Autophagy upregulated cancers cells express lower numbers of Foxp3$^+$ T regulatory cells and higher numbers of CD8$^+$ T cells and increased microtubule-associated protein 1A/1B light chain 3 (LC3) expression (Ladoire et al., 2016a, 2016b). Interestingly, it

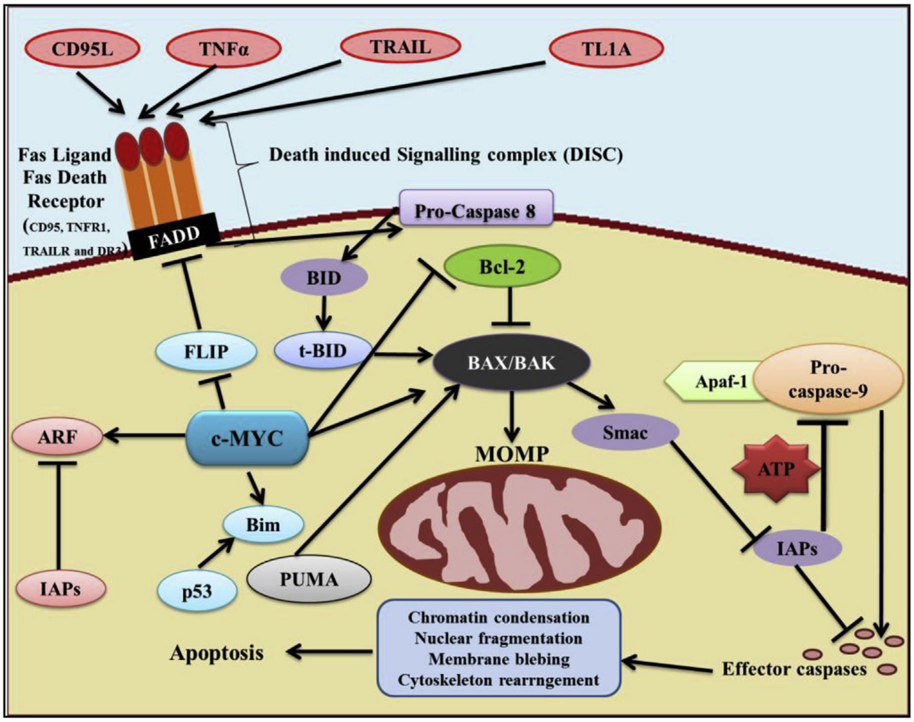

Fig. 1. Schematic representation of molecular targets in apoptosis for cancer therapy. Fas ligands bind with Fas death receptors, causing the formation of death induced signaling complex (DISC). Other downstream molecules have been activated by DISC and ultimately lead to production of effector caspase and apoptosis.

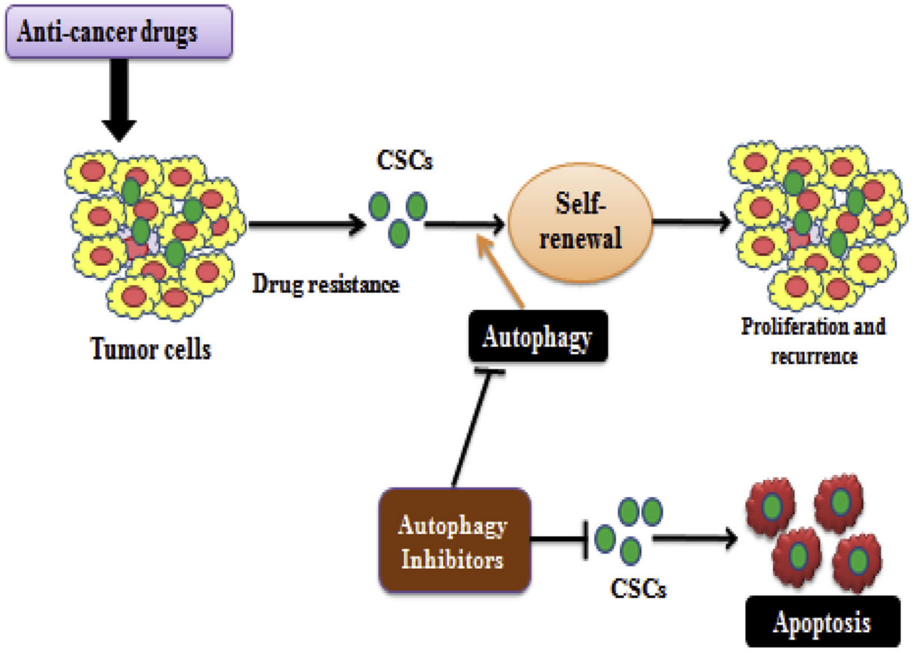

Fig. 2. Schematic representation of the formation of CSCs and the role of autophagy in cancer therapy. Different cancer therapy can decrease cancer cells survival by abolishing the highly proliferative cells but the dormant CSCs are beyond their limit. These drug resistant CSCs can initiate new cancer development. Therefore, cancer therapeutic drugs targeting CSCs might be a beneficial approach for inhibiting tumor regrowth and self-renewal.

has been found that increased autophagy leads to upregulation of antitumor immunity and its downregulation improves malignancy by impairing immune surveillance. In fact, oncogene activation can hinder autophagy, in a similar mechanism used for the inhibition of apoptosis (Amaravadi et al., 2007). (Fig. 2)

2.1.3. Natural compounds modulating cell death pathways in cancer

The use of different natural compounds as an anticancer drug is gaining great importance due to their availability and less side effects. The natural products suppressed the progression of the different form of cancer by interfering cooperative signaling and host gene expression (Giri and Narasu, 2000). Apoptosis pathways and autophagic pathways are mainly targeted by natural compounds for developing anti-cancer drugs. The mode of action of some natural compounds, having cell death pathway pathway modulating properties is being discussed below:

2.1.3.1. Quercetin. Quercetin, a polyphenolic phytonutrient flavonoid, extracted from fruits, vegetables and grains, induces E-cadherin and simultaneously suppresses vimentin as well as N-cadherin and reverses the epithelial to mesenchymal transition. It also potentially reduces the expression levels of MMP-2, MMP-9, PI3K/Akt, pGSK3β and Snail in breast cancer cells (Balakrishnan et al., 2016; Quagliariello et al., 2016) along with upregulation in the levels of Bax, cleaved caspases and JAK/STAT pathway thereby potentiating cancer cell apoptosis (Seo et al., 2016). In case of renal cancers, along with protection against DOX-induced nephrotoxicity, quercetin reduces TNF-α, IL-1β and iNOS expressions (Heeba and Mahmoud, 2016). In case of prostate cancer, it induces TGF-β-induced expressions of downstream genes (Baruah et al., 2016) and inhibits expressions of VEGF and Ki67 (Sharma et al., 2016). Quercetin also protects against lung cancer by triggering the hindrance of the migration of A549 cells and promoting Bcl2/Bax-mediated apoptosis (Klimaszewska-Wiśniewska et al., 2017). In pancreatic cancer, it activates caspases and inhibits the phosphorylations of ERK and JNK (Zou et al., 2015). It also retards tumor growth and inhibits drug resistance in this type of cancer. Further, in case of hepatic carcinoma, it reduces ROS in cancer cells, inhibits the activities of PKC, PI3K and COX-2 while elevating BAX and p53 expressions (Guan et al., 2016; Maurya and Vinayak, 2015). Different researchers have also shown that the anticancer activity of quercetin was increased by nano mediated targeted delivery (Bernela et al., 2018). In a docking study, using hierarchical inverse screening approach with SHAFTS-LIBRA and idTarget, different protein targets of quercetin was identified. The targets includes PI3K, xanthine oxidase, glycogen synthasekinase-3 beta, MAPK 14 and poly(ADP-ribose) polymerases (Carvalho et al., 2017). Thus, further research may reinstate this molecule as a promising anticarcinogen in near future.

2.1.3.2. Silymarin. Silymarin is an extract of the milk thistle (Silybum marianum) which exhibits anticancer effects on N-Nitrosodiethylamine (NDEA)-induced rat hepato-carcinogenesis by reducing the extent of lipid peroxidation, decreasing MMP-2, MMP-9 and COX-2 levels, restoring GSH levels and various antioxidant enzymes activities (Ramakrishnan et al., 2007, 2009a, 2009b). Silibinin induces apoptosis in MCF-7 breast cancer cells by inhibiting the expression of insulin growth factor receptor (IGFR) and suppressed the metastasis of MDA-MB-231 cells (Kim et al., 2009; Singh et al., 2004; Soria et al., 2007). It also inhibits mitomycin C-induced cell death in human melanoma A 375- S2 cells by downregulating p53 and Bcl-2 mediated apoptosis. Silibin is also effective against GI tract cancers. It inhibits the growth of LoVo cells (colon cancer cell line) by inducing apoptosis via PARP cleavage and caspase-3 activation. Silymarin inhibits the proliferation of RT4 cells (human bladder papilloma cells) and bladder tumor xenograft in mice by downregulating surviving proteins expressions and upregulating p53 expression (Boamah et al., 2007). In a molecular docking study and binding analysis, silibinin shows substantial binding interaction with vital residues (like ASP813, ARG817, MET769, ASN818 etc.) in the active site of EGFR (Hosen et al., 2016).

2.1.3.3. Resveratrol. Resveratrol (3, 5, 4-trihydroxystilbene), a naturally occurring polyphenol (stilbenoid), has two phenol rings linked to each other by an ethylene bridge. It resides in two isomeric forms, cis- and trans-resveratrol where the latter is most prevalent one (Akinwumi et al., 2018; Anisimova et al., 2011; Orallo, 2006). It is found in many fruits such as grapes, peanut, blueberries and also in red wine (Keylor et al., 2015). A recent study showed the efficacy of resveratrol to inhibit the growth of human colon cancer in ls174t cells, by upregulating pro-apoptotic Bax and downregulating anti-apoptotic Bcl-2 (Peng et al., 2015). It also reduces the growth of human HCT116 cells by Sirt1-mediated inhibition of NF-κB (Mukhtar et al., 2012). Another study reveals that 5 gm resveratrol daily administration increase the expression of cleaved caspase-3 by 39% in 9 patients with colon cancer (Singh et al., 2015). The possibility of topical application also makes the skin a suitable target. Skin cancer is the most common cancer in America and many studies indicated that resveratrol can be effective against it (Aziz and Aziz, 2018). A recent report showed that resveratrol reduces tumor volume in DMBA-induced skin cancer in male Wistar rats by arresting cell-cycle and subsequent apoptosis (Hu et al., 2016). Again resveratrol suppresses tumor growth in female C57Bl/6 N mice (Caltagirone et al., 2000) and induces apoptosis in melanoma cells suppressing survivin in a STAT3/β-catenin-dependent manner (Habibie et al., 2014). Resveratrol shows its anticancer activity through the induction of apoptosis and autophagy or by the inhibition of metastasis and angiogenesis. It can also reverse the Warburg effect by enhancing pyruvate dehydrogenase complex activity in colon cancer cells (Saunier et al., 2017). Resveratrol suppresses the NLRP3 inflammasome formation by inducing autophagy via Akt/mTOR pathway inhibition (Wang et al., 2017b). It also shows its anticancerous efficacy by suppressing inflammation via modulating MAP kinase (Andrews et al., 2016) and Nrf-2 pathways (Singh et al., 2014; Truong et al., 2018). Recent studies reveal that resveratrol can inhibit cyclooxygenase-1 and 2 and thereby decreases inflammation by downregulating NF-κB (Cianciulli et al., 2012). Furthermore, anticancer efficacy of resveratrol is due to the inhibited metabolic activity of the phase-I antioxidant enzyme, cytochromes P450 (CYPs) (Guthrie et al., 2017). Resveratrol have the ability to induce autophagy in different cancer cell lines by a prodeath or a prosurvival mechanism. According to Li et al. resveratrol (50 μM for 24 h), induces a substantial increase in autophagy leading to nonapoptotic programmed cell death in DU145 cells (Li et al., 2013a).

2.1.3.4. Melatonin. Melatonin (N-acetyl-5-methoxy tryptamine) is a neurohormone secreted by pineal gland in animals exhibits a wide range of physiological effects like antioxidant activity, circadian rhythm regulation, etc. (Pévet, 2002). In human neuroblastoma cell line SH-SY5Y, melatonin inhibits prion protein induced neuronal cell death by β-catenin activation which in turn upregulates anti-apoptotic protein survivin and Bcl-2 (Jeong et al., 2014). It suppresses oral cancer cells proliferation and induces apoptosis by downregulating cyclin D1, PCNA and Bcl-2 expression and upregulating Bax expression. Melatonin inhibits oral cancer cells migration by reducing Snail and Vimentin expression and elevating E-cadherin expression. It hinders vasculogenic activity of oral cancer cells via suppressing ERKs and Akt signaling cascade (Liu et al., 2018a). In gastric cancer, melatonin administration inhibits gastric tumor growth and its dissemination by suppressing epithelial-mesenchymal transition via ER stress-mediated pathway (Wu et al., 2016b). Melatonin treatment in SGC-7901 GC cells caused reduced CDC25A, phospho-CDC25A, p21 and phospho-p21 expression to block cell cycle progression. It induces the apoptosis of SGC-7901 GC cells by increasing phosphorylation of p-p38 and p-JNK protein and decreasing the expression of nucleic p-p65. Melatonin upregulates Bax/Bcl-2 ratio and induces mitochondria-mediated apoptosis. It efficiently decreases the expression of MDM2, phospho-MDM2 (at Ser166), Akt, phospho-Akt (at Thr308) and increased p53 expression (Song et al., 2018). In Cal-27 and SCC-9 (head and neck squamous cell carcinoma cell lines), melatonin treatment along with rapamycin synergistically inhibits Akt/mTOR pathway and induced mitophagy and apoptosis. In colorectal cancer, melatonin exerts an anticarcinogenic effect by downregulating PrPC and PINK1 levels and stimulating ER stress, mitochondrial dysfunction to promote apoptotic death (Yun et al., 2018). Melatonin treatment induces Mia PaCa-2 cells apoptosis by inactivating NF-κB p65 and activating c JNK and ERK1/2 which in turn upregulates Bax protein and cleaved caspase 3 expressions (Li et al., 2016). Melatonin along with sorafenib inhibits pancreatic ductal adenocarcinoma (PDAC) by stimulating mitochondrial dysfunction mediated apoptosis. It effectively downregulates melatonin receptor (MT)-mediated STAT3 and PDGFR-β/STAT3 signaling cascade (Fang et al., 2018). Melatonin inhibits p65 phosphorylation to suppress NF-κB signaling and stimulates ROS production. This upregulated redox stress mitigates the radio-resistance and growth of thyroid cancer cell (Zou et al., 2018). It increases HeLa cells apoptosis along with cisplatin treatment by inactivating JNK/Parkin/mitophagy signaling (Chen et al., 2018). Melatonin has been reported to exhibite a repressive effect on the catalytic activity of MMP-9 by binding with its active site in a gastric adenocarcinoma cell line (Rudra et al., 2013).

2.1.3.5. Taurine. Taurine (2-aminoethanesulfonic acid) is a sulphur-containing amino acid which is prevalent in animal tissue. Although it is synthesized endogenously, a major source of taurine comes from diet, mainly eggs, meat and seafoods (Das et al., 2009, 2012). It is an antioxidant and possesses anti-cancerous activity. It ameliorated mammary carcinogenesis by inducing apoptosis (Vanitha et al., 2018). In 7,12-dimethyl benz[a]anthracene (DMBA)-induced breast cancer model, taurine treatment sufficiently abrogated the progression of mammary carcinogenesis by downregulating Bcl-2 expression and upregulating p-53, Bax, caspase-3 and caspase-9 expression (Vanitha et al., 2015). It suppresses tumor growth by inducing apoptosis in MCF-7 cells by upregulating PUMA expression which in turn upregulates Bax/Bcl-2 ratio to increase caspase-3 activation (Zhang et al., 2015). Taurine treatment in Caco-2 cells causes enhanced apoptosis by activating MST1-JNK signaling pathway (Liu et al., 2018c). Taurine induces apoptosis in A549 cell by upregulating PUMA, Bax expression and downregulating Bcl-2 expression (Tu et al., 2018). In Nasopharyngeal carcinoma (NPC), taurine markedly suppressed NPC cells proliferation and stimulated apoptosis by activating mitochondrial and ER stress-mediated apoptosis. It also upregulated PTEN expression and inactivated Akt expression (He et al., 2018). Taurine treatment in melanoma cell line BI6F10 efficiently reduced melanoma progression by inducing apoptosis (Kim et al., 2015).

2.1.3.6. Astaxanthin. Astaxanthin, the king of carotenoids, extracted from microalgae, shrimp and trout, stimulated apoptotic cell death by downregulating the expression of Bcl-2, p-Bad, surviving (antiapoptotic) and upregulating Bax and Bad (proapoptotic), Smac/Diablo and cytochrome-c expression. Molecular docking study reveals that astaxanthin binds with STAT-3 and VEGF with a docking score of −5.081 and −2.94 respectively (Kowshik et al., 2014). The docking studies also exposes that astaxanthin interacts with the catalytic domains of ERK1, Akt1 and GSK3β to form hydrogen bonds with Ile 48 and Lys 131 of ERK1, Arg 273 and Cys 296 of Akt1, and Arg 113 of GSK3β (Kavitha et al., 2013). Astaxanthin treatment along with lutein and β-carotene synergistically caused apoptosis and inhibited the proliferation of MCF-10A. It arrests cell cycle at the G0/G1 phase and altered the expression of cyclin D1, p53, Bax and Bcl-2 expressions (Sowmya et al., 2017). Astaxanthin restored the radiosensitivity of esophageal squamous cell carcinoma (ESCC) cells. It stimulated apoptosis and caused G2/M cell cycle arrest by suppressing Bcl-2, CyclinB1, Cdc2 and inducing Bax expression (Qian et al., 2017). A549 lung cancer cell growth was inhibited in astaxanthin treatment by up-regulating Bax and down-regulating Bcl-2, JAK1 and STAT3 expression (Wu et al., 2016a). In H22 hepatoma cells, Astaxanthin prevented cell proliferation by introducing cell cycle arrest and stimulated apoptosis (Shao et al., 2016). In CBRH-7919 cell line (hepatocellular carcinoma cells), astaxanthin caused altered mitochondrial transmembrane potential that ultimately induced upregulation of Bax/Bcl-2 ratio to stimulate the process of apoptosis (Jiao et al., 2016). In 1, 2 dimethyl hydrazine (DMH)-induced rat colon carcinogenesis, it stopped the progression of tumor by inhibiting the expression of MMP-2/9. It induces apoptosis by downregulating the expression of NF-κB-p65, COX-2, ERK-2 and Akt (Nagendraprabhu and Sudhandiran, 2011) and suppresses colitis-associated colon cancer by inhibiting inflammatory cytokines expression (Yasui et al., 2011).

2.1.3.7. Tannic acid. Tannic acid extracted from green teas and red wines, stimulated ROS production and promoted disruption of mitochondrial membrane potential. It induced the activation of caspase-3 and caspase-9 and the cleavage of PARP (Zhang et al., 2018b). Tannic acid treatment in prostate cancer cells suppressed their invasive and migratory property by reducing the level of MMP-2 and MMP-9 and restoring E-cadherin activity. It induced ER stress-mediated cytotoxicity in prostate cancer cell by upregulation ER stress-related markers such as PERK and IRE1 and altered the expressions of various regulatory proteins such as ATF4, Bip and PDI. It upregulated Bim, caspase-3 and cleaved PARP and downregulated Bcl-2 and Bcl-xL to induce apoptosis in the cancerous cells (Nagesh et al., 2018). In gingival squamous cell carcinoma, tannic acid inhibited cell proliferation by cell cycle arrest at the G1/S phase and prevented JAK2/STAT3 pathway activation (Darvin et al., 2015).

2.1.3.8. Curcumin. Curcumin, isolated from Curcuma longa, induced apoptosis by stimulating p-53, caspase-3 and caspase-9 expression (Ghosh et al., 2015; Gogada et al., 2011). Curcumin treatment against malignant pleural mesothelioma (MPM) (cancer due to asbestos exposure) exhibits antiproliferative and antitumor effects with minimum toxicity. In RN5 MPM cell line, curcumin inhibited cell viability and stimulated apoptosis via the mitochondrial, caspase-independent and AIF-dependent pathways (Zhang et al., 2018a). Curcumin derivative L6H4 (curcuminL6H4) induced apoptosis on of BGC-823 cells modulating the expression levels of p53, p21, Bax and Bcl-2 (Mu et al., 2019). Curcumin, along with gallic acid, induced apoptosis in MDA-MB-231 cells by downregulating Bcl-2 and upregulating Bax, cleaved-caspase-3 and PARP levels (Moghtaderi et al., 2018). In T47D, MCF7, MDA-MB-231 and MDA-MB-468 cells, curcumin inhibited cell proliferation by arresting cell cycle at the G2/M phase and downregulating CDC25 and CDC2 expression. It induced apoptosis by inhibiting the phosphorylation of Akt/mTOR and altering Bax/Bcl-2 ratio (Hu et al., 2018). Curcumin induces autophagy in different cell lines. After curcumin treatment (20 μM for 24 h) the cell viability was observed to be reduced in 22Rv1 cells due to autophagy induction. It was found that the LC3-II was increased and the Bcl-XL expression was decreased (Naponelli et al., 2015). Molecular docking studies showed that curcumin formed a valid docked complex with ATP-binding site of Akt with glide score of −7.90 (Rana et al., 2015).

Ferulic acid (FA) is a derivative of curcumin and has gained therapeutic importance due to high bioavailability, low cost and minimal side-effects. FA inhibits cancer cell proliferation, progression and invasion. The survival of human cervical cancer cells (Hela and Caski) are significantly inhibited by FA treatment. It induces cell cycle arrest at G0/G1 phase by upregulating p53 and p21 expression and down-regulating Cyclin D1 level. It also decreased the level of autophagy markers such as Beclin1, LC3-II and Atg12-Atg5 (Gao et al., 2018). In another study, FA treatment induces human breast cancer cell proliferation dose-dependently by up-regulating HER2 and ERα expression (Zhou et al., 2018). Treatment of FA in prostate cancer cell lines (PC-3 and LNCaP) also inhibits the cell proliferation by suppressing invasion and colony formation ability of prostate cancer cells. FA up regulates the expression of ATM, ATR, CDKN1B, CDKN1A, CASP1, CASP2, CASP8, E2F4, CYCS, FAS, FASLG, TP53, TRADD and RB1 and down regulates the expressions of CDK2, CDK4, CDK6, CCND1, CCND2, CCND3, BCL2 and XIAP (Eroğlu et al., 2015).

2.1.3.9. Berberine. Berberine**,** an isoquinoline quaternary alkaloid, is isolated from different medicinal herbs such as Coptis japonica, Coptis chinensis, Berberis aristata, Hydrastis Canadensis, Phellondendron chinense Schneid, Phellondendron amurense, etc. (Guamán Ortiz et al., 2014). Berberine treatment directly induces apoptotic factors, promotes cell cycle arrest and initiates programmed cell death in various cancer cell lines. Berberine modulates dissociation/assembly of Bcl-2 family members which maintain the balance between apoptosis and autophagy (Wang et al., 2010a). Berberine disrupts MMP that initiates the release of cytochrome c and ultimately activates different caspases and induces cleavage of PARP-1(Lin et al., 2006). Berberine upregulated the expression of pro-apoptotic protein Bax (Bcl-2-associated X protein) (Choudhuri et al., 2002) and decreased the

Table 1
Natural anti-cancer compounds with their sources and cell death pathways modulating property. The molecules incorporated are quercetin, silymarin, resveratrol, melatonin, taurine, astaxanthin, tannic acid, curcumin, berberine, ellagic acid, icariin, epigallocatechin-3-gallate (EGCG), 3,3′-diindolylmethane (DIM) and vitamin D3.

Natural compounds	Source	Anticancer mechanism modulating cell death pathway
Quercetin	Fruits, vegetables and grains	Suppress N-cadherin, MMP-2, MMP-9, PI3K/Akt, pGSK3β, Snail, TNF-α, IL-1β, iNOS, ERK and JNK. Stimulate Bax, cleaved caspases and JAK/STAT.
Silymarin	Milk thistle (Silybum marianum)	Inhibits MMP-2, MMP-9, COX-2, IGFR and Bcl-2. Activate PARP cleavage and caspase-3.
Resveratrol	Grapes, peanut, blueberries and red wine.	Upregulates Bax, Suppresses NLRP3 inflammasome formation. Downregulates Bcl-2, NF-κB and cytochromes P450.
Melatonin	Pineal gland	Upregulates surviving, Bax, (p)-p38 and p-JNK. Downregulates cyclin D1, PCNA, Bcl-2 expression, Snail, Vimentin, CDC25A, Akt, phospho-CDC25A, p21 and phospho-p21.
Taurine	Eggs, meat and seafood	Downregulates Bcl-2, PTEN expression. Upregulates p-53, Bax, PUMA, PTEN, caspase-3 and caspase-9 expression.
Astaxanthin	Microalgae, shrimp and trout	Upregulates Bax, Bad, Smac/Diablo and cytochrome-c. Downregulates Bcl-2, p-Bad, surviving, CyclinB1, Cdc2, MMP-2/9, NF-κB-p65, COX-2, ERK-2, JAK1 and STAT3.
Tannic acid	Green tea and red wines	Induced Bim, caspase-3, caspase-9 and PARP cleavage. Inhibits MMP-2, MMP-9, Bcl-2 and Bcl-xL.
Curcumin	Curcuma longa	Downregulate Bcl-2, Akt/mTOR phosphorylation. Upregulate Bax, cleaved-caspase-3, PARP and LC3-II.
Berberine	*Coptis japonica, Coptis chinensis and Berberis aristata*	Induces cytochrome c, caspases, PARP-1 cleavage, Bax. Inhibits Bcl-2, NF-κB, AP-1, GTPase, FAK, u-PA, NF-κB, MMP-9 and MMP-2.
Ellagic acid	Pomegranates, raspberries, strawberries, blackberries and nuts	Decrease NF-κB, iNOS, COX-2, TNF-α, IL-6, MMP-2 and MMP-9. Induces cytochrome C.
Icariin	*Herba Epimedii*	Increases Bax/Bcl2 ratio, cytochrome c release, PARP cleavage, ATF, p-PERK, p-eIF2α, GRP78, CHOP and caspase activation. Downregulated Bcl-2, NF-κB, Cyclin D1, CDK4 and phosphorylated pRb.
Epigallocatechin-3-gallate (EGCG)	Green tea	Induces FAS, BAD, BAK, WNT11, IGF1R, and ZEB1. Inhibits TP53, CASP8, and MYC.
3,3′-Diindolylmethane (DIM)	Cruciferous vegetables	Upregulate Bid, CHOP and cleavage of caspase 3, caspase 8 and PARP
Vitamin D3	Salmon, tuna, egg, oyster, shrimp, mushroom	Initiate Beclin1 mediated autophagy

expression of Bcl-2/Bcl-xL in human prostate cancer, leukemia, gastric carcinoma and lung cancer cells (Choi et al., 2009). Pro-apoptotic effects of berberine were found to be regulated through the JNK/p38 and HER2/PI3K/Akt pathways (Kuo et al., 2011; Li et al., 2014; Tillhon et al., 2012). Moreover, it causes cell cycle arrest and triggers apoptosis by inhibiting the expression of NF-κB. Similarly, the downregulation of AP-1 by berberine, induces apoptosis in human oral, hepatoma, colon and breast cancer cells. It is also effective against TRAIL-sensitive and TRAIL-resistant breast cancer cells. Time and dose dependent application of berberine inhibited human papilloma virus transcription in cervical cancer cell lines (Ke et al., 2018). In addition, berberine suppressed tumor progression and metastasis by inhibiting GTPase, FAK, u-PA, NF-κB, MMP-9 and MMP-2 expression (He et al., 2014).

2.1.3.10. Ellagic acid. Ellagic acid, hugely available in berries and nuts, exhibits anti-proliferative activity and induces caspase-mediated apoptosis. It inhibits polycyclic aromatic hydrocarbon-induced tumor formation by suppressing CYPlAl-dependent activation of benzo[a] pyrene (Kaur et al., 2006). Pomegranate fruit juice (PFJ) which is a rich source of ellagic acid has been found to slow down the rate of cancer progression. PFJ treatment significantly decreases the proliferation and migration of the ovarian cancer cell line A2780. Ellagic acid and luteolin dose-dependently decrease MMP-2 and MMP-9 expressions. This reduced MMP-2 and MMP-9 expression successfully inhibited tumor growth in ES-2 cell line induced nude mice cancer model (Liu et al., 2017). In human pancreatic adenocarcinoma cells, ellagic acid treatment accelerated the process of apoptosis by inducing mitochondrial depolarization, cytochrome C release and suppressing cell proliferation. In 1, 2-dimethylhydrazine induced-colon cancer rat model, ellagic acid treatment restored the altered levels of diverse tumor marker enzymes (like glutamyl transpeptidase, nucleotidase, alphafetoprotein gamma carcinoembryonic antigen, cathepsin-D, etc.) and several pathophysiological markers (alkaline phosphatase and lactate dehydrogenase). Ellagic acid treatment downregulated the production of NF-κB, iNOS, COX-2, TNF-α and IL-6 expression to suppress inflammation and thus exhibited its chemopreventive effect in colon carcinoma (Umesalma and Sudhandiran, 2010, 2011). Recent molecular docking simulation suggested that ellagic acid can form aromatic and hydrogen bonds within the ATP-binding site of the VEGFR-2 kinase unit (Wang et al., 2012).

2.1.3.11. Icariin. Icariin is a prenylated flavonol glycoside extracted from the medical plant *Herba Epimedii* (Berberidaceae). It increases Bax/Bcl2 ratio, cytochrome c release, PARP cleavage and caspase activation (He et al., 2010; Li et al., 2010; Wu et al., 2015). In human hepatocellular carcinoma, icariin induced Fas-mediated caspase-dependent apoptotic pathway (Liu et al., 2015). In human adenocarcinoma and esophageal cancer cells, icariin upregulated endoplasmic reticulum stress-related molecules (like ATF, p-PERK, p-eIF2α, GRP78, CHOP, etc.) and downregulated anti-apoptotic Bcl-2 protein expression (Di et al., 2015; Fan et al., 2016). In colorectal carcinoma cells and gallbladder cancer cells, it inhibited NF-κB activity and induced G0/G1 and G2/M phase cell cycle arrest (Zhang et al., 2013a). In prostate cancer cells, icariin upregulated p16Ink4a, p27Kip1 and pRb expression and downregulated Cyclin D1, CDK4 and phosphorylated pRb expression to inhibit the cell proliferation (Huang et al., 2007). In NK/T cell lymphoma cells, icariin induced cell cycle arrest at the G2/M phase (Zhou et al., 2011). In hepatocellular and renal cell carcinoma xenograft tumors models, icariin and its derivatives have also shown their anti-angiogenic action. It significantly decreased pan-endothelial marker CD31 in mice tumors and suppressed the migration and adhesion of highly metastatic human lung carcinoma cells (Xu et al., 2010). Icariin suppressed human gastric cancer cell invasion and migration by regulating vasodilator-stimulated phosphoprotein expression (Wang et al., 2010b).

2.1.3.12. Other natural products. Other natural products could also regulate apoptosis and autophagy. Epigallocatechin-3-gallate (EGCG) is obtained from green tea. EGCG treatment dose-dependently and time-dependently suppresses the proliferation of human oral squamous cell (SSC-4) (Irimie et al., 2015a). EGCG directly activates the expression of the *FAS, BAD, BAK, WNT11, IGF1R,* and *ZEB1* genes and inhibits *TP53, CASP8,* and *MYC*. Subsequently, EGCG exposure activates apoptosis and autophagy (Irimie et al., 2015b). 3,3′-Diindolylmethane (DIM), inhibits the growth of pancreatic cancer cells (Panc-1 and Panc-28). DIM and its derivatives induce common receptor-dependent and receptor-independent (ER stress) pathways. In addition, DIM induces CHOP-dependent induction of DR5 (death receptor) by activating Bid and leading successive cleavage of caspase 3, caspase 8 and PARP (Abdelrahim et al., 2006). Similarly another natural compound, piperine inhibits the proliferation of the PCA cells. It induces G0/G1 cell cycle arrest and autophagy (Ouyang et al., 2013). Vitamin D3 inhibits human myeloid leukemia cells by inducing Beclin1 mediated autophagy (Wang et al., 2008). Anti-cancer properties (modulating cell death pathway) of different natural compounds have been represented in Table 1.

2.2. Embryonic developmental pathway and cancer

In last few decades' cancer stem cells (CSCs), draw therapeutic attention due to its slow growth rates, controversial origin and chemotherapeutic and/or radio-therapeutic resistance. CSCs exhibit many embryonic stem cells like features including activation of different conserved developmental signal transduction pathways like the Notch pathways, Wnt pathways and HH pathways (Phi et al., 2018; Takebe et al., 2015a).

2.2.1. Notch signaling pathway

The Notch signaling pathway is an evolutionarily conserved pathway, plays a crucial role in embryonic and postnatal development. Due to its pleiotropic nature, the pathway is susceptible to an anomalous opening of different signaling molecules that lead to the onset of several human diseases such as various developmental diseases, malignancies and so on (Angulo et al., 2017). At present, there are four genetic diseases occurred due to mutations of Notch signaling pathway proteins (Alagille Syndrome, tetralogy of Fallot, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts, spondylocostal dysostosis and Leukoencephalopathy) (Gridley, 2003). Notch signaling also found to be involved in the development of different type of cancers. T-cell leukemia and breast cancer can be initiated due to viral insertion or translocation induced elevation of the Notch receptor. Altered Notch expression levels are also observed in mucoepidermoid tumors, cervical cancer, lung cancer, etc. (Wang et al., 2010c). The complex, multifaceted Notch pathway comprises five canonical Notch ligands and four notch receptor paralogue. Diverse tumors express several Notch receptor and ligands. Post-translational modifications of its receptors can alter ligand-receptor affinity and intracellular dynamics (D'Souza et al., 2010). Different types of notch inhibitors (like γ-secretase inhibitors and anti dll4 antibodies) are clinically developed which significantly used against cancer (Ran et al., 2017). Emerging evidence indicated that the achievement of an epithelial–mesenchymal transition (EMT) phenotype contributes to drug resistance and tumor recurrence and Notch signaling regulates in this process. To mitigate the notch pathway as a therapeutic approach against cancer, further investigation of the role of Notch in various cancer and the identification of different notch is required (Fig. 3).

2.2.2. Wnt signaling pathway

Wnt signaling is an evolutionarily conserved cell signaling pathway which is responsible for various developmental events (like cell fate determination, cell migration, stem cell renewal, organogenesis, etc.) as well as diseases' progression (osteoporosis-pseudoglioma syndrome, Robinow syndrome, Brachydactyly and formation of different type of cancers in the breast, skin and colon) (Huang et al., 2015). Currently, Wnt signaling cascades include two major types of pathways, β-catenin dependent (canonical) and independent (non-canonical) signaling (Many and Brown, 2014). Mutations in Wnt signaling cascade cause the development of a diverse type of carcinomas. The APC gene mutations are commonly observed in adenomatous polyposis syndrome (hereditary colon cancer). A mutation in APC causes improper stabilization of β-catenin and leads to the formation of a complex between β-catenin and TCF7l2/TCF4 (TCF family member) (Hankey et al., 2018; MacDonald et al., 2009). Similarly in hereditary Axin2, mutations are found in colon cancer, colorectal cancers, melanoma and hepatocellular carcinomas (Mazzoni and Fearon, 2014). Recently, inactivating mutations are observed in ZNRF3 (E3 ligase genes) in both pancreatic cancer and adrenocortical carcinoma (Hao et al., 2016). Mutations in ß-catenin and axin-1 are also reported in different cancer cells. Wnt signaling can be downregulated by the action of the transmembrane molecule, ZNRF3 and RNF3. These signaling molecules have E3 ubiquitin ligase activity that causes ubiquitinilation of Frizzled molecules. Binding of RSPO with ZNRF3 causes down regulation of ZNRF3 activity and initiates Wnt signaling. In some cancer cells, ZNRF3 and RNF3 are found to be mutated (MacDonald and He, 2012). (Fig. 4)

2.2.3. HH pathway

The HH pathway has an important role in embryonic development and tissue repair mechanism. There are three types of HH ligands – SHH (Sonic HH), IHH (Indian HH) and DHH (Desert HH) (Skoda et al., 2018). These ligands remove inhibitory effect of patched (PTCH) cell membrane receptor on Smoothened (SMO). This activated SMO subsequently activates the nuclear localization of Zinc finger protein GLI transcription factors (glioma-associated oncogene). This leads to the expression of different HH target genes which are involved in angiogenesis, survival and proliferation (Rimkus et al., 2016). HH signaling cascades can be treated as prominent therapeutic targets for cancer therapy as an alteration in this cascade leads to tumor growth and carcinogenesis. In recent years, SMO inhibitors of HH signaling are successfully used in cancer therapy. But in case of basal cell carcinoma (BCC) patients, resistance against SMO inhibitors has been already reported (Yang and Dinehart, 2017). Further identification and therapeutic use of more downstream HH signaling inhibitors should be an effective strategy to control cancer cell proliferation. The use of GLI inhibitors is the most potent approach for the downstream regulation of HH signaling pathway. Reports suggest that the use of GLI1/2 inhibitor GANT61 showed promising result against human cancer cells and xenograft mouse models (Mastrangelo and Milani, 2018; Yang et al., 2017a). Furthermore, the non-canonical activation of the GLI transcription factors is mediated by different signaling pathways (e.g., MAPK, PI3K and TGF-β) and thereby targeting these pathways can provide more therapeutic importance against tumors which are insensitive to GLI inhibitors (Lauth and Toftgård, 2007). (Fig. 5)

2.2.4. Natural compounds modulating embryonic developmental pathways in cancer

In recent years, considerable progress has been made in understanding the diverse developmental (Wnt, Notch and HH) signaling with respect to cancer development. Different modulators of these pathways could be useful in cancer prevention and therapy. In this regard, various natural compounds have been identified as possible modulators of Wnt, Notch and HH signaling pathway (Kamdje et al., 2017; McCubrey et al., 2016; Takebe et al., 2015b). The mode of action of some natural compounds, having embryonic developmental pathway modulating properties is being discussed below:

2.2.4.1. Curcumin. Curcumin treatment showed protection against Burkitt lymphoma and acute myeloid leukemia by decreasing several CSC markers like Gli-1, Notch-1 and Cyclin D1 (Li et al., 2018b). In

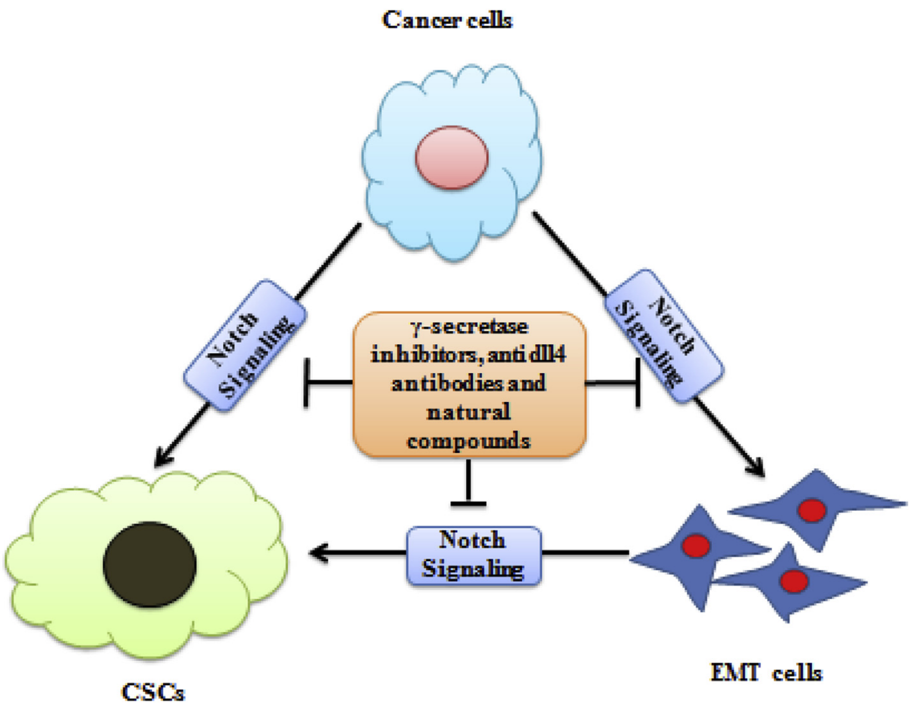

Fig. 3. Schematic representation of the relationship between cancer cells, CSCs, EMT cells and the role of Notch signaling as anticancer therapy.

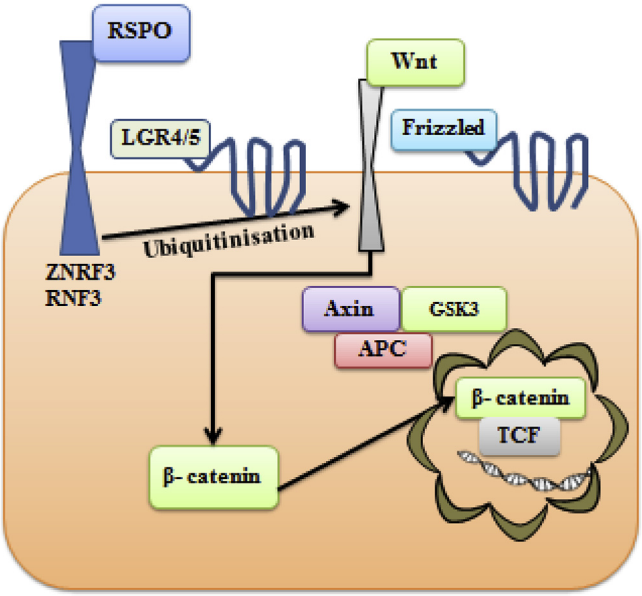

Fig. 4. Role of Wnt signaling in anticancer therapy. When Wnt signaling cascade is activated, the Wnt ligand binds to the Frizzled receptor and LRP co-receptor and stimulates LRP phosphorylation. Phosphorylated LRP recruits Axin to the membrane and disrupts the β-catenin degradation complex. β-catenin accumulates in the cytoplasm and subsequently translocates into the nucleus, where it binds to Tcf and triggers Wnt gene transcription. ZNRF3 and RNF3 are transmembrane molecules that can downregulate Wnt signaling cascade.

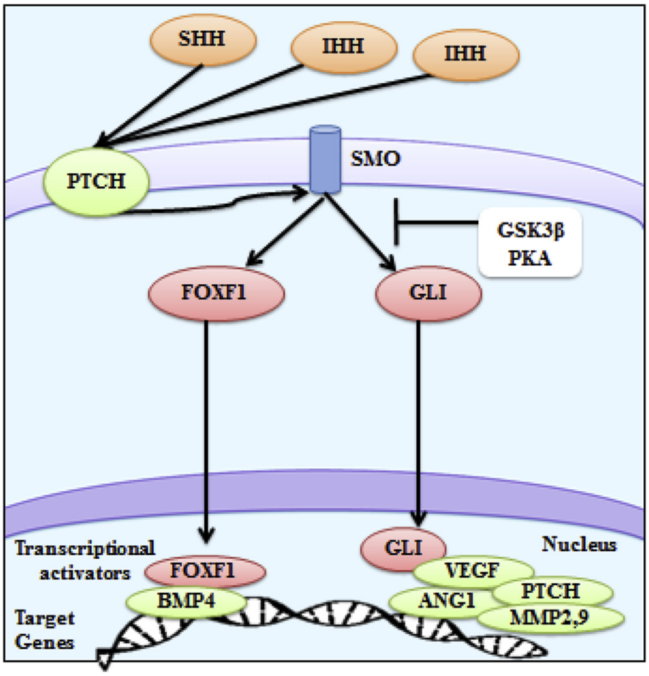

Fig. 5. Schematic representation of Hedgehog signal transduction pathway. Sonic hedgehog (SHH) and Indian hedgehog (IHH) bind to the patch-1 (PTCH1) membrane receptor. PTCH activates the transcription factors FOXF1 and GLI. FOXF1 and GLI can induce different downstream target genes including BMP-4, angiopoietin-1 (ANG1), MMP-2, MMP-9, Protein patched homolog (PTCH) and vascular endothelial growth factor (VEGF).

DU145 and PC3 cell line (prostate cancer cell line), curcumin suppressed cells proliferation and migration via inhibiting Notch-1 signaling pathway (Yang et al., 2017b). Curcumin caused downregulation of YAP (Yes-associated protein) and its close paralog TAZ (transcriptional coactivator with PDZ-binding motif) activity and consequently suppressed Notch-1 expression to inhibit pancreatic cancer progression (Zhou et al., 2016). Curcumin effectively downregulated breast CSCs and bladder CSCs markers like CD44, ALDH1A1, Nanog, Oct4, etc. and Shh and Wnt/β-catenin pathway to suppress breast and bladder CSCs inhibition (Li et al., 2018a; Wang et al., 2017a). It diminished lung CSC traits by inhibiting tumorsphere formation, reducing CD133-positive cells and CSC markers expression as well as suppressing activated HH pathways. In addition, curcumin significantly reduced CyclinD1 expression and downregulated UCA1

(UCA1 suppressed apoptosis) and subsequently Wnt and mTOR pathways (Wang et al., 2018). It could also reduce YAP expression and increase LC3-II, P-62 expression to promote autophagy in human colon cancer cells (Zhu et al., 2018).

2.2.4.2. Genistein. Genistein, abundantly available in the soy plants, exhibits anticancer activities by impeding cellular proliferation, invasion and angiogenesis in cancer cells with the alteration of the estrogen receptor-mediated molecular cascades and downregulating cyclin B1 expression. It also inhibits the activation of protein kinases and NF-κB. (Banerjee et al., 2005; Bhamre et al., 2010; Han et al., 2013; Nakamura et al., 2012; Salti et al., 2000). Further, being phytoestrogen by nature it averts metastatic breast cancer by binding with the estrogen receptors of the cancerous cells having diverse ratios of ERα/ERβ. Again, uncontrolled growth in colon cancer is inhibited by genistein supplementation by downregulating the upregulated EGF receptor via FOXO3 (Qi et al., 2010). The epigenetic modifications of the genes Sfrp2, Sfrp5 and Wnt5a as well as modulation of Wnt/β-catenin signaling pathway by genistein in a promoter-specific manner restrains the colon cancer development (Zhang et al., 2013b). It is also known to induce chromatin condensation and DNA fragmentation thereby changing morphological changes in colon cancer cells (Fan et al., 2010). In case of breast cancer, genistein hinders tumor progression by binding with estrogen receptors ERβ (owing to its structural similarity to estrogen) (McCarty, 2009). It also eliminates the cancer stem cells by decreasing the HH-Gli 1 signaling cascades (Fan et al., 2013). Genistein, by modulating the expressions of ERα, pAkt, IGF-1R and pIRS-1, causes death in ovarian cancer *in vitro* models (Hwang et al., 2013). Gastric cancer cell cycle arrest and loss of cell viability take place by reduced expression of KIF20A on genistein supplementation (Yan et al., 2012). Genistein potentially sensitizes the anticancer agents tamoxifen (Saha et al., 2014), cisplatin, quercetin (Hu et al., 2014; Tsuchiya et al., 2002), docetaxel and selenium (Kumi-Diaka et al., 2010; Li et al., 2006; Phillip et al., 2012).

2.2.4.3. 3, 3′-diindolylmethane (DIM). 3, 3′-diindolylmethane (DIM), a glucosinolates, derived from broccoli, can regulate Wnt signaling by modulating Akt/GSK-3β pathway. DIM inhibited GSK-3β phosphorylation and stimulated β-catenin phosphorylation in prostate cancer cells, which subsequently inhibited cell growth by inducing apoptosis (Li et al., 2013b; Sarkar et al., 2010b).

2.2.4.4. Lycopene. Another natural compound, lycopene, a biologically active carotenoid, prevented oxidative DNA damage, reduced inflammatory signals, and regulated the expression or activity of IGF/Akt, Wnt/β-catenin, and AR signaling (Trejo-Solís et al., 2013). Lycopene directly prevented β-catenin nuclear localization and inhibited IGF-1-stimulated prostate cancer growth, possibly by mitigating the effects of IGF-1 on phosphorylation of GSK-3β and Akt (Allen et al., 2008).

2.2.4.5. Piperine. Piperine a natural polyphenolic compound, isolated from peppers, has been found to minimize lung cancer occurrence in a rodent model (Rather and Bhagat, 2018). In recent studies, it has been found that piperine downregulates Wnt/β-catenin signaling pathway to successfully destroy breast CSCs (Tarapore et al., 2012). It was also found to suppress the NF-κB activation by hampering nuclear import of NF-κB, but its effect on sonic HH signaling is not properly understood still now (Kumar et al., 2007).

2.2.4.6. Epigallocatechin-3-gallate (EGCG). Epigallocatechin-3-gallate (EGCG) is novel catechin, derived from green tea. The inhibitory effects of EGCG on Wnt and HH signaling have been reported in various cancers at the dose of 2–25 μM. EGCG downregulated β-catenin/TCF-4 reporter activity and β-catenin expression dose-dependently, indicating the inhibitory effects of EGCG on Wnt signaling (Singh et al., 2011; Zhu et al., 2017). In lung cancer cell lines (H460 and A549) and colon cancer cell line (HT29 cells) EGCG treatment inhibited TCF/LEF reporter activity and also decreased cytosolic β-catenin protein level (Oh et al., 2014; Sarkar et al., 2010a). The combination of EGCG and fish oil treatment for 9 weeks significantly inhibited β-catenin-Wnt signaling cascade and thereby reducing the tumor number (Bose et al., 2007). By microarray gene expression profiling analysis, investigators also identified two signaling pathways, Wnt and HH signaling, involved in cell proliferation, and was inhibited by EGCG treatment, indicating the negative regulation of EGCG on cell proliferation (Laurendeau et al., 2010). Other mechanisms may be also involved in the EGCG-mediated inhibition of Wnt signaling. In breast cancer cells, EGCG dose dependently suppressed the transcription factor, HBP1 by inducing HBP1 mRNA stability which subsequently inhibited Wnt signaling. Furthermore, EGCG reduces both breast cancer cell invasiveness and proliferation (Kim et al., 2006). In prostate cancer cells, EGCG could inhibit Gli1 mRNA expression and down-regulate Gli reporter activity with a substantial inhibition of cancer cell growth. EGCG also found to reduce prostate cancer growth in TRAMP mice (Ślusarz et al., 2010; Thiyagarajan et al., 2007). In another recent study, EGCG was found to inhibit cellular proliferation and induce apoptosis of CRL-7891 and SW1353 human chondrosarcoma cells. In this study, EGCG was found to down regulate Indian HH pathway by decreasing PTCH and Gli-1 expression (Tang et al., 2010).

2.2.4.7. Vitamin D. Epidemiologic studies have indicated that vitamin D could be a protective agent against cancers (Giovannucci, 2005). Vitamin D has been found to suppress Wnt, IGF-1, Notch, and NF-κB signaling. Additionally, vitamin D receptor inhibits β-catenin-mediated transcription which significantly improved by wild-type APC (Chen et al., 2013). In colon cancer cells, macrophage-derived soluble factors could upregulate canonical Wnt signaling and endorse their growth with the help of STAT1 and IL-1β interaction. In colon cancer cells, Vitamin D, can be work as a chemopreventive agent by interrupting interaction between different macrophages and inhibit the activation of Wnt. In Caco-2 or HT-29 colon cancer cell lines, vitamin D induced DKK-1 gene transcription and inhibited tumor growth via Wnt signaling pathway (Kaler et al., 2009). Vitamin-D was also found to be effectively used for the treatment of basal medulloblastoma, cell carcinoma, pancreatic and gastrointestinal carcinoma by inhibiting HH. The HH signaling has also been found to be greatly activated in the proximal gastrointestinal tract. Vitamin D could prevent the gastrointestinal tract cell growth through inactivation of Smo and the downregulating HH signaling (Athar et al., 2014).

2.2.4.8. Resveratrol. Resveratrol is a stilbenoid extracted from peanuts and red grapes. In HT-29 colon cancer cells, resveratrol restricted cell proliferation by arresting cell-cycle at G_0/G_1-S phase. Resveratrol treatment suppressed IGF-1, Akt and Wnt protein levels (Vanamala et al., 2010). In colon-derived cells, resveratrol significantly minimizes the nuclear localization of β-catenin (Hope et al., 2008). Resveratrol could inhibit prostate cancer cell growth by mitigating HH signaling pathway. Resveratrol also down regulates Gli1 mRNA expression and Gli reporter activity. In TRAMP mice, resveratrol could reduce the growth of prostate cancer by targeting HH signaling (Mo et al., 2011). Molecular docking showed the interaction of resveratrol with β-catenin chain A and Smo receptor (Mayan et al., 2016).

2.2.4.9. Other natural products. Other natural products could also regulate HH and Wnt signaling. Selenium is a micronutrient found in fish, grains, eggs, poultry and meat. Selenium has been found to be effective against colorectal and prostate cancers. It also modulates Wnt, AR and Notch signaling (Greiner et al., 2014). Another plant flavonoid, fisetin can inhibit colon cancer growth and initiate apoptosis by downregulating COX-2 and Wnt signaling. Fisetin inhibited β-catenin

Table 2
Natural anti-cancer compounds with their natural sources and effect on modulation of embryonic developmental pathway. The molecules enlisted are curcumin, genistein, 3, 3′-diindolylmethane (dim), lycopene, piperine, epigallocatechin-3-gallate (EGCG), vitamin D, resveratrol, selenium, fisetin, dammarane-type triterpene sapogenin (PPD25), tannic acid and quercetin.

Natural compounds	Source	Anticancer mechanism modulating embryonic developmental pathways
Curcumin	Curcuma longa	Decrease Gli-1, Notch-1, Cyclin D1, YAP, TAZ, CD44, ALDH1A1, Nanog, Oct4, CyclinD1 and UCA1 expression. Increase LC3-II and P-62 expression.
Genistein	Soy plants,	Downregulates cyclin B1, FOXO3, Sfrp2, Sfrp5 and Wnt5a, Gli1, protein kinases and NF-κB expression.
3, 3′-diindolylmethane (DIM)	Broccoli	Inhibits GSK-3β phosphorylation. Stimulates β-catenin phosphorylation.
Lycopene	Tomato	Prevents β-catenin nuclear localization and inhibits IGF-1. Modulate GSK-3β and Akt pathway.
Piperine	Pepper	Suppress Wnt, β-catenin and NF-κB.
Epigallocatechin-3-gallate (EGCG)	Green tea	Downregulates β-catenin, TCF-4, LEF reporter activity, HBP1, Gli1, PTCH and β-catenin expression.
Vitamin D	Fatty fish, beef liver, cheese, egg yolks	Suppress Wnt, IGF-1, Notch, Hh and NF-κB Induce DKK-1
Resveratrol	Grapes, peanut, blueberries and red wine.	Suppress IGF-1, Akt, Gli1, Wnt protein levels and minimize localization of β-catenin.
Selenium	Fish, grains, eggs, poultry and meat	Modulates Wnt, AR and Notch signaling.
Fisetin	Strawberries, apples, persimmons, onions and cucumbers	Inhibits COX-2, β-catenin, TCF- 4, Wnt. MMP-7 and cyclin D1
Dammarane-type triterpene sapogenin, (PPD25)	Panax notoginseng leaves	Downregulates β-catenin, cyclin D1, c-Myc, TCF-4 and cdk4 expression.
Tannic acid	Green tea and red wines	Destabilizing transmembrane Wnt receptors LRP6 and inhibit Wnt.
Quercetin	Fruits, vegetables and grains	Suppress Notch and Wnt expression

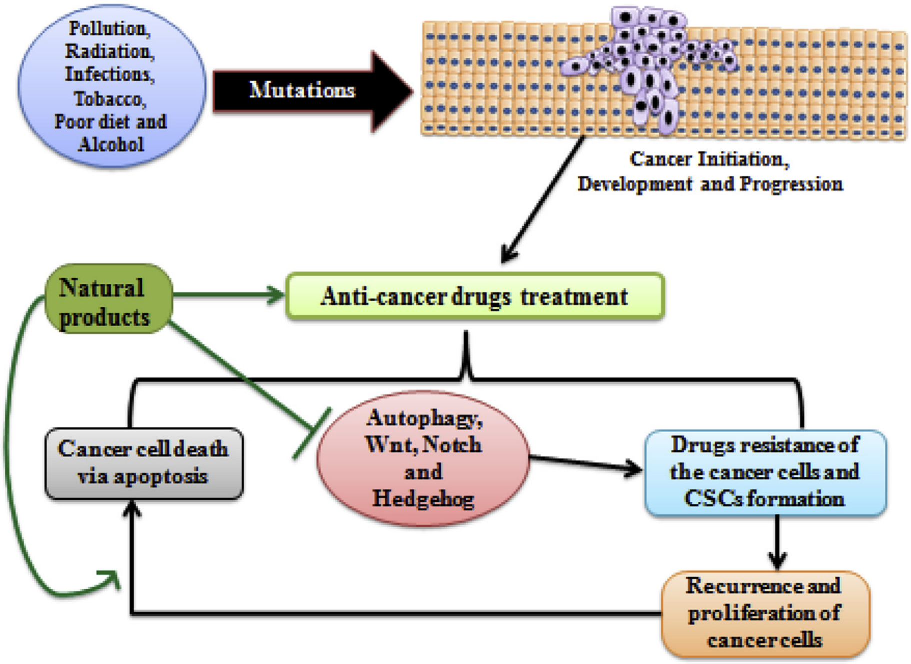

Fig. 6. Schematic representation of the protective mechanism of natural products against different stages of cancer.

and TCF- 4 expressions to downregulate Wnt signaling and decreased Wnt signaling target genes such as MMP-7 and cyclin D1 (Lall et al., 2016). Dammarane-type triterpene sapogenin, (PPD25) derived from the Panax notoginseng leaves, could reduce growth of lung and colon cancer cells. β-catenin expression levels and its transcriptional targets like cyclin D1, c-Myc, TCF-4, cdk4 etc., was found to be diminished by PPD25 treatment which ultimately inhibited Wnt signaling (Liu et al., 2018b). Tannic acid inhibited the proliferation of colorectal cancer cells by directly destabilizing LRP6 (transmembrane Wnt receptors) and inhibiting Wnt signaling cascade (Koval et al., 2018). Quercetin inhibits the growth of colon cancer, leukemia and lymphoma cells. It can also suppress the activity and expression of Notch1 in DND41 cells. Notch and Wnt may be interacting with each other to suppress cell growth (Kawahara et al., 2009; Shan et al., 2009). Anti-cancer properties (modulating embryonic developmental pathway) of different natural compounds have been represented in Table 2.

3. Conclusion

This review article provides a deep insight about the role of natural products in cancer therapy by modulating programmed cell death and self-renewal developmental pathway. Natural compounds are emerging as a potential therapeutic agent in the field of anticancer research due to their easy availability and cost-effectiveness. Numerous natural compounds are in preclinical or clinical trials for cancer treatment (Cragg and Newman, 2013a; Dutta et al., 2017). Different epidemiological studies indicated that high nutritional ingestion of vegetables and fruits reduced the threat of cancer (Zamora-Ros et al., 2018). Recent therapeutic approaches using natural compounds, not only include cytotoxic approaches but also the molecular management of cancer microenvironments. Plant and animal-derived natural products can be successfully used to treat altered protein homeostasis of cancer environment (Cheng et al., 2016). Studies on different natural compounds would help in understanding the role of low toxic natural compounds in the prevention of cancer by blocking proliferation, invasion, metastasis, angiogenesis, inflammation, immortality mutation and promoting apoptosis in accordance with inhibiting the self-renewal as well as survival mechanisms and drug resistant cancer stem cells. New drug development targeting these cells signaling pathways have become an attractive venture for biotechnology and pharmaceuticals industry. Most of the target-specific modern synthetic drugs failed to achieve the expected results. Consequently, the importance in drug development and discovery shifted to multi-targeted therapies using traditional and integrative natural products (Yuan et al., 2016). Recent studies indicated that natural products can be used as anti-cancer therapy with minimum side effects and can also regulate the formation and persistence of CSCs. Though the clinical applications of natural compounds are restricted due to their low aqueous solubility, quick catabolism, reduced bioavailability and poor intestinal absorption, recently different attempts have been made to overcome the limitations of the use of natural products and their derivatives with nanoparticles, micelles, lipids, liposome and metal complexes (Onoue et al., 2014). Further research on natural products and their limitations may result in the discovery of new potent anticancer therapeutic agents with targeted delivery. Fig. 6 represents the protective mechanism of natural products against different stages of cancer by the amelioration of several cell signaling pathways.

Conflict of interest statement

The authors declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.04.012.

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