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REVIEW ARTICLE

Natural Compounds as Modulators of Cell Cycle Arrest: Application for Anticancer Chemotherapies

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Abstract: Natural compounds from various plants, microorganisms and marine species play an important role in the discovery novel components that can be successfully used in numerous biomedical applications, including anticancer therapeutics. Since uncontrolled and rapid cell division is a hallmark of cancer, unraveling the molecular mechanisms underlying mitosis is key to understanding how various natural compounds might function as inhibitors of cell cycle progression. A number of natural compounds that inhibit the cell cycle arrest have proven effective for killing cancer cells *in vitro, in vivo* and in clinical settings. Significant advances that have been recently made in the understanding of molecular mechanisms underlying the cell cycle regulation using the chemotherapeutic agents is of great importance for improving the efficacy of targeted therapeutics and overcoming resistance to anticancer drugs, especially of natural origin, which inhibit the activities of cyclins and cyclin-dependent kinases, as well as other proteins and enzymes involved in proper regulation of cell cycle leading to controlled cell proliferation.

Keywords: Cancer, Natural compounds, Mitosis, Cell cycle arrest.

1. INTRODUCTION

Natural compounds play an important role in the discovery novel components that can be successfully used in numerous biomedical applications, including anticancer therapeutics [1-5]. More than 60% of currently used anticancer agents are derived from natural sources supporting the notion that natural compounds are high-impact sources of new "lead compounds" or new potential therapeutic agents [3, 4]. Numerous organisms have been studied as sources of anticancer drugs namely plants, microorganisms and marine organisms and the obtained natural compounds (e.g. natural compounds) can be considered a group of "privileged chemical structures" evolved in nature to interact with other organisms [3, 4]. Currently, there are more than 200 naturally produced drugs already in preclinical/clinical development or in the clinic [3].

Since tumors exhibit key traits, including ability of tumor cells to stimulate their own proliferation, resist inhibitory signals that might stop their proliferation, and thereby indefinitely proliferate, the search for compounds, which are able to control the tumor cell proliferation is an important venue for the anticancer therapies, such chemotherapy, hormonal therapy, immunotherapy and gene therapy [6]. Natural compounds, which exhibit to inhibit tumor cell proliferation and control mitosis and, particularly cell cycle, are important candidates for potential anticancer chemotherapies [6]. Therefore, the understanding of molecular mechanisms and functions of anticancer compounds of natural origin is prerequisite to successful application of these compounds in basic and translational research before going to clinical trials.

Mitosis is a complex process resulting in division of a cell into two daughter cells, and its failure often results in the death of the daughter cells (via apoptotic, necrotic, or proliferative/senescent death), as reviewed in [7-9]. Since uncontrolled and rapid cell division is a hallmark of cancer, unraveling the molecular mechanisms underlying mitosis is key to understanding how various natural compounds might function as antimitotic agents [8, 10-12]. Many natural compounds that inhibit the mitotic process (antimitotic drugs) have proven effective for killing cancer cells *in vitro, in vivo* and in clinical settings [8, 10-12]. Among the most studied

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antimitotic drugs are natural compounds including taxanes (e.g. taxol, paclitaxel, docetaxel) and vinca alkaloids (e.g. vincristine, vinblastine), whose validated targets are the spindle microtubules, as reviewed elsewhere [8, 13-18]. Natural compounds, including vinca alkaloids, were shown to induce cell cycle arrest in mitosis associated with aberrant mitotic spindles, while colchicine was found to exhibit the activities leading to blocking of mitosis, as indicated in [8, 13, 14]. Both vincristine and vinblastine were found to inhibit the tumor cell proliferation, and display remarkable efficacy in the treatment of testicular cancer, Hodgkin's lymphoma and acute lymphocytic leukemia, as reviewed in [8, 13-18].

Novel drugs and natural compounds that inhibit other proteins involved in mitosis (non-microtubule targets) have been sought in hopes of expanding available cancer-directed therapies [8]. Significant advances made in the understanding of molecular mechanisms underlying the cell cycle regulation using the chemotherapeutic agents are of a great importance for improving the efficacy of targeted therapeutics and overcoming resistance to anticancer drugs, especially of natural origin, which inhibit the activities of cyclins and cyclin-dependent kinases (CDKs), as well as other proteins and enzymes involved in proper regulation of cell cycle leading to controlled cell proliferation, as reviewed in [8, 19].

2. REGULATION OF CELL CYCLE PROGRESSION

Regulation of the cell cycle progression is critical for cell survival in the ever-changing microenvironment [20-26]. Molecular events underlying these regulatory processes are serving to detect and repair DNA damage, and to prevent uncontrolled cell division, and occur in orderly sequential irreversible fashion, called a cell cycle [26-31]. During cell cycle progression the activity of CDKs is tightly regulated by a number of mechanisms including phosphorylation, intracellular localization, and activation by cyclins and inhibition by CDK inhibitors [20-25]. Mammalian cells contain nine CDKs (CDK1-9) and 12 cyclins [20, 22, 25]. Many genes encoding cyclins and CDKs are conserved among all eukaryotes [20, 22, 25].

To successfully perform their functions to control cell cycle, cyclins (regulatory subunits) and CDKs (catalytic subunits) bind to each other forming activated heterodimers [20, 22, 25]. After binding to cyclins, CDKs phosphorylate target proteins leading to their activation or inactivation in order to coordinate entry into the next phase of the cell cycle, as reviewed in [20, 22, 25]. CDK proteins are constitutively expressed in cells, whereas cyclins are synthesized at specific stages of the cell cycle, in response to various molecular signals [20, 22, 25]. Upon receiving a pro-mitotic extracellular signal, G1 phase-specific cyclin-CDK complexes become active to prepare the cell for S phase, promoting the expression of transcription factors leading to the expression of S phase-specific cyclins and of enzymes required for DNA replication [20, 22, 25]. The G1-phase-specific cyclin-CDK complexes also promote the degradation of molecules that function as S phase inhibitors [24, 25]. Active S phase-specific cyclin-CDK complexes phosphorylate proteins involved in the pre-replication complexes and assembled during G1 phase on DNA replication origins [24, 25]. Mitotic cyclin-CDK complexes, which are synthesized during S and G2 phases, promote the initiation of mitosis by stimulating downstream proteins implicated in chromosome condensation and mitotic spindle assembly [20, 22, 25].

A number of cyclins specifically regulate the distinct cell cycle phases, as reviewed in [25-27]. For example, cyclin D is produced in response to extracellular signals, and then binds to existing CDK4, forming the active cyclin D-CDK4 complex, which in turn phosphorylates the retinoblastoma susceptibility protein (RB), as indicated in [25]. The latter dissociates from the E2F/DP1/RB complex (which was bound to the E2F-responsive gene promoters, effectively "blocking" them from transcription), thereby releasing E2F [23, 25]. Now active E2F induces transcription of various genes involved in cell proliferation and genome maintenance, including cyclins A and E, DNA polymerase, thymidine kinase [23, 25]. Cyclin E binds to CDK2 forming the cyclin E-CDK2 complex, which initiates the cell entry into S phase from G1 phase, and subsequently leads cell to the G2/M transition, as indicated in [27]. Cyclin B-CDC2 complex activation causes a breakdown of nuclear envelope and initiation of prophase, and then its deactivation causes the cell to exit mitosis, as reviewed elsewhere [23, 25].

In order to tightly control the cell cycle progression, cells develop molecular modulators of cell proliferation, called cyclin-dependent kinase inhibitors (CDKN), as reviewed in [27-29]. Two protein families, the CDK interacting protein/Kinase inhibitory protein (CIP/KIP) family and the Inhibitor of Kinase 4/Alternative Reading Frame (INK4A/ARF) protein family, prevent the progression of the cell cycle [27-29]. The CIP/KIP family includes the following proteins: p21 (CDKN1A), p27 (CDKN1B) and p57 (CDKN1C), as reviewed elsewhere [27-29]. They halt cell cycle in G1 phase, by binding to, and inactivating, cyclin-CDK complexes. P21 (CDKN1A) is activated by a transcriptional factor p53, whose expression and activation is triggered by DNA damage [27-29]. The INK4A/ARF family includes p16INK4A (CDKN2A), which binds to CDK4 and arrests the cell cycle in G1 phase, and p14ARF, (alternate reading frame protein product of the *CDKN2A* gene), which prevents p53 degradation, as reviewed in [27-29].

Cell cycle checkpoints are involved in monitoring and regulating the cell cycle progression [30-34]. Checkpoints prevent cell cycle progression at specific points, allowing verification of necessary phase processes and repair of DNA damage, as reviewed in [30-34]. There are several checkpoints to ensure that damaged or incomplete DNA is not passed on to daughter cells [31, 33, 34]. They include: the G1/S checkpoint, the G2/M checkpoint and the metaphase (mitotic) checkpoint [30-34]. Tumor suppressor protein p53 plays an important role in triggering the control mechanisms at both G1/S and G2/M checkpoints, as indicated [31-34]. A deregulation of the cell cycle components may lead to tumor formation [31-34]. When some genes capable to suppress tumor development (e.g. RB, p53) mutate, they might cause the cell to uncontrollably proliferate, thus forming a tumor [31-34]. Although the duration of cell cycle in tumor cells is

often equal to that of normal cell cycle, the proportion of cells that are in active cell division (versus quiescent cells in G0 phase) in tumors is much higher than that in normal tissue [31-34]. The cells, which are actively undergoing cell cycle, are targeted in cancer therapy, as the DNA is relatively exposed during cell division and hence susceptible to damage by drugs or radiation [31-35].

3. HALLMARKS OF CANCER AND CELL CYCLE PROGRESSION

The traits ("hallmarks") of cancer include but not limited to the abilities of cancer cells to: (1) stimulate their own growth (Self-sufficiency in growth signals); (2) resist inhibitory signals that might otherwise stop their growth (Insensitivity to anti-growth signals); (3) resist their programmed cell death (Evading apoptosis); (4) multiply indefinitely (Limitless replicative potential) (5) stimulate the growth of blood vessels to supply nutrients to tumors (Sustained angiogenesis); (6) invade local tissue and spread to distant sites (Tissue invasion and metastasis); (7) exhibit abnormal metabolic pathways (Deregulated metabolism); (8) exert genome instability (Unstable DNA); (9) evade the immune system, and (10) induce inflammation, as indicated elsewhere [36, 37].

Normal cells require external growth signals (growth factors) to grow and divide, while cancer cells do not need stimulation from external signals (in the form of growth factors) to proliferate [37]. Some cancer cells, such as glioblastomas can produce their own platelet-derived growth factor (PDGF), and sarcomas can produce their own tumor growth factor α leading to tumor cell proliferation, as indicated in [38, 39]. Furthermore, tumor cells exhibit the overexpression of the specific growth factor receptors [40-44]. The epidermal growth factor receptor (EGFR/ERB) was found overexpressed in stomach, brain and breast cancers, while the HER2/NEU receptor is upregulated in stomach and breast cancers [45]. Additionally, the mutated receptors can send signals triggering tumor cell proliferation cascade even in the absence of any growth factors [46]. Cancer cells are generally resistant to growth-preventing signals from the neighboring cells of their microenvironment, as indicated in [37].

Normal cells sustain a certain number of divisions, known as “Hayflick limit” that limits their multiplication to about 60–70 doublings, at which point they reach a stage of senescence [47-49]. However, cancer cells escape this limit and are apparently capable of indefinite growth and division (immortality), as reviewed in [50-52]. This limit can be overcome by disabling retinoblastoma (RB) and p53 tumor suppressor proteins, as well as upregulation of telomerase expression and activity, which allow cancer cells to continue doubling until being immortalized, as indicated elsewhere [50-52].

4. CELL CYCLE REGULATION BY NATURAL COMPOUNDS AFFECTING CYCLINS, CDKs AND CDK INHIBITORS

A change in phosphorylation status can stimulate or inhibit a protein's activity, induce conformational changes, assemble or disassemble protein complexes, and alter cellular localization [53]. The timing of the eukaryotic cell cycle is coordinated by successive waves of phosphorylation performed by the CDK protein kinases [12, 20, 21, 25, 54]. CDK proteins play a pivotal role in regulating the cell cycle, and their activity is tightly regulated by a number of mechanisms including phosphorylation, intracellular localization, and activation by cyclins, and inhibition by CDK inhibitors (e.g. CDKN1A [p21WAF1], and 1B [p27KIP]), as reviewed elsewhere [12, 22-25, 29, 54]

Accumulating evidence suggests that many of the components of the CDK regulatory network could often be mutated (CDK4, p16INK4A), amplified (CDK4, CDK2), overexpressed (CDK6, cyclins A1, D1, D2, D3, and E1, CDC25A and B), or deleted (p16INK4A, p15INK4B, RB) in various human cancers, as reviewed elsewhere [12, 23, 54, 55]. CDKs are serine/threonine protein kinases, which play an important role in cell cycle regulation, as reviewed [10-12, 26, 27, 54, 55]. Therefore, inhibition of CDKs, through the insertion of small molecules into its ATP-binding pocket has emerged as a potential therapy method for cancers [56]. Consequently, a number of natural compounds with CDK inhibitory properties have been identified in plants, microorganisms and marine live-forms [8, 10-12].

Historically, the derivative of plant cytokinins, trisubstituted purine Olomoucine isolated from the cotyledons of radish, *Raphanus sativus* L. (Brassicaceae), was found to be a first moderately potent inhibitor of starfish CDK1/cyclin B complex (IC50 = 7 mM) without inhibiting a panel of other kinases, as reviewed elsewhere [57-61]. Following these discoveries, a variety of natural compounds have been characterized as CDK inhibitors, as indicated in [58, 59]. Olomoucine was shown to act as an ATP-competitive inhibitor, which was bound to the ATP binding cleft of the protein kinase enzyme [60]. To improve the enzymatic potency of Olomoucine, a variety of analogs were prepared that ultimately resulted in the discovery of Roscovitine [61-67]. A crystal structure with roscovitine with CDK2 protein confirmed that the binding mode of Roscovitine was identical to that observed for Olomoucine [61].

Purine analogue Roscovitine was shown to exhibit strong anti-proliferative effects on non small-cell lung cancers, lymphomas, and glioblastomas by targeting CDK-2, -7 and -9, as reviewed elsewhere [62-67]. Roscovitine induces cycle arrest at the G2/M phase and down regulated the expression of p53, CDK7 and cyclins A and E, while up regulating CDKN1A (p21) expression in A172 glioma cells, as indicated in [61]. Intriguingly, the CDK7 protein forms a trimeric complex with cyclin H and CDK-activating kinase assembly factor, MAT1 (also known as MNAT1) functioning as a CDK-activating kinase (CAK), as described in [67-72]. CDK7 is an essential component involved in regulation of the TFIIH-derived RNA polymerase II preinitiation transcription complex, as reviewed in [69-71]. TFIIH consists of ten subunits, 7 of which (XPD, XPB, p62, p52, p44, p34 and TTDA), as indicated in [69, 70]. The cyclin activating kinase complex containing CDK7, MAT1, and cyclin H is linked to the core complex via ithe XPD protein, thereby serving as a direct link between the regulation of transcription and the cell cycle [69, 70]. Roscovitine was found to arrest human estrogen receptor-α (ER-α) positive MCF-7 breast cancer cells in the G2 phase of the cell cycle and concomitantly

induce apoptosis via a p53-dependent pathway [63, 66, 67]. Exposure of MCF-7 cells to Roscovitine abolished the phosphorylation of CDK7 at the Ser164/170 subsequently prevented phosphorylation of RNA polymerase II, as described elsewhere [67-76]. Sulforaphane induced a significant increase in the G2/M phase of the cell cycle, was associated with increased cyclin B1 and CDKN1A (p21) protein levels [73]. Preincubation of human colon colorectal adenocarcinoma HT29 cells with Roscovitine, a specific CDK2 inhibitor, blocked the G2/M phase accumulation of HT29 cells treated with sulforaphane, suggesting that CDK2 could be a key target for the latter in the regulation of G2/M block [73]. CYC202 (R-roscovitine) is a potent inhibitor of CDK2/cyclin E that is undergoing clinical trials, as reviewed in [74]. Treatment of human colon carcinoma HT29 and KM12 cell lines with CYC202 decreased the total and phosphorylated RB levels, while increased the phosphorylation level of extracellular signal-regulated kinases (ERK) 1/2, as indicated in [74]. CYC202 reduced expression of cyclin D1 protein, and mRNA levels for cyclin A, B1, and D1, whereas c-FOS mRNA level was markedly increased [74]. This was accompanied by a loss of RNA polymerase II phosphorylation and total RNA polymerase II protein, suggesting that CYC202 was inhibiting transcription, possibly via inhibition of CDK7 and CDK9 complexes, as indicated in [74].

Butyrolactone-I is one of the first natural compounds, shown to act as an inhibitor of CDK1 and CDK2 enzymes, and was isolated from *Aspergillus terreus* [77-80]. This compound was demonstrated to be an ATP-competitive inhibitor of CDK1/cyclin B complex and inhibits phosphorylation of RB in treated cells [77]. Similar to the trisubstituted purines, both G1 and G2/M arrest have been observed with apoptosis induction after longer exposure, as indicated in [77]. Butyrolactone-I was found to inhibit CDKN1A (p21WAF1) expression through a mechanism that may involve cellular targets other than CDK1, as indicated in [78-80]. Butyrolactone-I was also found acting as a potent inhibitor of CDKN1A (p21WAF1) expression [80].

The UCN-01 (7-Hidroxystaurosporine) is a staurosporine analog isolated from the culture broth of *Streptomyces species,* as indicated in [81-84]. The UCN-01 induced the cell cycle arrest in G1/S phase, induction of CDKN1A (p21WAF1) and dephosphorylation of both CDK2 and RB proteins [81-84]. The UCN-01 can also inhibit the activity of CDK1 and CDK2 [81]. This inhibition leads to activation of cyclin B/CDK1 and marked abrogation of the G2-phase point of control, promotion of the cells to undergo mitosis and early apoptotic death later, instead of cell cycle arrest [81, 82]. Several phase I studies have been conducted with UCN-01, both as a single agent and in combination with cytotoxic chemotherapy [81-83].

Hymenialdisine lactam from a marine sponge *Axinella sp*. is a nanomolar enzymatic inhibitor of CDK1/cyclin B, CDK5/CDK5 activator-1, glycogen synthase kinase-3B, casein kinase 1, and dual specificity mitogen-activated protein kinase kinase 1 (also known as MAP2K1 or MEK1), as indicated in [84, 85]. Hymenialdisine competes with ATP for binding to these kinases and a hymenialdisine forms a series of three hydrogen bonds to the Glu81 and Leu83 residues of CDK2 [85, 86]. The follow-up studies have identified ten new targets for these inhibitors, including ribosomal S6 kinase (p90 subunit), kinase insert domain receptor (also known as vascular endothelial growth factor receptor 2), mast/stem cell growth factor receptor (also known as c-KIT proto-oncogene), tyrosine-protein kinase FES/FPS (also known as proto-oncogene c-*FES/FPS*), MAPK1, PAK2, pyruvate dehydrogenase kinase-1 and 2, protein kinase C-β, and myosin light chain kinase 4 (MLCK4, also known as SGK085), as indicated in [86].

Chromone alkaloids and flavoalkaloids are an important group of natural compounds exhibiting promising anticancer properties, as reviewed in [87]. A chromone alkaloid rohitukine is a major bioactive chemical constituent of plant *Dysoxylum binectariferum Hook*, which led to discovery of flavopiridol (Sanofi), as indicated in [87, 88]. Flavopiridol has been shown to inhibit the proliferation of a various human tumor cells and is currently undergoing clinical evaluation in cancer treatment [89]. Although the anti-proliferative effect of flavopiridol has been attributed to the inhibition of CDK-2 and -4, some reports indicate that the mechanism responsible for the cell death induced by this agent is more complex [88]. Flavopiridol is the first and most thoroughly investigated clinical-stage CDK inhibitor having been tested in a variety of human cancers including lung, breast, bladder and leukemia [89-92]. Flavopiridol was initially reported as a cell cycle blocker with potent activity against CDK1/cyclin B complex, and subsequently shown to inhibit CDK4 and CDK7, as reviewed in [93, 94].

Indirubin was isolated as the "active" principal of a traditional Chinese antileukemia medicine and later shown to be a potent and fairly selective inhibitor of CDK-1 and -2, as described in [95]. Chebulagic acid from *Terminalia chebula* was shown to have anti-proliferative properties in cancerous cell lines, especially in human retinoblastoma cells, by inducing the cell cycle arrest in G1 phase associated with increased expression of CDKN1B (p27), and decreased expression of NF-κB, as described in [96]. The broth from a fermented culture of *Antrodia camphorata* has been shown to induce G1 cell-cycle arrest in human promyelocytic leukemia HL-60 cells by reducing the levels of cyclin D1, CDK4, cyclin E, CDK2, cyclin A, and phosphorylated RB protein, as well as increased expression levels of CDKN1A (p21WAF1) and CDKN2B (p15INK4B), as described elsewhere [97]. Wogonin, a naturally occurring mono-flavonoid from *Scutellaria radix*, has been reported to exhibit anti-proliferative effects in human colorectal HCT116 cells, as indicated in [98]. The cell cycle-related proteins, such as cyclin A, E, D1, and CDK-2, and -4 were downregulated by wogonin [98]. Wogonin inhibited β-catenin-mediated transcription by interfering in the transcriptional activity of TCF/LEF, and repressing the kinase activity of CDK8, an oncogene involved in the development of colorectal cancers [98]. Lycoris is aurea agglutinin, which triggers the cell cycle arrest in G2/M phase via upregulating CDKN1A (p21) expression, as well as downregulating CDK1/cyclin A signaling pathway in human lung adenocarcinoma A549 cells [99].

Fangchinoline, an alkaloid derived from the dry roots of *Stephaniae tetrandrine S. Moore*, has been shown to decrease the proliferation of human breast cancer MCF-7 and

MDA-MB-231 cells, as described in [100]. Fangchinoline induced the cell cycle arrest in G1 phase, and reduced expression of cyclins D1, D3, and -E, while increased expression of CDKNs, CDKN1A (p21WAF1), and CDKN1B (p27KIP1), as indicated in [100]. Fangchinoline also inhibited the CDK-2, -4, and -6 kinase activities [100].

Berberine is a isoquinoline alkaloid found in Berberis species [e.g. *Berberis aquifolium*, *Berberis vulgaris*, *Berberis aristata, Hydrastis canadensis, Xanthorhiza simplicissima, Phellodendron amurense, Coptis chinensis, Tinospora cordifolia, Argemone mexicana, and Eschscholzia californica,* as reviewed elsewhere [101-104]. Berberine was shown to exert anti-proliferative effects on numerous human cancer cells *in vitro*, including breast cancer, leukemia, melanoma, epidermoid carcinoma, hepatoma, cholangiocarcinoma, colorectal cancer, ovarian cancer, pancreatic cancer, oral carcinoma, tongue carcinoma, nasopharyngeal carcinoma, glioblastoma, prostate carcinoma and gastric carcinoma, uterine leiomyoma, as indicated in [105-126]. *In vivo* studies using animals models with xenografted human tumors have shown that berberine can suppress prostate cancer, neuroblastoma, and leukemia, and inhibit the growth and development of lung metastases in hepatocellular carcinoma, as reviewed in [111-113, 127]. Down-regulation of cyclin B1 and up-regulation of Wee1 by berberine promotes entry of leukemia cells into the G2/M-phase of the cell cycle [113]. Berberine decreased cell viability of human cholangiocarcinoma QBC939 cells in a dose-dependent manner, which was associated with the cell cycle arrest in G1 phase, as described elsewhere [128]. Berberine was found to increase the expression of CDKN1A and CDKN1B, and a simultaneously decrease the protein levels of CDK2 and CDK4 and cyclin D1, as well as to reduce activity of the cyclin-CDK complexes, as described elsewhere [128]. *Berberis libanotica Ehrenb* is a plant rich in alkaloids possessing anti-cancer activity and a high potential for eliminating cancer stem cells [129]. The extract from this plant was found to significantly reduce the viability of prostate cancer cells (DU145, PC3 and 22Rv1) in a dose- and time-dependent manner, while inducing the cell cycle arrest in G0-G1 phase [129]. Alkaloids, berberine and palmatine, isolated from the extracts of *Berberis lycium Royle* (Berberidacea) were found to inhibit proliferation of human promyelocytic HL-60 cells by the cell cycle arrest in S phase, as described in [130]. The compounds were shown to activate CHEK2, and degradation of CDC25A, and the subsequent inactivation of CDK1, as indicated in [130]. Berberine also downregulated the cyclin D1 expression, and induced the acetylation of α-tubulin [130].

Limonoids are triterpenoids (e.g. methyl nomilinate, isoobacunoic acid, isolimonexic acid, and limonexic acid) found in citrus and possess anti-proliferative activity towards human colon adenocarcinoma SW480 cells *in vitro* and *in vivo* [131]. For example, methyl nomilinate induced the cell cycle arrest at G0/G1 phase and suppressed the expression of CDK-4, -6, cyclin D3 and CDK inhibitors [131]. Meridianins A-G (1-7) are indole alkaloids from tunicate *Aplidium meridianum* and are found to exhibit anti-proliferative activity in several cancer cell lines, while inhibiting CDK-1, and -5, as shown for meridianin E [132]. A sponge-derived bisindole alkaloid fascaplysin exhibited an anti-proliferative activity against numerous cancer cell lines via specific inhibition of CDK-4 (IC50, 350 nM), and intercalating DNA [133]. 5, 3'-dihydroxy-3, 6, 7, 8, 4'-pentamethoxyflavone (DH-PMF) from *Gardenia obtusifolia* was shown to inhibit the proliferation of prostate, colon, kidney, lung, head/neck, pancreas, breast, leukemia, and myeloma cancer cell lines at the concentration 1 μM, as indicated in [134]. DH-PMF also suppressed the colony-forming ability of tumor cells, with 50% inhibition at a dose less than 10 nM, as indicated in [134]. DH-PMF induced the the cell cycle arrest in G2/M and sub-G1 phases, by inducing the CDKN1A (p21WAF1) and CDKN1B (p27KIP1) protein expression, while reducing the expression of cyclin D1, CDC2, and c-MYC proteins [134]. Furthermore, DH-PMF inhibited AKT and glycogen synthase kinase 3β activation [134].

Water extract of white cocoa tea was found to inhibit a proliferation of human prostate cancer PC-3 cells *in vitro* and *in vivo*, which was associated with G2/M phase arrest of cell cycle and induction of CDKN1A (p21WAF1), CDKN1B (p27KIP1), reduction of cyclins D1, D2 and E, CDK-2, -4 and -6, inhibition of nuclear translocation and phosphorylation of nuclear factor -kappa B (NF-κB), inhibition of phosphorylation and degradation of nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα), and activation of IκB kinase-alpha (IKKα), as indicated elsewhere [135]. Polyphenols from the mulberry leaf extract were found to inhibit tumor cell growth, and induce a phosphorylation of p53, promote expression of CDKN1A (p21) and CDKN1B (p27), decreased CDK-2, and -4 activities, inhibited phosphorylation of RB, thereby blocking the G1 to S transition of tumor cells in the cell cycle [136]. Isoliquiritigenin, a flavonoid chalcone present in licorice, shallot, and bean sprouts, was found to exhibit anti-proliferative activities toward human prostate cancer DU145 cells via decrease of the protein levels for cyclins D1 and E, CDK4, and CDC25C, and increase of CDKN1B (p27KIP1) level, and CDC2 phosphorylation at the Tyr-15 position [137]. Acetylbritannilactone, a naturally occurring *Inula britannica L.*, was found to induce the the cell cycle arrest in G1 phase and reduce the expression of cyclins A, D1, and E, and CDK-2, -4, and -6 proteins, as well as induce the expression of CDKN1A (p21), as indicated in [138]. The anti-proliferative effects of the ethanol extract of *Artemisia princeps Pampanini* against human brain glioblastoma A172 cells were found to associate with the cell cycle arrest in G1 phase, increase of the CDKN1A (p21WAF1), 1B (p27KIP1), and 2A (p16INK4A) protein levels, and decrease of the CDK-2, -4, and -6 activities [139]. Furthermore, the total level of E2F1 and phosphorylation level of RB were also decreased, while total level of p53 and phosphorylation of p53 at the Ser-15 position were increased [139].

Quercetin treatment resulted in an increased cell arrest in G1 phase of the cell cycle, with pronounced decrease in CDK-2, -6, cyclin A, D, and E proteins, decreased RB phosphorylation and increased CDKN1A (p21) and 1B (p27) expression, as indicated in [140]. Three flavonoids homogenous compounds from tartary buckwheat seeds and bran (e.g. quercetin, isoquercetin, and rutin) leads to the G2/M phase arrest accompanied by p53 and CDKN1A (p21) upregulation, and cyclin D1, CDK-2, and -7 downregulation [141]. Quercetin-3-methyl ether, a naturally occurring compound present in various plants, has potent anticancer activity

[142]. It caused a significant growth inhibition of lapatinib-sensitive and -resistant breast cancer cells [142]. However, quercetin-3-methyl ether caused a pronounced G2/M block mainly through the CHEK1-CDC25c-cyclin B1/CDK1 pathway in lapatinib-sensitive and -resistant cells, as indicated in [142]. Isoquercitrin, the flavonoid from *Bidens bipinnata L.* extract, was found to inhibit the proliferation of human liver cancer cells, and block the cell cycle in the G1 phase [143]. Isoquercitrin, inhibited the expression level of extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (p38 MAPK) protein phosphorylation, and promoted the phosphorylation of c-Jun N-terminal kinases (JNK), as indicated in [143]. Isoquercitrin was also found to significantly inhibit the growth of transplanted tumors in nude mice *in vivo* [143]. Isorhamnetin, a flavonoid isolated from the fruits of herbal medicinal plants, such as *Hippophae rhamnoides L.*, exerts anticancer effects on the proliferation of cells from the human colorectal cancer cell lines, HT-29, HCT116 and SW480, as described in [144]. Isorhamnetin induced the cell cycle arrest in G2/M phase and inhibit the PI3K-AKT-mTOR pathway [144]. Isorhamnetin also reduced the phosphorylation levels of AKT (at the Ser473 position), phospho-p70S6 kinase (at the Thr389 position) and phospho-4E-BP1 (at the Thr37/46 position) proteins, and enhanced the expression of cyclin B1 protein, as indicated in [144]. Flavonoid tamarixetin from *Tamarix ramosissima* exerted an anti-proliferative effect on human leukemia cells by blocking cell cycle progression at G2/M phase, as described elsewhere [145]. This was associated with the accumulation of cyclin B1, mitotic checkpoint serine/threonine-protein kinase (also known as Budding Uninhibited by Benzimidazoles 1, BUB1) and CDKN1A (p21WAF1), changes in the phosphorylation status of cyclin B1, CDK1, CDC25C and MPM-2, and inhibition of tubulin polymerization, as indicated in [145]. The methanol extract from *Maytenus royleanus* leaves (enriched with flavonoids and tannins) exhibited G2 phase arrest of cell cycle, down-regulation of cyclin/CDK network and increase in CDK inhibitors (CDKN1A [p21] and 1B [p27]), as described in [146]. Huanglian inhibited tumor growth and colony formation of gastric, colon, and breast cancer cell lines and was associated with suppression of cyclin B1 protein, as described elsewhere [147]. This resulted in complete inhibition of CDC2 kinase activity and accumulation of cells in G2 phase, as indicated in [147]. The bis-indole indirubin is an active ingredient of Danggui Longhui Wan, a traditional Chinese medicine recipe, was shown to inhibit CDK1/cyclin B, and CDK5/p25 complexes in leukemia cells, and subsequently induce the abnormal hyperphosphorylation of the microtubule-binding protein TAU, as indicated in [148].

Polyphenol epigallocatechin-3-gallate (EGCG), a major and most effective constituent of green tea, exerts anti-proliferative effects on tumor cells of various human cancers, including prostate, lung and skin cancers, as reviewed in [149-152]. EGCG causes the cell cycle arrest in G0/G1 phase in human epidermoid carcinoma A431 cells through the inhibition of nuclear factor kappa B (NF-κB), as described elsewhere [149]. EGCG treatment resulted in significant upregulation of the CDKN1A (p21WAF1), 1B (p27KIP1), 2A (p16) and 2C (p18) protein levels, downregulation of cyclin D1, E, CDK-2, -4 and -6 protein levels, and activities, as well as reduction of the phosphorylation of retinoblastoma RB protein, as described in [149-151]. This study suggests that EGCG causes an induction of G1-phase-specific CDK inhibitors, which negatively modulated the formation of cyclin/CDK complexes causing a G0/G1-cell cycle arrest, as indicated in [152]. Proanthocyanidins from grape seeds of *Vitis vinifera* are composed of polymerized oligomers of monomeric catechins, and have been shown to exhibit potent anti-proliferative properties in various *in vitro* and *in vivo* tumor models by regulation of cell cycle progression in cancer cells, as reviewed in [153]. Treatment of human epidermoid carcinoma A431 cells with proanthocyanidins inhibited tumor cell proliferation, which was associated with the cell cycle arrest in G1 phase, resulted in a marked reduction in CDK-2, -4 and -6 protein levels [154]. Proanthocyanidins also reduced the expression levels of cyclins D1, D2 and E, while induced the CDKN1A and 1B protein levels *in vitro* [154]. Proanthocyanidins were then shown to inhibit the growth of A431 tumor-xenografts in athymic nude mice *in vivo,* associated with reduction of cyclin D1 expression, as indicated in [155]. Similar observations were noted when the prostate cancer cells, DU145 and LNCaP, were treated with grape seed extract resulted in reduction of tumor cell proliferation, G1 phase arrest, induction of CDKN1A, and reduction of CDK-2, -4, and cyclin E protein levels [156].

Resveratrol, a polyphenol found at high concentrations in grapes and red wine, inhibits proliferation of cancer cells by inhibiting cell-cycle progression at different stages of the cell cycle [157-160]. Treatment of human prostate LNCaP and PC-3 cells with resveratrol reduced levels of expression of cyclins D1 and E and CDK4, as well as cyclin D1/CDK4 protein complex-associated kinase activity [161, 162]. Resveratrol also reduced proliferation in human epidermoid carcinoma A431 cells and human colon cancer cells associated with reduced levels of cyclins D1, D2 and E2, CDK-2, -4 and -6 proteins and enhanced levels of CDKN1A and 1B proteins [158, 163]. The dietary flavonoid apigenin, which is abundantly present in fruits and vegetables, induces G2/M phase arrest in two p53-mutant cancer cell lines, HT-29 and MG63, while enhancing the CDKN1A protein level [164]. Apigenin inhibited the growth of prostate tumor xenografts in athymic nude mice *in vivo* through the reduction of cyclins D1, D2 and E, CDK-2, -4, and -6, and induction of the CDKN1A and 1B protein levels [165, 166]. Apigenin induced the cell cycle arrest in G2/M phase and reduced the levels of cyclin A, cyclin B, phosphorylated forms of CDC2 and CDC25, and induced the CDKN1A level in human pancreatic and hepatoma cancer cell lines [167, 168]. Extensive research within the last decade has shown that silymarin suppressed the proliferation of a variety of tumor cells (e.g., prostate, breast, ovary, colon, lung, bladder) through the cell cycle arrest in G1/S-phase, induction of CDKN1A, 1B, and 2B, inhibition of cell-survival kinases (AKT, PKC and MAPK) and inhibition of inflammatory transcription factors (e.g., NF-κB), as indicated in [169]. Silymarin can also down-regulate gene compounds involved in the proliferation of tumor cells (cyclin D1, EGFR, COX-2, TGF-beta, IGF-IR), invasion (MMP-9), angiogenesis and metastasis [169].

Curcumin from *Curcuma longa* was found to exhibit multiple *in vitro* and *in vivo* anti-proliferative effects on various human tumor cells, derived from lung carcinoma (A549), hepatocellular carcinoma (HepG2), breast cancer (MCF-7), cervical cancer, chronic myelogenous leukemia (K562), non-small lung cancer (H1299), osteoclastoma, pancreatic adenocarcinoma, skin squamous carcuinoma (A431), thyroid carcinoma (BCPAP), as indicated elsewhere [170-186]. Circumin was shown to inhibit cell cycle progression of immortalized human umbilical vein endothelial cells by up-regulating the cyclin-dependent kinase inhibitors, CDKN1A, 1B, and p53 transcription factor [187]. In human neuroblastoma cells, both curcumin and resveratrol upregulate p53 expression and induce nuclear translocation of p53, followed by induction of CDKN1A expression [188]. Treatment of human colon adenocarcinoma LOVO cells and HCT-116 cells with curcumin resulted in an accumulation of the cells in the G2/M phase and prevented cells from entering the next cell cycle [189-191]. Curcumin inhibited the growth of human glioma U251 cells inducing G2/M cell cycle arrest, as well as S phase arrest [192]. Curcumin induces the expression of p53 and up-regulates the levels of CDKN1A and inhibitor of growth family, member 4 (ING4) in glioma U251 cells [192].

Indole-3-carbinol produced by plants from the genus *Brassicaceae* (e.g., cabbage, radishes, cauliflower, broccoli, Brussels sprouts, and daikon) was shown to suppress the proliferation of various tumor cells, including breast cancer, prostate cancer, endometrial cancer, colon cancer, and leukemia cells, as reviewed elsewhere [193]. Indole-3-carbinol induces G1/S arrest of the cell cycle through downregulation of cyclins D1, E, CDK-2, -4, -6 and upregulation of CDKN1A (p21), 1B (p27), and 2B (p15), as indicated in [193]. Indole-3-carbinol tetramer was shown to suppress the growth of both estrogen receptor (ER) -positive (MCF-7, 734B, and BT474) and ER-negative (BT20, MDA-MB-231, and BT539) human breast cancer cell lines by inducing G1 cell cycle arrest via reduction of CDK6 and RB protein levels, and induction of CDKN1B (p27KIP1) expression, as described elsewhere [194]. Chloroform extract of *Angelica sinensis* was found to exhibit inhibitory effect on proliferation of Glioblastoma multiforme (GBM) brain tumors *in vitro* and *in vivo*, as indicated in [195]. The chloroform extract was shown to increase the level of CDKN1A (p21), decrease phosphorylation of RB proteins resulting in cell arrest at the G0-G1 phase for DBTRG-05MG glioma cells *in vitro*, as well as decrease the volumes of *in situ* GBM *in vivo*, as indicated in [195]. The fresh rhizome of *Zingiber zerumbet (L.) Roscoe ex Smith* (Zingiberaceae) was found to serve as source of zerumbone, which was shown to induce G2/M cell cycle arrest in human promyelocytic leukemia HL-60 cells by decreasing the cyclin B1 and CDK1 protein levels, as described elsewhere [196]. Natural antioxidant derived from spinach extract was found to exert anti-proliferative effect on human prostate cancer PC3 cells [197]. Polyphenols derived from the spinach extract were shown to increase the protein levels of CDKN1A (p21), and decrease levels of cyclin A and CDK2 proteins, as described in [197]. At the same time spinach extract polyphenols decreased the phosphorylated RB protein level, and total protein levels of retinoblastoma-like 1 (p107, also known as RBL1), and E2F1 transcription factor, as indicated in [197].

Dineolignan (saucernetin-7) isolated from *Saururus chinensis* was found to negative affect the proliferation of human promyelocytic leukemia HL-60 cells through reducing the levels of the G1 phase cell cycle regulators, CDK-6 and cyclin D1, as well as by increasing the level of CDKN1A (p21), as described in [198]. Saucernetin-7 markedly enhanced the binding of CDKN1A (p21) with CDK-2 and -6, resulting in the reduced activity of both kinases and preventing the phosphorylation of RB protein, as indicated in [198]. Tetrandrine, isolated from the root of *Stephania tetrandra*, inhibited tumor cell growth and cyclin D1 expression, induced the expression of CDKN1A (p21), and also affected the expression patterns of cytoskeletons including distribution of F-actin and expression level of microtubule, as described in [199]. Silibinin is the primary active component isolated from the crude seed extract from the milk thistle plant (*Silybum marianum*), and was found to induce the cell cycle arrest in G2-M phase in human colon carcinoma FET and GEO cell lines, and at the G1 phase in HCT116 cells, as noted elsewhere [200]. Silibinin was shown to decrease the protein levels of cyclins B1, D1 and CDK-2, as described in [200]. Silibinin also increased expression of cell cycle inhibitors, CDKN1A (p21) and 1B (p27), as indicated in [200]. An aqueous extract of *Magnolia officinalis* inhibited cell proliferation in cultured human urinary bladder cancer 5637 cells, which was associated with G1 cell cycle arrest [201]. Treatment with the *M. officinalis* extract blocked the cell cycle in the G1 phase, downregulated the expression of cyclins and CDKs and upregulated the expression of CDKN1A (p21WAF1) and 1B (p27KIP1), as well as induced a marked activation of p38 MAPK and JNK, as indicated in [201].

Propolis is a resinous substance collected by bees (*Apis mellifera*) from various tree buds, and was found to inhibit tumor growth associated with the cell cycle arrest in S- or G2- phases [202]. Propolis was shown to inhibit the expression of cyclins B1 and D1, and CDK4, and induce CDKN1A (p21) expression, as indicated in [202]. A novel phenylbutenoid dimer (+/-)-trans-3- (3, 4-dimethoxyphenyl)-4-[(E)-3, 4-dimethoxy-styryl] cyclohex-1-ene (PSC), isolated from *Zingiber cassumunar ROXB* (Zingiberaceae), inhibited proliferation of various human cancer cells [203]. PSC was shown to induce a cell cycle arrest of human lung cancer A549 cells at the G0/G1 phase, and induce expression of CDKN1A (p21), while reducing expression of cyclins A and D1, CDK-2, and -4, as indicated in [203]. Glycyrrhizin from Japanese herbal supplement 'Sho-saiko-to' (also known as minor bupuleurum formula and *Xiao Chai Hu Tang* in Chinese) was shown to block proliferation of murine malignant melanoma Mel-ret cells in G1 phase by decreasing the expression of CDK-4 and -6 protein levels, as indicated in [204]. Rosamultic acid, a natural triterpenoid from *Rosa multiflora*, was found to induce cytotoxicity towards human gastric cancer SGC-7901 cells in a dose- and time-dependent manner, as described in [205]. The studies revealed that this cytostatic effect was associated with the cell cycle arrest in sub-G1 phase and downregulation of the CDK4, CDK6 and cyclin D1 protein levels [205]. A prenylated benzophenone (7-epiclusianone) from *Garcinia brasiliensis* (Clusiaceae

family) was shown to exhibit anti-proliferative activity against various cancer cell lines, including human lung carcinoma A549 cells [206]. 7-epiclusianone was found to reduce the viability of A549 cells in a concentration-dependent manner (IC50 of 16.13 ± 1.12 μM), as well as induce the cell cycle arrest in G1/S phase [206]. 7-hydroxydehydronuciferine (7-HDNF) isolated from the leaves of *Nelumbo nucifera Gaertn cv*. was shown to reduce melanoma tumor cell growth *in vitro* and in mice xenograft model *in vivo* by increasing cell cycle arrest in G2/M phase [207]. 7-HDNF was found to display a minor cytotoxicity towards normal human skin cells, including epidermal keratinocytes and melanocytes, and dermal fibroblasts, as indicated in [207].

The purified *Thymus vulgaris* ethanol extract contains several compounds including the known flavanone, Nar, which was shown to inhibit the growth of both human colorectal and breast cancer cells in a dose- and time-dependent manner through cell cycle arrest at S and G2/M phases [208]. Nar was found to downregulate the CDK4, CDK6, CDK7 expression, and upregulate the p18 (CDKN2C), p19 (CDKN2D), p21 (CDKN1A) protein levels in both colorectal and breast cancer cells [208]. Among flavonoids, genistein was found to exhibit the most significant cytotoxic activity toward cancer cells modulating various phases of the cell cycle, DNA replication and cell growth, as reviewed in [209]. Genistein was shown to reduce the expression of MCM2-7 and MCM10 helicases involved in the S phase control [209]. Genistein also caused the cell cycle arrest in G2/M phase, which was accompanied by activation of the CDKN1A, CDKN1C, CDKN2A, CDKN2B, CDKN2C, and GADD45A protein expression, as described in [209]. Ethanolic extract from the leaves of lemon balm (*Melissa officinalis*) was shown to exhibit the anti-proliferative effects on human colon carcinoma HT-29 and T84 cells through a G2/M cell cycle arrest and reduced expression of CDK-2, -4, and -6, and cyclin D3, and induced expression of CDKN2C (p18) and CDKN1A (p21) proteins [210]. The ethanol extract from *Tetrastigma hemsleyanum* was found to induce the cell cycle arrest in S phase in hepatocellular carcinoma HepG2 cells associated with decreasing expression of CDK1, and downregulating of cyclin A-CDK1 complex [211]. Tanshinone IIA (Tan-IIA) extracted from *Salviae miltiorrhizae radix* was found to upregulate the CDKN1A (p21) protein expression, but reduce CDC2, cyclin A, and cyclin B1 protein levels in human gastric carcinoma AGS cells [212]. The results also showed that Tan-IIA dose-dependently induced G2/M phase arrest, as indicated in [212]. *Patrinia scabiosaefolia* has long been used as an important component in traditional Chinese medicine formulas to treat gastrointestinal malignancies including colorectal cancer (CRC), as reviewed in [213]. The ethanol extract from the *Patrinia scabiosaefolia* was found to inhibit the tumor cell proliferation of human colorectal cancer HT-29 cells *in vitro* and *in vivo*, which was associated with the cell cycle arrest in G1/S phase, and downregulation of cyclin D1 and CDK4 protein levels [213]. Glycyrol is a coumestan from *Glycyrrhiza uralensis* was found to exert the antitumor activity *in vitro* and *in vivo* via inducing the G0/G1 phase cell cycle arrest as indicated by increase in CDKN1A (p21) expression [214].

Extracts of *Neuolaena lobata* (an anti-protozoan ethnomedicinal plant of the Maya) exhibited anti-proliferative effects on human promyelocytic leukemia HL-60 cells through blocking the cell cycle at the G2/M phase [215]. The extract induced the expression of checkpoint kinases (CHEK1 and 2) and modulated the expression of CDC25 protein, which was paralleled with the upregulation of p53, and CDKN1A (p21) and downregulation of anaplastic large-cell lymphoma kinase (ALK), and JUNB and c-MYC transcription factors, as described in [215]. Compounds from *Venenum bufonis*, bufotalin, bufalin, telocinobufagin and cinobufagin, were shown to inhibit the growth of human hepatocellular carcinoma HepG2 cells, as indicated in [216]. Bufotalin, the most potent inhibitor of the viability of multidrug resistant liver cancer cells (R-HepG2) was shown to induce the cell cycle arrest in G2/M phase through downregulation of CDC25, CDK1, cyclin A and cyclin B1, as well as upregulation of p53 and CDKN1A (p21), as described elsewhere [216]. The apolar petroleum ether extract from the rainforest plant *Critonia morifolia* (Asteraceae) was found to exhibit the most potent anti-proliferative effect on promyelocytic leukemia HL-60 cells by triggering the cell cycle arrest in G2/M phase and dowregulation of CDC25A, B, and C, WEE1, AKT1, and cyclin D1 expression, as indicated in [217]. The extract also inhibited the c-MYC expression, as well as induced phosphorylation of CHEK2 and histone H2AX (serving as marker of DNA damage), as described in [217]. The extract from the root of *Polygonum multiflorum Thunb* exhibits anti-proliferative effect on human breast cancer MCF-7 cells through downregulation of CDC25B and C protein phosphatases, accompanied by an increase in the phosphorylated CDK1 protein, as described elsewhere [218].

The extracts from *Aracea Anthurium schlechtendalii* and *Syngonium podophyllum* exerted the anti-proliferating effects on human promyelocytic leukemia HL-60 cells, and human breast cancer MCF-7 cells, which correlated with the activation of CHEK2, downregulation of CDC25A and cyclin D1, as described in [219]. Organic extracts from *Scutellaria baicalensis, Scutellaria barbata* and *Scutellaria orientalis L. ssp. carica Edmondson*, were shown a strong ability to inhibit various human cancer cells, as indicated in [220]. The methanol extracts were found to contain apigenin, baicalein, chrysin, luteolin and wogonin, and inhibited proliferation of leukemia cells, which correlated with downregulation of cyclin D1 and CDC25A protein levels [220]. The extract from *Physalis angulata* was found to induce G2/M arrest in human breast cancer MAD-MB 231 and MCF-7 cell lines [221]. The extract was shown to downregulate the protein levels of cyclin A and B1, upregulate the CDKN1A (p21WAF1) and CDKN1B (p27KIP1) protein levels, increase in CDC25C phosphorylation/inactivation, as indicated elsewhere [221]. Squamocin, one of the Annonaceous acetogenins, was shown to inhibit the growth of human immortalized myelogenous leukemia K562 cells by inducing cell cycle arrest in G2/M phase [222]. Squamocin exposure increased the expression of CDKN1A (p21) and CDKN1B (p27), but decreased the protein levels of CDK1 and CDC25C, as indicated in [222].

5. CELL CYCLE REGULATION BY NATURAL COMPOUNDS AFFECTING OTHER ENZYMES

Various enzymes involve in cell cycle regulation and DNA replication process, including protein phosphatases, proteasome enzymes, and topoisomerases, as reviewed elsewhere [8]. Cell division cycle 25 (CDC25) phosphatases are dual-specificity phosphatases that dephosphorylate phosphoserine, phospho-threonine, and phospho-tyrosine and activate the CDK/cyclin complexes, thereby playing a fundamental role in transitions between cell cycle phases [8, 19, 223-227]. Upon DNA damage, CDC25 phosphatases act to ensure genomic stability [172-174]. In mammalian cells, three isoforms of CDC25 phosphatases have been identified: CDC25A, CDC25B and CDC25C, as reviewed elsewhere [224, 225]. The CDC25 proteins, CDC25A and CDC25B, are proto-oncogenes, and overexpressed in various human cancers [228-234]. Deregulation of CDC25 expression or function was shown in human cancers correlated with tumor aggressiveness and poor prognosis [228-234]. CDC25A was shown to activate the CUTL1/CUX1 transcription factor leading to a downregulation of CDKN1A (p21WAF1) expression in S phase of cell cycle, as indicated elsewhere [235]. Accumulating evidence supports the notion that CDC25A and CDC25B might represent promising targets for the development of novel anticancer agents, as reviewed in [236-240]. A large number of potent small-molecule CDC25 Inhibitors have been identified that bind to the active site and belong to various chemical classes including natural compounds, lipophilic acids, quinonoids, electrophilies, sulfonylated aminothiazoles and phosphate bioisosteres, as reviewed elsewhere [236-239]. Some natural compounds were shown activities leading to inhibition of protein phosphatases, including CDC25 [8, 19, 240].

Alpha-pinene from a steam distillation extract of pine needles exhibits anti-proliferative effect on human hepatocellular carcinoma BEL-7402 cells by arresting cell cycle at the G2/M phase, downregulating CDC25C expression, while reducing CDK1 activity [241]. Rocaglamide-A (Roc-A), a natural anticancer compound from *Aglaia*, induces a rapid phosphorylation of CDC25A and its subsequent degradation, thereby blocking cell cycle progression of tumor cells at the G1-S phase [242]. Roc-A was shown to inhibit tumor proliferation via induction of CDC25A degradation mediated through the ATM (ATR)-CHEK1 (CHEK2) pathway, as indicated elsewhere [242]. Pseudolaric acid B purified from *Pseudolarix kaempferi Gordon* was shown to inhibit the growth of human melanoma SK-MEL-28 cells and induced G2/M arrest in SK-MEL-28 cells, and induce the CDC2 phosphorylation, and a subsequent downregulation of CDC2 expression and CDC25C phosphatase [243]. In addition, pseudolaric acid B activated the checkpoint kinase, CHEK2, and increased the expression of p53, as indicated [243]. CDC25A inhibitory activity and antitumor activity were also exhibited by the extracts isolated from medicinal herbs *Agrimona pilosa, Herba solani lyrati,* and *Galla chinesis* [244].

Nine compounds (halenaquinone, xestoquinone, adociaquinones A and B, 3-ketoadociaquinones A and B, tetrahydrohalenaquinones A and B, and 13-O-methyl xestoquinol sulfate) from *Xestospongia sp*. were found to inhibit CDC25B activity, as indicated in [245]. Natural compounds (polyprenyl-hydroquinones and polyprenyl-furans [furanoterpenoids, furospongins, furospinosulins]) were isolated from sponge species *Spongia officinalis, Ircinia spinulosa,* and *Ircinia muscarum*, collected at different locations in the Mediterranean Sea, as described in [246]. They were shown exhibit potent CDC25 phosphatase inhibitor activities [246]. Aqueous extract of *Phyllanthus amarus* inhibited a growth of 20-methylcholanthrene-induced sarcoma in mice [247]. The extract was found to inhibit DNA topoisomerase II and CDC25 tyrosine phosphatase (IC = 50-25 μg/ml), as indicated in [247]. Coscinosulfate 1, a sesquiterpene sulfate from the New Caledonian sponge *Coscinoderma matthewsi*, along displayed a significant inhibitory activity towards CDC25A (IC50 - 3 μM), as described elsewhere [248]. A new antibiotic TMC-69 has been isolated from the fermentation broth of a fungal strain *Chrysosporium sp*. *TC 1068*, as described in [249]. TMC-69 exhibited cytotoxic activity against murine P388 leukemia and B16 melanoma *in vitro* and *in vivo*, and specifically inhibited CDC25A and B phosphatases, as indicated in [249].

A variety of cell cycle regulatory proteins (e.g. cyclins, CDK-inhibitors) undergo a proteasome-dependent degradation in a temporally controlled fashion [250]. For example, the synthesis of cyclin B leads cells to initiating of mitosis, while ubiquitin-mediated degradation of cyclin B regulates the exit of cells from mitosis and reentry into G1 phase, as reviewed elsewhere [251, 252]. Similarly, synthesis and degradation of cyclin E are essential to late G1 progression, and S phase entry, respectively [253, 254]. Accumulating evidence suggests that the pharmacological inhibition of the proteasome results in cell cycle arrest [250-252]. Proteasome inhibitors are therefore potential candidates as antimitotic drugs [8, 19, 115, 250]. Several natural product inhibitors showing greater specificity have been discovered, as reviewed elsewhere [8, 19, 115, 250]. Lactacystin isolated from *Streptomyces sp*. is the first known natural irreversible specific proteasome inhibitor [255, 256]. Additionally, Salinosporamide and Epoxomicin are the prominent proteasome inhibitors acquired from nature [257-259].

DNA topoisomerase are essential nuclear enzymes that create DNA breaks, thereby allowing the DNA strands to unravel and separate, as reviewed elsewhere [8, 19, 260-262]. Topoisomerases are categorized on type I (single-stranded, TOPO-I) or type II (double-stranded, TOPO-II), as reviewed in [8, 260-262]. Topoisomerase II (TOPO-II) is the molecular target for the most widely used anticancer drugs acting to prevent the enzyme from religating DNA strand breaks [8, 260-262]. TOPO-II inhibition results in the accumulation of double stranded DNA breaks, which essentially lead to cell death [8, 260-263]. TOPO-II inhibitors affect cell cycle progression during G2/M phase with little effect on S phase transit, while TOPO-I inhibitors alter cell cycle progression at the S phase [263-265]. A few reports linked the DNA topoisomerase activities with cell cycle regulation [260, 263-265]. Vincristine-resistant human leukemia cells were shown to display a delayed G2/M transit and prolonged early mitosis, as indicated in [263-265]. These changes were accompanied by down-regulation of DNA topoisomerase II-alpha (TOPO-IIA), as indicated elsewhere [263-265]. Initiation of chromosome condensation during early prophase is

linked a formation of CDC2 kinase/TOPO-II protein complexes in the nucleus, and is coupled to chromatin remodeling, as described elsewhere [263-265]. The topoisomerase inhibitors are additionally divided into two types depending on their mode of action [264]. Inhibitors that are able to stabilize the covalent DNA topoisomerase II complex (also known as the cleavable complex) are called topoisomerase II poisons, while agents acting on any of the other steps in the catalytic cycle are called catalytic inhibitors [264]. Catalytic topoisomerase II inhibitors are a diverse group of compounds that might interfere with the binding between DNA and topoisomerase II (aclarubicin and suramin), stabilize noncovalent DNA topoisomerase II complexes (merbarone), or inhibit ATP binding (novobiocin), as reviewed in [264].

Aclarubicin, an anthracycline isolated from *Streptomyces* species, used clinically in the treatment of acute myelocytic leukemia [266]. Aclarubicin is a potent DNA intercalating agent that prevents the binding of TOPO-II to DNA, and also inhibits TOPO-I in a concentration-dependent manner [266, 267]. Cellular exposure to aclarubicin leads to DNA damage as well as the cell cycle arrest in G2 phase [268-270]. Novobiocin, an antibiotic from *Streptomyces niveus* was found to inhibit mammalian topoisomerase II by blocking the ATP-binding site, as described elsewhere [271-273]. Quercetin-3-O-glucoside has been shown to possess anti-proliferative activity associated with the cell cycle arrest in S phase and inhibition of DNA topoisomerase II, as described in [274].

6. CELL CYCLE REGULATION BY NATURAL COMPOUNDS AFFECTING MICROTUBULES

Microtubules are involved in maintaining the structure of the cell and, together with microfilaments and intermediate filaments, they form the cytoskeleton [275-278]. They provide platforms for intracellular transport and are involved in a variety of cellular processes, including the movement of secretory vesicles, organelles, and intracellular macromolecular assemblies [275-278]. They are also involved in chromosome separation (mitosis and meiosis), and are the major constituents of mitotic spindles, which are used to pull apart eukaryotic chromosomes [275-278]. The microtubule network is recognized for its role in regulating cell growth and movement as well as key signaling events, which modulate fundamental cellular processes [275-278].

Emerging evidence suggests that it is critically involved in cell stress responses, including cancer, as reviewed [279]. Diverse changes in the microtubule network have been characterized in various human cancers, including altered expression of tubulin isotypes, alterations in tubulin post-translational modifications, and changes in the expression of microtubule-associated proteins (MAPs), as reviewed elsewhere [279, 280]. Microtubule alterations might be involved in various responses of tumor cells to chemotherapeutics and tumor microenvironment (e.g. hypoxia, oxidative stress, metabolic stress, endoplasmic reticulum/protein folding stress), thereby contributing to chemotherapy resistance, tumor development, and cell survival, as reviewed in [279].

Microtubules are long cylindrical polymers composed of monomers of alpha- and beta-tubulin that display highly dynamic properties, as reviewed elsewhere [8, 10, 15-18, 275-283]. Cell cycle progression is associated with microtubule dynamics [8, 10, 15-18, 275-278, 281]. The tubulin-interacting class of antimitotic agents can be classified by their influence on the tubulin polymerization and by their binding site on tubulin [8, 10, 15-18, 275-278]. Some compounds promote microtubule polymerization and stabilize microtubules (e.g. taxoids, epothilones, and discodermolide), as reviewed in [8, 10, 14-18, 275-278, 282, 283]. Other compounds affect microtubules by inhibiting polymerization (e.g. vinca alkaloids, colchicines, cryptophycins, halichondrins, and estramustine), as reviewed elsewhere [8, 10, 15-18, 280-288].

Paclitaxel, isolated from the stem bark of the Pacific yew tree *Taxus brevifolia*, was found to have potent antimitotic activity against leukemia cells [8, 10, 15-18, 280]. Paclitaxel blocks mitosis by stabilizing tubulin polymers and thereby inhibiting disassembly of microtubules [10, 281, 283]. Two important prototypes, Epothilone A and B, were isolated from myxobacterium *Sorangium cellulosum* and exhibit significant cytotoxic activities [280-290]. Epothilones were shown to stabilize tubulin polymers leading to mitotic arrest and cell death [288-292]. Epothilone A and B bind competitively with paclitaxel to tubulin suggesting that they share a common binding site, as described elsewhere [288-292]. Epothilones exhibit potent cytotoxic effects against numerous cancer cell lines, including multiple drug resistant (MDR) cells and paclitaxel-resistant cells with mutations in beta-tubulin, as indicated in [288-292]. Their potent cytotoxicity, unlimited availability by bacterial fermentation, as well as absence of tumor resistance to these drugs highly increased enthusiasm towards epothilones [291-294]. Epothilone D, a natural analog of epothilone B, was found to inhibit the proliferation of malignant glioma cell lines at low nanomolar levels and leads to tubulin damage [295]. Epothilones B and F were shown to be efficient in inhibiting proliferation of human colon carcinoma HCT-116 cells and human leukemia K562 cells xenografted into mice *in vivo* [296]. Phase II trials of epothilone B (EPO-906TM) have been completed for colorectal, ovarian, and kidney cancers, whereas phase II trials of epothilone D were initiated in 2003 for colorectal, non-small cell lung cancer and metastatic breast cancer, as reviewed elsewhere [294] (Table **1**).

Discodermolide, a polyhydroxylated lactone structure, was isolated from the marine sponge *Discodermia dissoluta*, was shown acting as microtubule-stabilizing agent, as described [297]. Discodermolide induces assembly of purified tubulin *in vitro* (EC50=2.3 mM), and microtubule rearrangement in breast carcinoma cells at 10 nM (100 times greater potency than paclitaxel), as indicated in [297]. It also potently inhibits the growth of paclitaxel-resistant, multidrug-resistant carcinoma cell lines [298]. Discodermolide is now in Phase I clinical trials as a potential drug for solid tumors, as reviewed elsewhere [299]. The combrestatins are antimitotic agents isolated from the bark of the willow tree *Combretum caffrum* [300, 301]. Combrestatin A4, the most potent antimitotic drug, binds to the colchicine site of tubulin [300, 301]. Podophyllotoxin is a lignan isolated from the roots of *Podophyllum peltphylum*, and was found to inhibit the hydrolysis of GTP by tubulin [302]. Curacins A and D is a marine natural compound from the blue–green cyanobacterium *Lyngbya majuscule* [299, 303-311]. Curacins were found to be active against breast, colon and renal

cancer cell lines acting as antimitotic agents [303-305]. Curacin A binds to the colchicine site of tubulin with an association constant 3400 times greater than tubulin itself when forming dimers [303-306]. Curacin A inhibits tubulin polymerization with an IC50 = 0.72 mM [303-306]. The Vinca alkaloids are derived from the periwinkle plant *Catharanthus roseus G. Don* (also known as *Vinca rosea Linn*). The first natural compounds to be identified are vinblastine and vincristine, which differs only in the presence of a formyl or methyl group in the vindoline moiety, as reviewed elsewhere [8, 15-18, 307-309]. The anti-proliferative activity of the Vinca alkaloids is attributed to their ability to disrupt microtubules, causing dissolution of mitotic spindles and metaphase arrest in dividing cells [308-312]. However, disruption of microtubules can also lead to toxicity in non-mitotic cells. Although the Vinca alkaloids are classified as mitotic inhibitors, their anti-proliferative activity in the clinical treatment of cancer probably arises from suppression of microtubule dynamics as well as from disruption of the cell cycle, as reviewed elsewhere [8, 10, 311, 312].

Dolastatin-10 and -15 are polypeptide natural compounds isolated from marine sea hare *Dolabella auricularia*, as reviewed elsewhere [313]. Both of these compounds are more potent than vinblastine in tubulin polymerization assays, although dolastatin-10 is nine times more potent than its closely related analog [313, 314]. This family of compounds acts as non-competitive inhibitors of vinblastine binding to tubulin, as indicated in [315]. Dolastatins were shown exhibit cytotoxic activity toward various cancer cells of hematological origin by inhibiting microtubule assembly [316-318]. Several clinical phase II studies have already begun for patients with hormone-refractory metastatic prostate adenocarcinoma, as reviewed in [319]. Dolastatin 15 was found to induce the cell cycle arrest in G2/M phase in various human myeloma cell lines (RPMI8226, U266, and IM9), as indicated in [320].

Rhizoxin is an antitumor antibiotic isolated from the culture broth of *Rhizopus chinensis* and *Rhizopus microspores*, as reviewed elsewhere [18, 321]. Rhizoxin was observed to be a competitive inhibitor of the binding of both vincristine, as well as ansamitocin P-3, a maytansine analog to tubulin [322]. Rhizoxin inhibits the polymerization of purified tubulin with an IC50 of 6.8 μM, as indicated in [322]. Using the high-resolution crystal structure of the complex, between tubulin and maytansine (the drug used for the treatment of advanced breast cancer), Prota and coworkers have shown that the drug binds to a site on β-tubulin that is distinct from the vinca domain blocking the formation of longitudinal tubulin interactions in microtubules [323]. They also found that rhizoxin bound to the same site as maytansin [323]. Rhizoxin was shown anti-proliferative effect on human and murine tumor cells resistant to vincristine and adriamycin when compared to maytansine *in vitro* and *in vivo*, as indicated in [324]. Rhizoxin inhibits microtubule assembly at a 10-fold lower concentration (10 ng/ml) than vincristine and is 8- to 43-fold more active than vincristine in P-glycoprotein-mediated vincristine-resistant murine and human leukemia cell lines (P388/VCR and K562/VCR), as described in [324]. Rhizoxin was active against human small-cell lung cancer H69/VDS cells with non-P-glycoprotein-mediated resistance to vindesine *in vitro*, as described in [325]. Tubulin polymerization in H69/VDS was inhibited markedly by rhizoxin compared with that in H69, in a dose-dependent manner, as described [325]. A drug-accumulation study showed that the intracellular rhizoxin level in H69/VDS was 15% lower than that in H69, as indicated in [325]. With the aid of mice with severe combined immunodeficiency xenografted with H69/VDS tumor cells, Arioka and coworkers have shown that *in vivo* tumor growth was markedly reduced by rhizoxin [325]. Rhizoxin also demonstrated significant antitumor activity in a number of human tumor xenografts, including melanoma (LOX), breast cancer (MX-1), nonsmall-cell lung cancer (A549), small-cell lung cancer (LXFS 605), and a vincristine-resistant small-cell lung cancer (LXF 650), as indicated in [326]. In a multicentre trial of the European Organization for Research and Treatment of Cancer-Early Clinical Trials Group, thirty-one of chemotherapy-naive patients with advanced non-small cell lung cancer were treated with rhizoxin, a novel tubulin-binding agent, which showed a single agent antitumor activity [327].

The spongistatins are a group of complex macrocyclic lactones isolated from the sponges *Spirastrella spinispirulifera* and *Hyrtios erecta*, as described elsewhere [328]. Spongistatin 1 is a potent inhibitor of the binding of vinblastine and GTP to tubulin, but has no effect on the binding of colchicine to tubulin [329-331]. Spongistatin 1 has exhibited potent activity against leukemic (IC50 = 20 pM against L1210 murine leukemia cells) and melanoma, prostate and colon cancer cell lines *in vitro* [329, 330, 332]. It also exhibited a significant antitumor activity in the LOX-IMVI human melanoma xenograft model *in vivo*, as well as modulated a pancreatic tumor progression and metastasis [330, 333]. Calvatic acid is a known cytostatic agent isolated from *Calvatica liacina* was found to exhibit cytostatic properties by prevention of microtubule assembly [334, 335].

Assembly and disassembly of microtubules is controlled by a number of microtubule-associated proteins (MAPs) that stabilize microtubules against disassembly, as reviewed elsewhere [276, 280, 282]. MAP family includes the following proteins: MAP1, MAP2, MAP4 and TAU, as reviewed in [276, 280, 282]. MAPs bind to the tubulin subunits that make up microtubules to regulate their stability, therefore contributing to assembly and disassembly of microtubules [276, 280, 282]. The C-terminal domain of the MAP interacts with tubulin, while the N-terminal domain can bind with cellular vesicles, intermediate filaments or other microtubules [276, 280, 282, 336]. The binding of MAPs to microtubules is regulated through MAP phosphorylation by microtubule-affinity-regulating-kinase (MARK) protein [336]. Phosphorylation of MAP4 by p34cdc2 kinase abolished its microtubule stabilizing activity [337]. MAP4 phosphorylation by the CDK1/cyclin B complex decreases its microtubule stabilizing ability at mitosis [337]. Tryprostatin-A is a secondary metabolite from *Aspergillus fumigatus* and is the first natural compound that inhibits microtubule assembly by interfering with the binding of MAPs with the carboxyl-terminal domain of tubulin [338]. Tryprostatin-A only inhibits MAP2-, TAU-, and poly-L-lysine-induced tubulin polymerization [338].

Table 1. Anti-proliferative effects of phytometabolites on various phases of cell cycle in human tumor cells.

Cell Cycle Phase	Name of the Drug	Source of the Drug	Human Tumor Cells	Affected Targets	Refs.
G1/S, G2/M	Butyrolactone-I	*Aspergillus terreus*	H460 lung cancer, SW480 colon cancer	Inhibition of CDK1/cyclin B complex, CDKN1A	[81]
G1/S	Chebulagic acid	*Terminalia chebula*	retinoblastoma cells	Increase in CDKN1B, decrease in NF-κB	[97]
G1/S	Wogonin	*Scutellaria radix*	HCT116 colorectal cancer	Decrease in cyclin A, D1, E, and CDK-2 and -4	[99]
G1/S	Fangchinoline	*Stephaniae tetrandrine S. Moore*	breast cancer MCF-7 and MDA-MB-231 cells	Decrease of cyclins D1, D3, and -E, CDK-2,- 4, -6. Increase in CDKN1A and 1B	[101]
G1/S	Berberine	*Berberis sp.,*	cholangiocarcinoma QBC939 cells	Increase in CDKN1A and 1B, and decrease in CDK-2 and -4, and cyclin D1	[102]
G2/M	5, 3'-dihydroxy-3, 6, 7, 8, 4'-pentamethoxyflavone	*Gardenia obtusifolia*	prostate, colon, kidney, lung, head/neck, pancreas, breast, leukemia, and myeloma cancer	Increase CDKN1A and 1B, decrease in cyclin D1, CDC2, and c-MYC	[106]
G1/S	Acetylbritannilactone	*Inula britannica L.*	HT-29 colorectal cancer	Decrease in cyclins A, D1, and E and CDK-2, -4, -6, and an increase in CDKN1A	[110]
G1/S, G2/M	Quercetin	*Quercus sp.*	Leukemia, breast cancer, liver cancer	Decrease in CDK-2, -6, -7, cyclin A, D1, and E, and increased CDKN1A and 1B	[112-114]
G2/M	Isorhamnetin	*Hippophae rhamnoides L*	colorectal cancer cell lines, HT‑29, HCT116 and SW480	inhibit the PI3K‑AKT‑mTOR pathway, increase in cyclin B1	[116]
G2/M	Tamarixetin	*Tamarix ramosissima*	leukemia cells	Increase in cyclin B1, BUB1, and CDKN1A, inhibits tubulin polymerization	[117]
G1/S	Epigallocatechin-3-gallate	Green tea	prostate, lung and skin cancers	Increase in CDKN1A, 1B, 2A, and 2C, decrease in cyclin D1, E, CDK-2, -4 and -6	[122-124]
G1/S	Proanthocyanidins	*Vitis vinifera*	epidermoid carcinoma A431 cells, prostate cancer cells, DU145 and LNCaP	Decrease in CDK-2, -4 and -6, cyclins D1, D2 and E, while increase in CDKN1A and 1B	[125-128]
G2/M	Apigenin	parsley, celery, celeriac, and chamomile tea	HT-29 and MG63 colorectal adenocarcinoma cells, pancreatic and hepatoma cells	Decrease in cyclins A, B, D1, D2 and E, CDK-2, -4, and -6, and increase in CDKN1A and 1B	[136-140]

(Table 1) contd….

Cell Cycle Phase	Name of the Drug	Source of the Drug	Human Tumor Cells	Affected Targets	Refs.
G2/M, and S-phase	Curcumin	*Curcuma longa*	neuroblastoma cells, colon adenocarcinoma LOVO cells and HCT-116 cells, glioma U251 cells	Increase in CDKN1A and 1B, and ING4	[142-147]
G1/S	Indole-3-carbinol	*Brassicaceae*	breast cancer, prostate cancer, endometrial cancer, colon cancer, and leukemia cells	Decrease in cyclins D1, E, CDK-2, -4, -6 and increase in CDKN1A, 1B, and 2B	[148, 149]
G2/M	Zerumbone	*Zingiber zerumbet (L.) Roscoe ex Smith*	promyelocytic leukemia HL-60 cells	Decrease in cyclin B1 and CDK1	[151]
G1/S	Dineolignan (saucer-netin-7)	*Saururus chinensis*	promyelocytic leukemia HL-60 cells	Decrease in CDK-6 and cyclin D1, and increase in CDKN1A	[153]
G1/S, G2/M	Silibinin	*Silybum marianum*	colon carcinoma FET and GEO cells	Decrease in cyclins B1, D1 and CDK-2, increased in CDKN1A and 1B	[155]
G0/G1	phenylbutenoid dimer (+/-)-trans-3-(3, 4-dimethoxyphenyl)-4-[(E)-3, 4-dimethoxy-styryl] cyclohex-1-ene	*Zingiber cassumunar ROXB*	lung cancer A549 cells	Increase in CDKN1A, and decrease in cyclins A and D1, CDK-2, and -4,	[158]
G1/S	Rosamultic acid	*Rosa multiflora*	gastric cancer SGC-7901 cells	Decrease in CDK4, CDK6 and cyclin D1	[160]
G2/M	Tanshinone IIA	*Salviae miltiorrhizae*	gastric carcinoma AGS cells	Decrease in CDC2, cyclin A, and cyclin B1	[167]
G1/S	Rocaglamide-A	*Aglaia*	leukemic cells	Induces phosphorylation and degradation of CDC25A, induces the ATM (ATR)-CHEK1 (CHEK2) pathway	[190]
G2/M	Bufotalin	*Venenum Bufonis*	hepatocellular carcinoma HepG2 cells	Decrease in CDC25, CDK1, cyclin A and cyclin B1, and increase in p53 and CDKN1A	[192]
S-phase	Berberine and Palmatine	*Berberis lycium Royle*	promyelocytic HL-60 cells	Increase in CHEK2, decrease in CDC25A, cyclin D1, and CDK1	[195]
G2/M	Pseudolaric acid B	*Pseudolarix kaempferi Gordon*	melanoma SK-MEL-28 cells	Decrease in CDC2 and CDC25C, increase in CHEK2, and p53	[198]
G2/M	Squamocin	*Annonaceous sp.*	myelogenous leukemia K562 cells	Increased in CDKN1A and 1B, but decrease in CDK1 and CDC25C	[200]

(Table 1) contd….

Cell Cycle Phase	Name of the Drug	Source of the Drug	Human Tumor Cells	Affected Targets	Refs.
G2/M	Aclarubicin	*Streptomyces* sp.	acute myelocytic leukemia	TOPO-I and II	[223-226]
G2/M	Paclitaxel	*Taxus brevifolia*	leukemia cells, nasopharyngeal carcinoma	Stabilize tubulin polymers and inhibiting disassembly of microtubules	[236-239]
G2/M	Epothilone A, B, D, and F	*Sorangium cellulosum*	prostate cancer, glioma cells, leukemia K562 cells	Stabilize tubulin polymers leading to mitotic arrest	[234-252]
G2/M	Discodermolide	*Discodermia dissoluta*	paclitaxel-resistant, multidrug-resistant carcinoma cell lines	Microtubule-stabilizing agent	[253, 254]
	Curacins A and D	*Lyngbya majuscule*	breast, colon and renal cancer cell lines	Inhibit tubulin polymerization	[255, 259-263]
G2/M	Dolastatin-10 and 15	*Dolabella auricularia*	cancer cells of hematological origin, hormone-refractory metastatic prostate adenocarcinoma, myeloma cell lines (RPMI8226, U266, and IM9)	Inhibit microtubule assembly	[269-276]
	Rhizoxin	*Rhizopus chinensis* and *Rhizopus microspores*	small-cell lung cancer H69/VDS cells with non-P-glycoprotein-mediated resistance to vindesine, tumor xenografts, including melanoma (LOX), breast cancer (MX-1), nonsmall-cell lung cancer (A549), small-cell lung cancer (LXFS 605), and a vincristine-resistant small-cell lung cancer (LXF 650), nonsmall-cell lung cancer	Binds to a site on β-tubulin	[277-283]
	Spongistatin 1	*Spirastrella spinispirulifera* and *Hyrtios erecta*	leukemia, melanoma, pancreatic, prostate and colon cancer cell lines, LOX-IMVI human melanoma xenograft model *in vivo*	Binds to a site on β-tubulin	[284-289]
G2/M	Tryprostatin A	*Aspergillus fumigatus*	breast cancer, multiple myeloma, gastric carcinoma cells, prostate, and lung cancer cell lines	Inhibits MAP2-, TAU-induced tubulin polymerization	[294]

CONCLUSION AND FUTURE PERSPECTIVES

To summarize current review, it is fair to view naturally produced natural compounds as effective regulators and modulators of cell cycle regulation in tumor cells. Natural compounds from plants, microorganisms and marine life forms were often showed to exhibit strong abilities to inhibit tumor cell proliferation *in vitro* and even block tumor growth *in vivo*. Accumulating evidence shows that many natural compounds from numerous biological sources are able to regulate various phases of cell cycle leading to cell cycle arrest in tumor cells originated from a number of human cancers. Furthermore, emerging evidence reveals that many natural compounds exert their anti-proliferative activities through similar molecular mechanisms involving downregulation of phase-specific cyclins and CDKs, while upregulating CDK inhibitors. Moreover, other enzymes, (such as protein phosphatase, DNA topoisomerases), as well as proteins implicated in regulation of microtubule architecture and function were shown to be affected by certain natural compounds and compounds from microorganisms and marine life forms. Natural compounds described in this review are categorized in Table and their chemical structures depicted in (Figs. **1** and **2**). Selected natural compounds schematically depicted in the (Fig. **3**), as modulators of specific phases of cell cycle regulation. In order to define critical checkpoints allowing to differentiate the potential effects of the natural anticancer compounds on the tumor cells versus normal cells, the inhibitory specificity of drugs on various phases of the cell cycle leading to blocking tumor cell proliferation should be analyzed in future studies *in vitro.* Moreover, the more detailed analysis of potential targets affected by anticancer natural compounds needed to increase specificity for blocking cell proliferation of tumor cells, decrease unwanted side effects associated with damage to normal cells, and to address potential chemoresistance often occurred in tumor cells upon treatment.

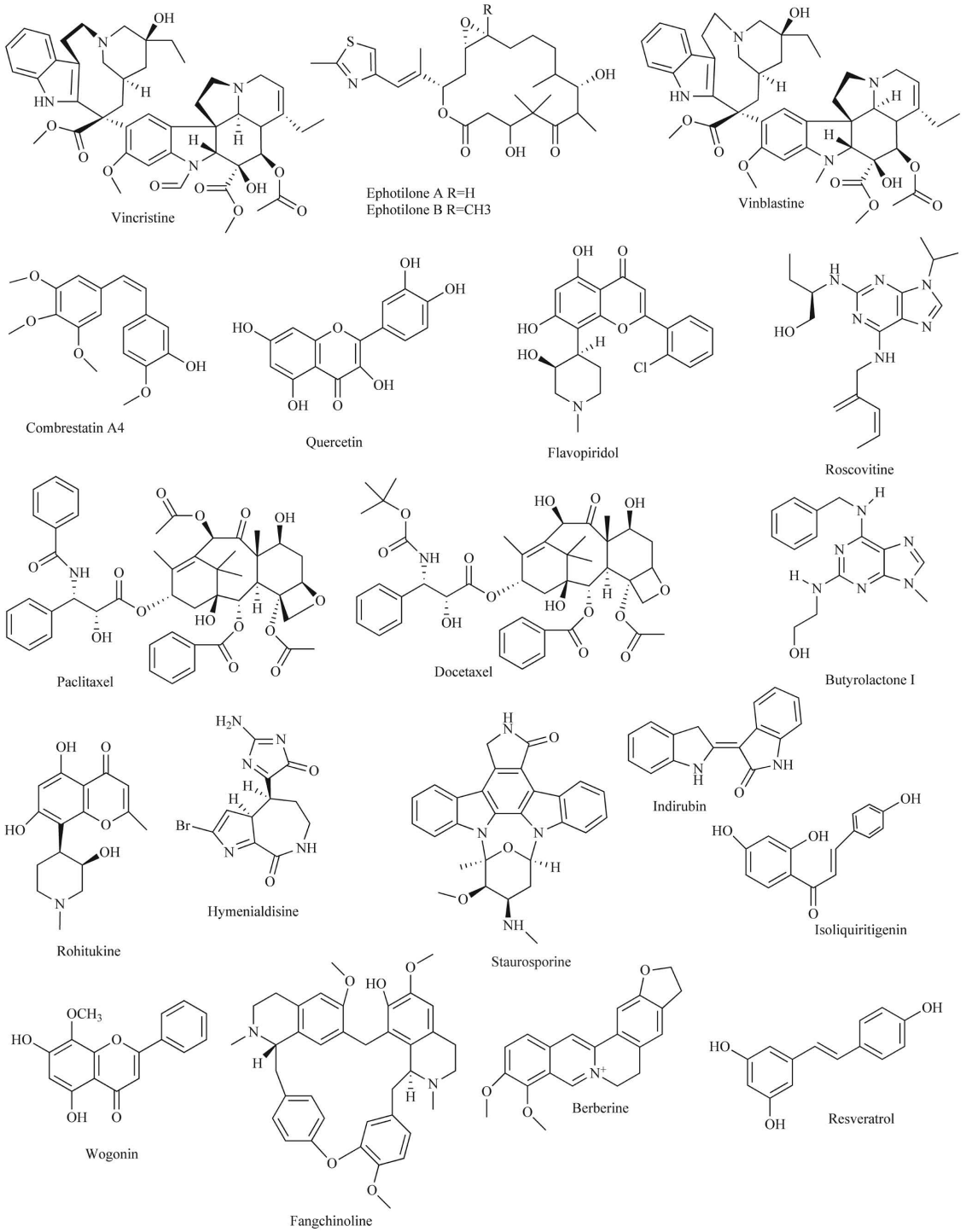

Fig. (1). Chemical structures of selected natural compounds that exhibited anti-proliferative properties associated with the cell cycle regulation.

Natural compounds have been widely used *in vitro*, *in vivo*, and in preclinical cancer prevention and phase II clinical treatment studies, as reviewed elsewhere [339]. Some of these clinical trials have shown various degrees of success. As cancer chemoprevention and treatment using natural phytochemicals have been such an attractive approach, further studies especially *in vivo* using xenograft models needed to understand their potencies, pharmacokinetic performances, pharmacodynamic responses, metabolisms, toxicities, drug-drug interactions, polymorphisms, and then formulations, stabilities and degradations, and dosage regimens [339]. Furthermore, to address potential chemoresistance of tumor cells to natural compounds or existing anticancer drugs, the combination approach should be taken using two or several compounds of natural or synthetic origin. The future full convergence of prevention-therapy drug development will open new avenues for natural compounds in reducing the public health impact of major cancers. However, more preclinical

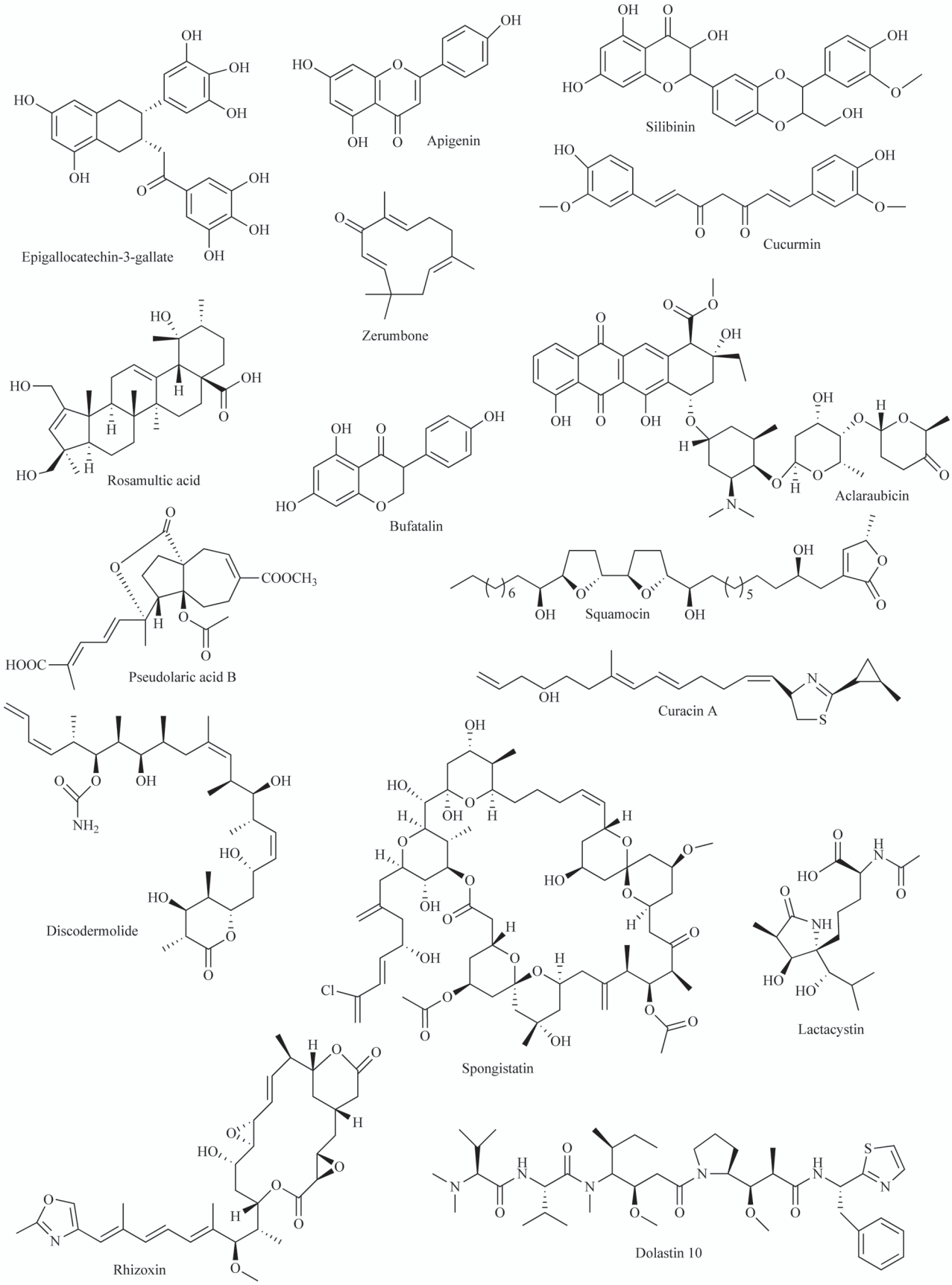

Fig. (2). Chemical structures of selected natural compounds that exhibited anti-proliferative properties associated with the cell cycle regulation.

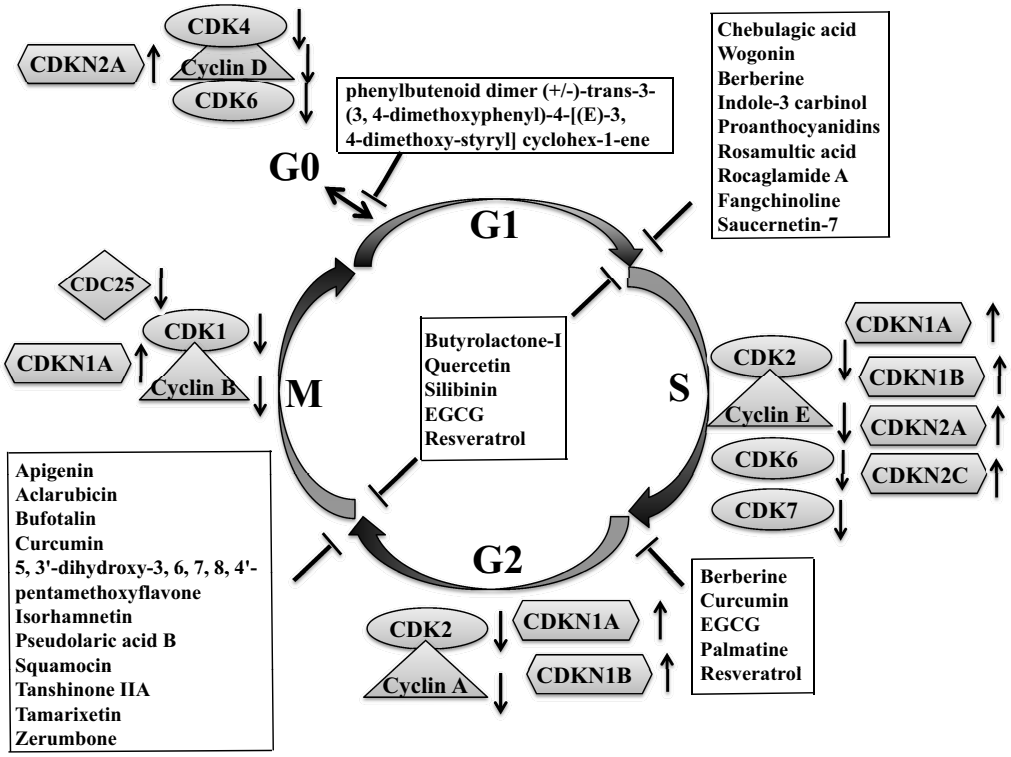

Fig. (3). Schematic representation of natural compounds that affect various phases of cell cycle in human tumor cells. Selected natural compounds act on multiple checkpoints or targets. The arrows indicate activation and blocked signs indicate inhibitory effects of natural compounds in the cell cycle regulation. Up and down arrows indicate the upregulated and downregulated levels of specific cell cycle regulators upon treatment with indicated natural compounds.

studies and clinical trials are certainly needed to validate the usefulness of these agents either alone or in combination with existing therapies.

LIST OF ABBREVIATIONS

BUB1	=	Budding Uninhibited by Benzimidazoles 1
CDK	=	Cyclin-Dependent Kinase
CDKN	=	Cyclin-Dependent Kinase Inhibitor
CAK	=	CDK-Activating Kinase
DH-PMF	=	5, 3'-dihydroxy-3, 6, 7, 8, 4'-pentamethoxy-flavone
EGFR	=	Epidermal Growth Factor Receptor
ERK	=	Extracellular Signal-Regulated Kinase
GBM	=	Glioblastoma Multiforme
7-HDNF	=	7-hydroxydehydronuciferine
IkBα	=	Nuclear Factor of Kappa light polypeptide gene enhancer in B-cells inhibitor, Alpha
JNK	=	IκB Kinase-Alpha
IKKα	=	c-Jun N-terminal Kinase
MAP	=	Microtubule-associated Protein
MAP2K1	=	Mitogen-activated Protein Kinase Kinase 1
MLCK4	=	Myosin Light Chain Kinase 4
NF-κB	=	Nuclear Factor -kappa B
PSC	=	Phenylbutenoid Dimer (+/-)-trans-3- (3, 4-dimethoxyphenyl)-4-[(E)-3, 4-dimethoxy-styryl] cyclohex-1-ene
PDGF	=	Platelet-derived Growth Factor
RB	=	Retinoblastoma
RBL1	=	Retinoblastoma-like 1
Tan-IIA	=	Tanshinone IIA
TOPO	=	Topoisomerase

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES

[1] Farnsworth, N. R.; Akerele, O.; Bingel, A. S.; Soejarto, D. D.; Guo, Z. Medicinal plants in therapy. *Bull. World Health Organ*., **1985**, *63*(6), 965-981.

[2] Mann, J. Natural compounds in cancer chemotherapy: past, present and future. *Nat. Rev. Cancer*, **2002**, *2*(2), 143-148.

[3] Newman, D.J.; Cragg, G.M. Natural compounds as sources of new drugs over the last 25 years. *J. Nat. Prod*., **2007**, *70*(3), 461-477

[4] Cragg, G.M.; Newman, D.J. Natural compounds: a continuing source of novel drug leads. *Biochim. Biophys. Acta,* **2013**, 1830(6), 3670-3695.

[5] Bailón-Moscoso, N.; Romero-Benavides, J.C.; Ostrosky-Wegman, P. Development of anticancer drugs based on the hallmarks of tumor cells. *Tumour Biol*., **2014**, *35*(5), 3981-3995.

[6] Amin, A.R.; Karpowicz, P.A.; Carey, T.E.; Arbiser, J.; Nahta, R.; Chen, Z.G.; Dong, J.T.; Kucuk, O.; Khan, G.N.; Huang, G.S.; Mi,

S.; Lee, H.Y.; Reichrath, J.; Honoki, K.; Georgakilas, A.G.; Amedei, A.; Amin, A.; Helferich, B.; Boosani, C.S.; Ciriolo, M.R.; Chen, S.; Mohammed, S.I.; Azmi, A.S.; Keith, W.N.; Bhakta, D.; Halicka, D.; Niccolai, E.; Fujii, H.; Aquilano, K.; Ashraf, S.S.; Nowsheen, S.; Yang, X.; Bilsland, A.; Shin, D.M. Evasion of anti-growth signaling: A key step in tumorigenesis and potential target for treatment and prophylaxis by natural compounds. *Semin. Cancer Biol*., **2015**, Mar 6.

[7] De Souza, C.P.; Osmani, S.A. Mitosis, not just open or closed. *Eukaryotic Cell,* **2007**, *6* (9), 1521-1527.

[8] Rao, C.V.; Kurkjian, C.D.; Yamada, H.Y. Mitosis-targeting natural compounds for cancer prevention and therapy. *Curr. Drug Targets*, **2012**, *13*(14), 1820-1830.

[9] Kadauke, S; Blobel, G. A. Mitotic bookmarking by transcription factors. *Epigenet. Chromatin*, **2013**, *6* (1), 6.

[10] Dall'Acqua, S. Natural compounds as antimitotic agents. *Curr. Top Med. Chem*., **2014**, *14*(20), 2272-2285.

[11] Fischer, P.M.; Lane, D.P. Inhibitors of cyclin-dependent kinases as anti-cancer therapeutics. *Curr. Med. Chem*., **2000**, *7*(12), 1213-1245.

[12] Sharma, P.S.; Sharma, R.; Tyagi, R. Inhibitors of cyclin dependent kinases: useful targets for cancer treatment. *Curr. Cancer Drug Targets*, **2008**, *8*(1), 53-75.

[13] Palmer, C. G.; Livengood, D.; Warren, A. K.; Simpson, P. J.; Johnson, I. S. The action of the vincaleukolastine on mitosis *in vitro*. *Exp. Cell Res*., **1960**, *20*, 198-201.

[14] Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from Taxus brevifolia. *J. Am. Chem. Soc.,* **1971**, *93*(9), 2325-2327.

[15] Liu, Z.; Xu, P.; Wu, T.; Zeng, W. Microtubule-targeting anticancer agents from marine natural substance. *Anticancer Agents Med. Chem*., **2014**, *14*(3), 409-417.

[16] Mukhtar, E.; Adhami, V.M.; Mukhtar, H. Targeting microtubules by natural agents for cancer therapy. *Mol. Cancer Ther*., **2014**, *13*(2), 275-284.

[17] Yue, Q.X.; Liu, X.; Guo, D.A. Microtubule-binding natural compounds for cancer therapy. *Planta Med*., **2010**, *76*(11), 1037-1043.

[18] Kingston, D.G. Tubulin-interactive natural compounds as anticancer agents. *J. Nat. Prod.,* **2009**, *72*(3), 507-515.

[19] Johansson, M.; Persson, J.L. Cancer therapy: targeting cell cycle regulators. *Anticancer Agents Med. Chem.,* **2008**, *8*(7), 723-731.

[20] Nigg, E.A. Cyclin-dependent protein kinases: key regulators of the eukaryotic cell cycle. *BioEssays*, **1995**, *17* (6), 471-480.

[21] Vermeulen, K.; Van Bockstaele, D.R.; Berneman, Z. N. The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Prolif*., **2003**, *36* (3), 131–149.

[22] Malumbres, M.; Barbacid, M. Cell cycle, CDKs and cancer: a changing paradigm. *Nat. Rev. Cancer*, **2009**, *9* (3), 153–166.

[23] Bertoli, C.; Skotheim, J.M.; de Bruin, R.A.M. Control of cell cycle transcription during G1 and S phases. *Nat. Rev. Mol. Cell Biol*., **2013**, *14* (8), 518–528.

[24] Skotheim, J.M.; Di Talia, S.; Siggia, E.D.; Cross, F.R. Positive feedback of G1 cyclins ensures coherent cell cycle entry. *Nature*, **2008**, 454 (7202), 291–296.

[25] Satyanarayana, A.; Kaldis, P. Mammalian cell-cycle regulation: several Cdks, numerous cyclins, and diverse compensatory mechanisms. *Oncogene*, **2009**, *28*, 2925-2939.

[26] Morgan, D.O. Principles of CDK regulation. *Nature*, **1995**, *374*, 131-133.

[27] Roberts, J.M.; Koff, A.; Polyak, K.; Firpo, E.; Collins, S.; Ohtsubo, M.; Massagué, J. Cyclins, Cdks, and cyclin kinase inhibitors. *Cold Spring Harb. Symp. Quant. Biol*., **1994**, *59*, 31-38.

[28] Lehner, C.F. The role of cyclin E in the regulation of entry into S phase. *Progr. Cell Cycle Res.,* **1995**, *1*, 125-139.

[29] Peter, M. The regulation of cyclin-dependent kinase inhibitors (CKIs). *Progr. Cell Cycle* Res., **1997**, *3*, 99-108.

[30] Elledge S.J. Cell Cycle Checkpoints: Preventing an Identity Crisis. *Science*, **1996**, *274*, (5293), 1664-1672.

[31] Bartek, J.; Lukas, J. Mammalian G1- and S-phase checkpoints in response to DNA damage. *Curr. Opin. Cell Biol*., **2001**, *13* (6), 738-747.

[32] Wang, Y.; Ji, P.; Liu, J.; Broaddus, R.R.; Xue, F.; Zhang, W. Centrosome-associated regulators of the G2/M checkpoint as targets for cancer therapy. *Mol. Cancer*, **2009**, *8* (1), 8.

[33] Löbrich, M.; Jeggo, P.A. The impact of a negligent G2/M checkpoint on genomic instability and cancer induction. *Nat. Rev. Cancer*, **2007**, *7* (11), 861-869.

[34] Kastan, M.B; Bartek, J. Cell-cycle checkpoints and cancer. *Nature*, **2004**, *432* (7015), 316-323.

[35] Sausville, E.A. Complexities in the development of cyclin-dependent kinase inhibitor drugs. *Trends Mol. Med*., 2002, *8*, S32-S37.

[36] Hanahan, D.; Weinberg, R.A. The hallmarks of cancer. *Cell*, **2000**, *100*(1), 57-70.

[37] Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. *Cell*, **2011**, *144*(5), 646-674.

[38] Ma, D.; Nutt, C.L.; Shanehsaz, P.; Peng, X.; Louis, D.N.; Kaetzel, D.M. Autocrine platelet-derived growth factor-dependent gene expression in glioblastoma cells is mediated largely by activation of the transcription factor sterol regulatory element binding protein and is associated with altered genotype and patient survival in human brain tumors. *Cancer Res*., **2005**, *65*(13), 5523-5534.

[39] Hesselager, G.; Uhrbom, L.; Westermark, B.; Nistér, M. Complementary effects of platelet-derived growth factor autocrine stimulation and p53 or Ink4a-Arf deletion in a mouse glioma model. *Cancer Res*., **2003**, *63*(15), 4305-4309.

[40] Sinkovics, J.G. Oncogenes and growth factors. *Crit. Rev. Immunol*., **1988**, *8*(4), 217-298.

[41] Deuel, T.F. Polypeptide growth factors: roles in normal and abnormal cell growth. *Annu. Rev. Cell Biol*., **1987**, *3*, 443-492.

[42] Heldin, C.H.; Westermark, B. PDGF-like growth factors in autocrine stimulation of growth. *J. Cell. Physiol. Suppl*., **1987**, Suppl. *5*, 31-34.

[43] Sporn, M.B.; Roberts, A.B. Autocrine growth factors and cancer. *Nature*, **1985**, *313*(6005), 745-747.

[44] Eccles, S.A. The epidermal growth factor receptor/Erb-B/HER family in normal and malignant breast biology. *Int. J. Dev, Biol.,* **2011**, *55*(7-9), 685-696.

[45] Lorimer, I.A. Mutant epidermal growth factor receptors as targets for cancer therapy. *Curr. Cancer Drug Targets*, **2002**, *2*(2), 91-102.

[46] Hayflick, L.; Moorhead, P.S. The serial cultivation of human diploid cell strains. *Exp. Cell Res*., **1961**, *25* (3), 585-621.

[47] Hayflick, L. The limited *in vitro* lifetime of human diploid cell strains. *Exp. Cell Res.*, **1965**, *37* (3), 614-636.

[48] Shay, J.W.; Wright, W.E. Hayflick, his limit, and cellular ageing. *Nat. Rev. Mol. Cell Biol.,* **2000**, *1* (1), 72–76.

[49] Carnero, A.; Blanco-Aparicio, C.; Kondoh, H.; Lleonart, M.E.; Martinez-Leal, J.F.; Mondello, C.; Scovassi, A.I.; Bisson, W.H.; Amedei, A.; Roy, R.; Woodrick, J.; Colacci, A.; Vaccari, M.; Raju, J.; Al-Mulla, F.; Al-Temaimi, R.; Salem, H.K.; Memeo, L.; Forte, S.; Singh, N.; Hamid, R.A.; Ryan, E.P.; Brown, D.G.; Wise, J.P. Sr.; Wise, S.S.; Yasaei, H. Disruptive chemicals, senescence and immortality. Carcinogenesis, 2015, *36* (Suppl. 1), S19-37.

[50] Stewart, S.A.; Weinberg, R.A. Telomerase and human tumorigenesis. *Semin. Cancer Biol*., **2000**, *10*(6), 399-406.

[51] Hayflick, L. A brief history of the mortality and immortality of cultured cells. *Keio J. Med*., **1998**, *47*(3), 174-182.

[52] Cohen, P. The origins of protein phosphorylation. *Nat. Cell Biol*., **2002**, *4*(5), E127-130.

[53] Collins, I.; Garrett, M.D. Targeting the cell division cycle in cancer: CDK and cell cycle checkpoint kinase inhibitors. *Curr. Opin. Pharmacol*., **2005,** *5*(4), 366-373.

[54] Johansson, M.; Persson, J.L. Cancer therapy: targeting cell cycle regulators. *Anticancer Agents Med. Chem.,* **2008**, *8*(7), 723-731.

[55] O'Connor, D. S.; Wall, N. R.; Porter, A. C.; Altieri, D. C. A p34(cdc2) survival checkpoint in cancer. *Cancer Cell*, **2002**, *2*(1), 43-54.

[56] Veselý, J.; Havlicek, L.; Strnad, M.; Blow, J.J.; Donella-Deana, A.; Pinna, L.; Letham, D.S.; Kato, J.; Detivaud, L.; Leclerc, S.; Meijer, L. Inhibition of cyclin-dependent kinases by purine analogues. *Eur. J. Biochem.,* **1994**, *224*(2), 771-786.

[57] Vermeulen, K.; Strnad, M.; Krystof, V.; Havlícek, L.; Van der Aa, A.; Lenjou, M.; Nijs, G.; Rodrigus, I.; Stockman, B.; van Onckelen, H.; Van Bockstaele, D.R.; Berneman, Z.N. Antiproliferative effect of plant cytokinin analogues with an inhibitory activity on cyclin-dependent kinases. *Leukemia*, **2002**, *16*(3), 299-305.

[58] Glab, N.; Labidi, B.; Qin, L.X.; Trehin, C.; Bergounioux, C.; Meijer, L. Olomoucine, an inhibitor of the cdc2/cdk2 kinases activity, blocks plant cells at the G1 to S and G2 to M cell cycle transitions. *FEBS Lett*., **1994**, *353*(2), 207-211.

[59] Hassling, J.L.; Jullian, N. Recent advances in cyclin-dependent

kinase inhibition. Purine-based derivatives as anti-cancer agents. Roles and perspectives for the future. *Curr. Top. Med. Chem*., **2002**, *2*(9, 1037-1050.

[60] De Azevedo, W.F.; Leclerc, S.; Meijer, L.; Havlicek, L.; Strnad, M.; Kim, S.H. Inhibition of cyclin-dependent kinases by purine analogues: crystal structure of human cdk2 complexed with roscovitine. *Eur. J. Biochem*., **1997**, *243*(1-2), 518-526.

[61] Kolodziej, M.; Goetz, C.; Di Fazio, P.; Montalbano, R.; Ocker, M.; Strik, H.; Quint, K. Roscovitine has anti-proliferative and pro-apoptotic effects on glioblastoma cell lines: A pilot study. *Oncol. Rep*., **2015**, *34*(3), 1549-1556.

[62] Węsierska-Gądek, J.; Gritsch, D.; Zulehner, N.; Komina, O.; Maurer, M. Interference with ER-α enhances the therapeutic efficacy of the selective CDK inhibitor roscovitine towards ER-positive breast cancer cells. *J. Cell. Biochem.*, **2011**, *112*(4), 1103-1117.

[63] Zhang, F.; Zhang, T.; Gu, Z.P.; Zhou, Y.A.; Han, Y.; Li, X.F.; Wang, X.; Cheng, Q.S.; Mei, Q.B. Enhancement of radiosensitivity by roscovitine pretreatment in human non-small cell lung cancer A549 cells. *J. Radiat. Res*., **2008**, *49*(5), 541-548.

[64] Lacrima, K.; Rinaldi, A.; Vignati, S.; Martin, V.; Tibiletti, M.G.; Gaidano, G.; Catapano, C.V.; Bertoni, F. Cyclin-dependent kinase inhibitor seliciclib shows *in vitro* activity in diffuse large B-cell lymphomas. *Leuk. Lymphoma*, **2007**, *48*(1), 158-167.

[65] Wesierska-Gadek, J.; Gueorguieva, M.; Wojciechowski, J.; Horky, M. Cell cycle arrest induced in human breast cancer cells by cyclin-dependent kinase inhibitors: a comparison of the effects exerted by roscovitine and olomoucine. *Pol. J. Pharmacol*., **2004**, *56*(5), 635-641.

[66] Cicenas, J,; Kalyan, K.; Sorokinas, A.; Stankunas, E.; Levy, J.; Meskinyte, I.; Stankevicius, V.; Kaupinis, A.; Valius, M. Roscovitine in cancer and other diseases. *Ann. Transl. Med*., **2015**, *3*(10), 135.

[67] Kelso, T.W.; Baumgart, K.; Eickhoff, J.; Albert, T.; Antrecht, C.; Lemcke, S.; Klebl, B.; Meisterernst, M. Cyclin-dependent kinase 7 controls mRNA synthesis by affecting stability of preinitiation complexes, leading to altered gene expression, cell cycle progression, and survival of tumor cells. *Mol. Cell. Biol*., **2014**, *34*(19), 3675-3688.

[68] Garrofé-Ochoa, X.; Cosialls, A.M.; Ribas, J.; Gil, J.; Boix, J. Transcriptional modulation of apoptosis regulators by roscovitine and related compounds. *Apoptosis*, **2011**, *16*(7), 660-670.

[69] Krystof, V.; Uldrijan, S. Cyclin-dependent kinase inhibitors as anticancer drugs. *Curr. Drug Targets*, **2010**, *11*(3), 291-302.

[70] Wesierska-Gadek, J.; Borza, A.; Komina, O.; Maurer, M. Impact of roscovitine, a selective CDK inhibitor, on cancer cells: bi-functionality increases its therapeutic potential. *Acta Biochim. Pol*., **2009**, *56*(3), 495-501.

[71] Whittaker, S.R.; Te Poele, R.H.; Chan, F.; Linardopoulos, S.; Walton, M.I.; Garrett, M.D.; Workman, P. The cyclin-dependent kinase inhibitor seliciclib (R-roscovitine; CYC202) decreases the expression of mitotic control genes and prevents entry into mitosis. *Cell Cycle*, **2007**, *6*(24), 3114-3131.

[72] Parnaud, G.; Li, P.; Cassar, G.; Rouimi, P.; Tulliez, J.; Combaret, L.; Gamet-Payrastre, L. Mechanism of sulforaphane-induced cell cycle arrest and apoptosis in human colon cancer cells. *Nutr. Cancer*, **2004**, *48*(2), 198-206.

[73] Whittaker, S.R.; Walton, M.I.; Garrett, M.D.; Workman, P. The Cyclin-dependent kinase inhibitor CYC202 (R-roscovitine) inhibits retinoblastoma protein phosphorylation, causes loss of Cyclin D1, and activates the mitogen-activated protein kinase pathway. *Cancer Res*., **2004**, *64*(1), 262-272.

[74] Senderowicz, A.M. Novel small molecule cyclin-dependent kinases modulators in human clinical trials. *Cancer Biol. Ther*., **2003**, *2*(4 Suppl 1), S84-95.

[75] Vermeulen, K.; Van Bockstaele, D.R.; Berneman, Z.N. The cell cycle: a review of regulation, deregulation and therapeutic targets in cancer. *Cell Prolif*., **2003**, *36*(3), 131-149.

[76] Braña, M.F.; García, M.L.; López, B.; de Pascual-Teresa, B.; Ramos, A.; Pozuelo, J.M.; Domínguez, M.T. Synthesis and biological evaluation of analogues of butyrolactone I and molecular model of its interaction with CDK2. *Org. Biomol. Chem*., **2004**, *2*(13), 1864-1871.

[77] Kitagawa, M.; Higashi, H.; Takahashi, I. S.; Okabe, T.; Ogino, H.; Taya, Y.; Hishimura, S.; Okuyama, A. A cyclin-dependent kinase inhibitor, butyrolactone I, inhibits phosphorylation of RB protein and cell cycle progression. *Oncogene*, **1994**, *9*(9), 2549-2557.

[78] Kitagawa, M.; Okabe, T.; Ogino, H.; Matsumoto, H.; Suzuki-Takahashi, I.; Kokubo, T.; Higashi, H.; Saitoh, S.; Taya, Y.; Yasuda, H.; Ohba, Y.; Nishimura, S.; Tanaka, N.; Okuyama, A. Butyrolactone I, a selective inhibitor of cdk2 and cdc2 kinase. *Oncogene*, **1993**, *8*(9), 2425-2432.

[79] Sax, J. K.; Dash, B. C.; Hong, R.; Dicker, D. T.; El-Deiry, W. S. The cyclin-dependent kinase inhibitor butyrolactone is a potent inhibitor of p21WAF1/CIP1 expression. *Cell Cycle*, **2002**, *1*(1), 90-96.

[80] Dai, Y.; Grant, S. Small molecule inhibitors targeting cyclin-dependent kinases as anticancer agents. *Curr. Oncol. Rep*., **2004**, *6*(2), 123-130.

[81] Diaz-Padilla, I.; Siu, L.L.; Duran, I. Cyclin-dependent kinase inhibitors as potential targeted anticancer agents. *Invest. New Drugs*, **2009**, *27*(6), 586-594.

[82] Senderowicz, A.M. Inhibitors of cyclin-dependent kinase modulators for cancer therapy. Progr. Drug Res., **2005**, 63, 183-206

[83] Facchinetti, M.M.; De Siervi, A.; Toskos, D.; Senderowicz, A.M. UCN-01-induced cell cycle arrest requires the transcriptional induction of p21 (waf1/cip1) by activation of mitogen-activated protein/extracellular signal-regulated kinase kinase/extracellular signal-regulated kinase pathway. *Cancer Res*., **2004,** *64*(10), 3629-3637.

[84] Meijer, L.; Thunnissen, A. M.; White, A. W.; Garnier, M.; Nikolic, M.; Tsai, L. H.; Walter, J.; Cleverley, K. E.; Salinas, P. C.; Wu, Y.Z.; Biernat, J.; Mandelkow, E. M.; Kim, S. H.; Pettit, G. R. Inhibition of cyclin-dependent kinases, GSK-3beta and CK1 by hymenialdisine, a marine sponge constituent. *Chem. Biol*., **2000**, *7*(1), 51-63.

[85] Wan, Y.; Hur, W.; Cho, C. Y.; Liu, Y.; Adrian, F. J.; Lozach, O.; Bach, S.; Mayer, T.; Fabbro, D.; Meijer, L.; Gray, N. S. Synthesis and target identification of hymenialdisine analogs. *Chem. Biol.,* **2004**, *11*(2), 247-259.

[86] Jain, S.K.; Bharate, S.B.; Vishwakarma, R.A. Cyclin-dependent kinase inhibition by flavoalkaloids. *Mini Rev. Med. Chem*., **2012**, *12*(7), 632-649.

[87] Lü, X.; Burgan, W.E.; Cerra, M.A.; Chuang, E.Y.; Tsai, M.H.; Tofilon, P.J.; Camphausen, K. Transcriptional signature of flavopiridol-induced tumor cell death. *Mol Cancer Ther*., **2004**, *3*(7), 861-872.

[88] Tan, A. R.; Swain, S. M. Review of flavopiridol, a cyclin-dependent kinase inhibitor, as breast cancer therapy. *Semin. Oncol*., **2002**, *29*(3 Suppl. 11), 77-85.

[89] Li, Y.; Chinni, S. R.; Senderowicz, A. M.; Sarkar, F. H. Induction of growth inhibition and apoptosis in prostate cancer cells by flavopiridol. *Int. J. Oncol*., 2000, 17(4), 755-759.

[90] Senderowicz, A. M. Flavopiridol: the first cyclin-dependent kinase inhibitor in human clinical trials. *Invest. New Drugs*, **1999**, *17*(3), 313-320.

[91] Patel, V.; Senderowicz, A.M.; Pinto, D. Jr.; Igishi, T.; Raffeld, M.; Quintanilla-Martinez, L.; Ensley, J.F.; Sausville, E.A.; Gutkind, J.S. Flavopiridol, a novel cyclin-dependent kinase inhibitor, suppresses the growth of head and neck squamous cell carcinomas by inducing apoptosis. *J. Clin. Invest*., **1998**, *102*(9), 1674-1681.

[92] Sedlacek, H. H. Mechanisms of action of flavopiridol. *Crit. Rev. Oncol. Hematol.,* **2001**, *38*(2), 139-170.

[93] Ruetz, S.; Fabbro, D.; Zimmermann, J.; Meyer, T.; Gray, N. Chemical and biological profile of dual Cdk1 and Cdk2 inhibitors. *Curr. Med. Chem. Anticancer Agents*, **2003**, *3*(1), 1-14.

[94] Munro, M. H.; Blunt, J. W.; Dumdei, E. J.; Hickford, S. J.; Lill, R. E.; Li, S.; Battershill, C. N.; Duckworth, A. R. The discovery and development of marine compounds with pharmaceutical potential. *J. Biotechnol.,* **1999**, *70*(1-3), 15-25.

[95] Kumar, N.; Gangappa, D.; Gupta, G.; Karnati R. Chebulagic acid from Terminalia chebula causes G1 arrest, inhibits NFκB and induces apoptosis in retinoblastoma cells. *BMC Complement. Altern. Med*., **2014**, *14*, 319.

[96] Yang, H.L.; Kumar, K.J.; Kuo, Y.T.; Chang, H.C.; Liao, J.W.; Hsu, L.S.; Hseu, Y.C. Antrodia camphorata induces G(1) cell-cycle arrest in human premyelocytic leukemia (HL-60) cells and suppresses tumor growth in athymic nude mice. *Food Funct.,* **2014**, *5*(9), 2278-2288.

[97] He, L.; Lu, N.; Dai, Q.; Zhao, Y.; Zhao, L.; Wang, H.; Li, Z.; You, Q.; Guo, Q. Wogonin induced G1 cell cycle arrest by regulating Wnt/β-catenin signaling pathway and inactivating CDK8 in human

colorectal cancer carcinoma cells. *Toxicology*, **2013**, *312*, 36-47

[98] Li, C.Y.; Wang, Y.; Wang, H.L.; Shi, Z.; An, N.; Liu, Y.X.; Liu, Y.; Zhang, J.; Bao, J.K.; Deng, S.P. Molecular mechanisms of Lycoris aurea agglutinin-induced apoptosis and G2/ M cell cycle arrest in human lung adenocarcinoma A549 cells, both *in vitro* and *in vivo*. *Cell Prolif.,* **2013**, *46*(3), 272-282.

[99] Xing, Z.; Zhang, Y.; Zhang, X.; Yang, Y.; Ma, Y.; Pang, D. Fangchinoline induces G1 arrest in breast cancer cells through cell-cycle regulation. *Phytother. Res*., **2013**, *27*(12), 1790-1794.

[100] Birdsall, T.C.; Kelly, G.S. Berberine: Therapeutic potential of an alkaloid found in several medicinal plants. *Altern. Med. Rev*., **1997**, *2* (2), 94-103.

[101] Zhang, S.; Zhang, B.; Xing, K.; Zhang, X.; Tian, X.; Dai, W. Inhibitory effects of golden thread (Coptis chinensis) and berberine on Microcystis aeruginosa. *Water Sci. Technol.,* **2010**, *61* (3), 763.

[102] Sun, Y.; Xun, K.; Wang, Y.; Chen, X. A systematic review of the anticancer properties of berberine, a natural product from Chinese herbs. *Anticancer Drugs*, **2009**, *20* (9), 757-769.

[103] Tang, J.; Feng, Y.; Tsao, S.; Wang, N.; Curtain, R.; Wang, Y. Berberine and Coptidis Rhizoma as novel antineoplastic agents: a review of traditional use and biomedical investigations. *J. Ethnopharm*., **2009**, *126* (1), 5-17.

[104] Kim, J.B.; Yu. J.H.; Ko, E.; Lee, K.W.; Song, A.K.; Park, S.Y.; Shin, I.; Han, W.; Noh, D.Y. The alkaloid Berberine inhibits the growth of Anoikis-resistant MCF-7 and MDA-MB-231 breast cancer cell lines by inducing cell cycle arrest. *Phytomedicine*, **2009**, *17* (6), 436-440.

[105] Serafim, T.L.; Oliveira, P.J.; Sardao, V.A.; Perkins, E.; Parke, D.; Holy, J. Different concentrations of berberine result in distinct cellular localization patterns and cell cycle effects in a melanoma cell line. *Cancer Chemother. Pharmacol*., **2008**, *61* (6), 1007-1018.

[106] Pinto-Garcia, L.; Efferth, T.; Torres, A.; Hoheisel, J.D.; Youns, M. Berberine Inhibits Cell Growth and Mediates Caspase-Independent Cell Death in Human Pancreatic Cancer Cells. *Planta Med.,* **2010**, *76* (11), 1155-1161.

[107] Ho, Y.T.; Lu, C.C.; Yang, J.S.; Chiang, J.H.; Li, T.C.; Ip, S.W.; Hsia, T.C.; Liao, C.L.; Lin, J.G.; Wood, W.G.; Chung, J.G. Berberine induced apoptosis via promoting the expression of caspase-8, -9 and -3, apoptosis-inducing factor and endonuclease G in SCC-4 human tongue squamous carcinoma cancer cells. *Anticancer Res*., **2009**, *29* (10), 4063-4070.

[108] Auyeung, K.K.; Ko, J.K. Coptis chinensis inhibits hepatocellular carcinoma cell growth through nonsteroidal anti-inflammatory drug-activated gene activation. *Int. J. Mol. Med.,* **2009**, *24* (4), 571-577.

[109] Tang, F.; Wang, D.; Duan, C.; Huang, D.; Wu, Y.; Chen, Y.; Wang, W.; Xie, C.; Meng, J.; Wang, L.; Wu, B.; Liu, S.; Tian, D.; Zhu, F.; He, Z.; Deng, F.; Cao, Y. Berberine inhibits metastasis of nasopharyngeal carcinoma 5-8F cells by targeting Rho kinase-mediated Ezrin phosphorylation at threonine 567. *J. Biol. Chem*., **2009**, *284* (40), 27456–27466.

[110] Mantena, S.K.; Sharma, S.D.; Katiyar, S.K. Berberine, a natural product, induces G1-phase cell cycle arrest and caspase-3-dependent apoptosis in human prostate carcinoma cells. *Mol. Cancer Ther.,* **2006**, *5* (2), 296-308.

[111] Choi, M.S.; Oh, J.H.; Kim, S.M.; Jung, H.Y.; Yoo, H.S.; Lee, Y.M.; Moon, D.C., Han, S.B.; Hong, J.T. Berberine inhibits p53-dependent cell growth through induction of apoptosis of prostate cancer cells. *Inter. J. Oncol.,* **2009**, *34* (5), 1221-1230.

[112] Lin, C.C.; Lin, S.Y.; Chung, J.G.; Lin, J.P.; Chen, G.W.; Kao, S.T. "Down-regulation of cyclin B1 and up-regulation of Wee1 by berberine promotes entry of leukemia cells into the G2/M-phase of the cell cycle". *Anticancer Res*., **2006**, 26 (2A), 1097-1104.

[113] Khan, M.; Giessrigl, B.; Vonach, C.; Madlener, S.; Prinz, S.; Herbaceck, I.; Hölzl, C.; Bauer, S.; Viola, K.; Mikulits, W.; Quereshi, R.A.; Knasmüller, S.; Grusch, M.; Kopp, B.; Krupitza, G. Berberine and a Berberis lycium extract inactivate Cdc25A and induce α-tubulin acetylation that correlate with HL-60 cell cycle inhibition and apoptosis. *Mutat. Res*., **2010**, *683* (1–2), 123-130.

[114] Li, D.X.; Zhang, J.; Zhang, Y.; Zhao, P.W.; Yang, L.M. Inhibitory effect of berberine on human skin squamous cell carcinoma A431 cells. *Genet. Mol. Res*., **2015**, *14*(3), 10553-10568.

[115] Chen, Q.; Qin, R.; Fang, Y.; Li, H. Berberine Sensitizes Human Ovarian Cancer Cells to Cisplatin Through miR-93/PTEN/Akt Signaling Pathway. *Cell. Physiol. Biochem*., **2015**, *36*(3), 956-965.

[116] Su, Y.H.; Tang, W.C.; Cheng, Y.W.; Sia, P.; Huang, C.C.; Lee, Y.C.; Jiang, H.Y.; Wu, M.H.; Lai, I.L.; Lee, J.W.; Lee, K.H. Targeting of multiple oncogenic signaling pathways by Hsp90 inhibitor alone or in combination with berberine for treatment of colorectal cancer. *Biochim. Biophys. Acta*, **2015**, *1853*(10 Pt A), 2261-2272.

[117] Liu, X.; Ji, Q.; Ye, N.; Sui, H.; Zhou, L.; Zhu, H.; Fan, Z.; Cai, J.; Li, Q. Berberine Inhibits Invasion and Metastasis of Colorectal Cancer Cells via COX-2/PGE2 Mediated JAK2/STAT3 Signaling Pathway. *PLoS One*, **2015**, *10*(5), e0123478.

[118] Yi T, Zhuang L, Song G, Zhang B, Li G, Hu T. Akt signaling is associated with the berberine-induced apoptosis of human gastric cancer cells. Nutr Cancer. 2015;67(3):523-31.

[119] Song, Y.C.; Lee, Y.; Kim, H.M.; Hyun, M.Y.; Lim, Y.Y.; Song, K.Y.; Kim, B.J. Berberine regulates melanin synthesis by activating PI3K/AKT, ERK and GSK3β in B16F10 melanoma cells. *Int. J. Mol. Med*., **2015**, *35*(4), 1011-1016.

[120] Wu, H.L.; Chuang, T.Y.; Al-Hendy, A.; Diamond, M.P.; Azziz, R.; Chen, Y.H. Berberine inhibits the proliferation of human uterine leiomyoma cells. *Fertil. Steril*., **2015**, *103*(4), 1098-1106.

[121] Kim, J.S.; Oh, D.; Yim, M.J.; Park, J.J.; Kang, K.R.; Cho, I.A.; Moon, S.M.; Oh, J.S.; You, J.S.; Kim, C.S.; Kim do, K.; Lee, S.Y.; Lee, G.J.; Im, H.J.; Kim, S.G. Berberine induces FasL-related apoptosis through p38 activation in KB human oral cancer cells. *Oncol. Rep*., **2015**, *33*(4), 1775-1782.

[122] Lu, W.; Du, S.; Wang, J. Berberine inhibits the proliferation of prostate cancer cells and induces G_0/G_1 or G_2/M phase arrest at different concentrations. *Mol. Med. Rep*., **2015**, *11*(5), 3920-3924.

[123] Jin, P.; Zhang, C.; Li, N. Berberine exhibits antitumor effects in human ovarian cancer cells. *Anticancer Agents Med. Chem*., **2015**, *15*(4), 511-516.

[124] Park, S.H.; Sung, J.H.; Kim, E.J.; Chung, N. Berberine induces apoptosis via ROS generation in PANC-1 and MIA-PaCa2 pancreatic cell lines. *Braz. J. Med. Biol. Res.,* **2015**, *48*(2), 111-119.

[125] Liu, Q.; Xu, X.; Zhao, M.; Wei, Z.; Li, X.; Zhang, X.; Liu, Z.; Gong, Y.; Shao, C. Berberine induces senescence of human glioblastoma cells by downregulating the EGFR-MEK-ERK signaling pathway. *Mol. Cancer Ther*., **2015**, *14*(2), 355-363.

[126] Huang, Z.H.; Zheng, H.F.; Wang, W.L.; Wang, Y.; Zhong, L.F.; Wu, J.L.; Li, Q.X. Berberine targets epidermal growth factor receptor signaling to suppress prostate cancer proliferation *in vitro*. *Mol. Med. Rep.,* **2015,** *11*(3), 2125-2128.

[127] Tsang, C.M.; Cheung, K.C.; Cheung, Y.C.; Man, K.; Lui, V.W.; Tsao, S.W., Feng. Y. Berberine suppresses Id-1 expression and inhibits the growth and development of lung metastases in hepatocellular carcinoma. *Biochim. Biophys. Acta*, **2015**, *1852*(3), 541-551.

[128] He, W.; Wang, B.; Zhuang, Y.; Shao, D.; Sun, K.; Chen, J. Berberine inhibits growth and induces G1 arrest and apoptosis in human cholangiocarcinoma QBC939 cells. *J. Pharmacol. Sci.,* **2012**, *119*(4), 341-348.

[129] El-Merahbi, R.; Liu, Y.N.; Eid, A.; Daoud, G.; Hosry, L.; Monzer, A.; Mouhieddine, T.H.; Hamade, A.; Najjar, F.; Abou-Kheir, W. Berberis libanotica Ehrenb extract shows anti-neoplastic effects on prostate cancer stem/progenitor cells. *PLoS One*, **2014**, *9*(11), e112453.

[130] Khan, M.; Giessrigl, B.; Vonach, C.; Madlener, S.; Prinz, S.; Herbaceck, I.; Hölzl, C.; Bauer, S.; Viola, K.; Mikulits, W.; Quereshi, R.A.; Knasmüller, S.; Grusch, M.; Kopp, B.; Krupitza, G. Berberine and a Berberis lycium extract inactivate Cdc25A and induce alpha-tubulin acetylation that correlate with HL-60 cell cycle inhibition and apoptosis. *Mutat. Res*., **2010**, *683*(1-2), 123-130.

[131] Kim, J.; Jayaprakasha, G.K.; Vikram, A.; Patil, B.S. Methyl nomilinate from citrus can modulate cell cycle regulators to induce cytotoxicity in human colon cancer (SW480) cells *in vitro*. *Toxicol. In Vitro,* **2012**, *26*(7), 1216-1223.

[132] Bharate, S.B.; Yadav, R.R.; Battula, S.; Vishwakarma, R.A. Meridianins: marine-derived potent kinase inhibitors. *Mini Rev. Med. Chem*., **2012**, *12*(7), 618-631.

[133] Bharate, S.B.; Manda, S.; Mupparapu, N.; Battini, N.; Vishwakarma, R.A. Chemistry and biology of fascaplysin, a potent marine-derived CDK-4 inhibitor. *Mini Rev. Med. Chem*., **2012**, *12*(7), 650-664.

[134] Phromnoi, K.; Reuter, S.; Sung, B.; Limtrakul, P.; Aggarwal, B.B. A Dihydroxy-pentamethoxyflavone from Gardenia obtusifolia suppresses proliferation and promotes apoptosis of tumor cells through modulation of multiple cell signaling pathways. *Anticancer Res*., **2010**, *30*(9), 3599-3610.

[135] Peng, L.; Khan, N.; Afaq, F.; Ye, C.; Mukhtar, H. *In vitro* and *in vivo* effects of water extract of white cocoa tea (Camellia ptilophylla) against human prostate cancer. *Pharm. Res*., **2010**, *27*(6), 1128-1137.

[136] Chan, K.C.; Ho, H.H.; Peng, C.H.; Lan, K.P.; Lin, M.C.; Chen, H.M.; Wang, C.J. Polyphenol-rich extract from mulberry leaf inhibits vascular smooth muscle cell proliferation involving upregulation of p53 and inhibition of cyclin-dependent kinase. *J. Agric. Food Chem*., **2010**, *58*(4), 2536-2542.

[137] Lee, Y.M.; Lim, do Y.; Choi, H.J.; Jung, J.I.; Chung, W.Y.; Park, J.H. Induction of cell cycle arrest in prostate cancer cells by the dietary compound isoliquiritigenin. *J. Med. Food*, **2009**, *12*(1), 8-14.

[138] Liu, B.; Han, M.; Sun, R.H.; Wang, J.J.; Liu, Y.P.; Wen, J.K. Acetylbritannilactone induces G1 arrest and apoptosis in vascular smooth muscle cells. *Int. J. Cardiol*., **2011**, *149*(1), 30-38.

[139] Park, E.Y.; Lee, K.W.; Lee, H.W.; Cho, Y.W.; Baek, N.I.; Chung, H.G.; Jeong, T.S.; Choi, M.S.; Lee, K.T. The ethanol extract from Artemisia princeps Pampanini induces p53-mediated G1 phase arrest in A172 human neuroblastoma cells. *J. Med. Food*, **2008**, *11*(2), 237-245.

[140] Maso, V.; Calgarotto, A.K.; Franchi, G.C. Jr; Nowill, A.E.; Filho, P.L.; Vassallo, J.; Saad, S.T. Multitarget effects of quercetin in leukemia. *Cancer Prev. Res. (Philadelphia),* **2014**, *7*(12), 1240-1250.

[141] Li, Y.; Duan, S.; Jia, H.; Bai, C.; Zhang, L.; Wang, Z. Flavonoids from tartary buckwheat induce G2/M cell cycle arrest and apoptosis in human hepatoma HepG2 cells. *Acta Biochim. Biophys. Sin. (Shanghai),* **2014**, *46*(6), 460-470.

[142] Li, J.; Zhu, F.; Lubet, R.A.; De Luca, A.; Grubbs, C.; Ericson, M.E.; D'Alessio, A.; Normanno, N.; Dong, Z.; Bode, A.M. Quercetin-3-methyl ether inhibits lapatinib-sensitive and -resistant breast cancer cell growth by inducing G(2)/M arrest and apoptosis. *Mol. Carcinog*., **2013**, *52*(2), 134-143.

[143] Huang, G.; Tang, B.; Tang, K.; Dong, X.; Deng, J.; Liao, L.; Liao, Z.; Yang, H.; He, S. Isoquercitrin inhibits the progression of liver cancer *in vivo* and *in vitro* via the MAPK signalling pathway. *Oncol. Rep*., **2014**, *31*(5), 2377-2384.

[144] Li, C.; Yang, X.; Chen, C.; Cai, S.; Hu, J. Isorhamnetin suppresses colon cancer cell growth through the PI3K−Akt−mTOR pathway. *Mol. Med. Rep*., **2014**, *9*(3), 935-940.

[145] Nicolini, F.; Burmistrova, O.; Marrero, M.T.; Torres, F.; Hernández, C.; Quintana, J.; Estévez, F. Induction of G2/M phase arrest and apoptosis by the flavonoid tamarixetin on human leukemia cells. *Mol. Carcinog*., **2014**, *53*(12), 939-950.

[146] Shabbir, M.; Syed, D.N.; Lall, R.K.; Khan, M.R.; Mukhtar, H. Potent anti-proliferative, pro-apoptotic activity of the Maytenus royleanus extract against prostate cancer cells: evidence in in-vitro and in-vivo models. *PLoS One*, **2015**, *10*(3), e0119859.

[147] Li, X.K.; Motwani, M.; Tong, W.; Bornmann, W.; Schwartz, G.K. Huanglian, A chinese herbal extract, inhibits cell growth by suppressing the expression of cyclin B1 and inhibiting CDC2 kinase activity in human cancer cells. *Mol. Pharmacol*., **2000**, *58*(6), 1287-1293.

[148] Leclerc, S.; Garnier, M.; Hoessel, R.; Marko, D.; Bibb, J.A.; Snyder, G.L.; Greengard, P.; Biernat, J.; Wu, Y.Z.; Mandelkow, E.M.; Eisenbrand, G.; Meijer, L. Indirubins inhibit glycogen synthase kinase-3 beta and CDK5/p25, two protein kinases involved in abnormal tau phosphorylation in Alzheimer's disease. A property common to most cyclin-dependent kinase inhibitors? *J. Biol. Chem*., **2001**, *276*(1), 251-260.

[149] Ahmad, N.; Feyes, D.K.; Nieminen, A.L.; Agarwal, R.; Mukhtar, H. Green tea constituent epigallocatechin-3-gallate and induction of apoptosis and cell cycle arrest in human carcinoma cells. *J. Natl. Cancer Inst*., **1997**, *89*, 1881–1886.

[150] Ahmad, N.; Cheng, P.; Mukhtar, H. Cell cycle dysregulation by green tea polyphenol epigallocatechin-3-gallate. *Biochem. Biophys. Res. Commun*., **2000**, *275*(2), 328-334.

[151] Gupta, S.; Ahmad, N.; Nieminen, A.L.; Mukhtar, H. Growth inhibition, cell-cycle dysregulation, and induction of apoptosis by green tea constituent (−)-epigallocatechin-3-gallate in androgen-sensitive and androgen-insensitive human prostate carcinoma cells. *Toxicol. Appl. Pharmacol.,* **2000**, *164*, 82-90.

[152] Shankar, S.; Suthakar, G.; Srivastava, R.K. Epigallocatechin-3-gallate inhibits cell cycle and induces apoptosis in pancreatic cancer. *Front. Biosci*., **2007**, *12*, 5039-5051.

[153] Prieur, C.; Rigaud, J.; Cheynier, V.; Moutounet, M. Oligomeric and polymeric procyanidins from grape seeds. *Phytochemistry*, **1994**, *36*, 781-789.

[154] Meeran, S.M.; Katiyar, S.K. Grape seed proanthocyanidins promote apoptosis in human epidermoid carcinoma A431 cells through alterations in Cdki-Cdk-cyclin cascade, and caspase-3 activation via loss of mitochondrial membrane potential. *Exp. Dermatol.,* **2007**, *16*, 405-415.

[155] Meeran, S.M.; Katiyar, S.K. Proanthocyanidins inhibit mitogenic and survival-signaling *in vitro* and tumor growth *in vivo*. *Front. Biosci.,* **2008**, *13*, 887-897.

[156] Agarwal, C.; Sharma, Y.; Agarwal, R. Anticarcinogenic effect of a polyphenolic fraction isolated from grape seeds in human prostate carcinoma DU145 cells: modulation of mitogenic signaling and cell-cycle regulators and induction of G1 arrest and apoptosis. *Mol. Carcinog.,* **2000**, *28*, 129-138.

[157] Estrov, Z.; Shishodia, S.; Faderl, S.; Harris, D.; Van, Q.; Kantarjian, H.M.; Talpaz, M.; Aggarwal, B.B. Resveratrol blocks interleukin-1beta-induced activation of the nuclear transcription factor NF-kappaB, inhibits proliferation, causes S-phase arrest, and induces apoptosis of acute myeloid leukemia cells. *Blood*, **2003**, *102*, 987-995.

[158] Ahmad, N.; Adhami, V.M.; Afaq, F.; Feyes, D.K.; Mukhtar, H. Resveratrol causes WAF-1/p21-mediated G(1)-phase arrest of cell cycle and induction of apoptosis in human epidermoid carcinoma A431 cells. *Clin. Cancer Res*., **2001**, *7*, 1466-1473.

[159] Hsieh, T.C.; Juan, G.; Darzynkiewicz, Z.; Wu, J.M. Resveratrol increases nitric oxide synthase, induces accumulation of p53 and p21(WAF1/CIP1), and suppresses cultured bovine pulmonary artery endothelial cell proliferation by perturbing progression through S and G2. *Cancer Res.,* **1999**, *59*, 2596-2601.

[160] Liang, Y.C.; Tsai, S.H.; Chen, L.; Lin-Shiau, S.Y.; Lin, J.K. Resveratrol-induced G2 arrest through the inhibition of CDK7 and p34CDC2 kinases in colon carcinoma HT29 cells. *Biochem. Pharmacol*., **2003**, *65*, 1053-1060.

[161] Kuwajerwal.; N.; Cifuentes, E.; Gautam, S.; Menon, M.; Barrack, E.R.; Reddy, G.P. Resveratrol induces prostate cancer cell entry into s phase and inhibits DNA synthesis. *Cancer Res*., **2000**, *62*, 2488-2492.

[162] Benitez, D.A.; Pozo-Guisado, E.; Alvarez-Barrientos, A.; Fernandez-Salguero, P.M.; Castellón, E.A. Mechanisms involved in resveratrol-induced apoptosis and cell cycle arrest in prostate cancer-derived cell lines. *J. Androl*., **2007**, *28*, 282-293.

[163] Wolter, F.; Akoglu, B.; Clausnitzer, A.; Stein, J. Downregulation of the cyclin D1/Cdk4 complex occurs during resveratrol-induced cell cycle arrest in colon cancer cell lines. *J. Nutr*., **2001**, *131*, 2197-2203.

[164] Takagaki, N.; Sowa, Y.; Oki, T.; Nakanishi, R.; Yogosawa, S.; Sakai, T. Apigenin induces cell cycle arrest and p21/WAF1 expression in a p53-independent pathway. *Int. J. Oncol.,* **2005**, *26*, 185-189.

[165] Shukla, S.; Gupta, S. Molecular targets for apigenin-induced cell cycle arrest and apoptosis in prostate cancer cell xenograft. *Mol. Cancer Ther*., **2006**, *5*, 843-852.

[166] Shukla, S.; Gupta, S. 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*, **2007**, *6*, 1102-1114.

[167] Ujiki, M.B.; Ding, X.Z.; Salabat, M.R.; Bentrem, D.J.; Golkar, L.; Milam, B.; Talamonti, M.S.; Bell, R.H. Jr; Iwamura, T.; Adrian, T.E. Apigenin inhibits pancreatic cancer cell proliferation through G2/M cell cycle arrest. *Mol. Cancer*, **2006**, *5*, 76.

[168] Chiang, L.C;, Ng, L.T.; Lin, I.C.; Kuo, P.L.; Lin, C.C. Antiproliferative effect of apigenin and its apoptotic induction in human Hep G2 cells. *Cancer Lett.,* **2006**, 237, 207-214.

[169] Agarwal, R.; Agarwal, C.; Ichikawa, H.; Singh, R.P.; Aggarwal, B.B. Anticancer potential of silymarin: from bench to bed side. *Anticancer Res.,* **2006**, *26*, 4457-4498.

[170] Balakrishna, A.; Kumar, M.H. Evaluation of Synergetic Anticancer Activity of Berberine and Curcumin on Different Models of A549, Hep-G2, MCF-7, Jurkat, and K562 Cell Lines. *Biomed. Res. Int*., **2015**, *2015*, 354614.

[171] Kim, K.C.; Baek, S.H.; Lee, C. Curcumin-induced downregulation of Axl receptor tyrosine kinase inhibits cell proliferation and circumvents chemoresistance in non-small lung cancer cells. *Int. J. Oncol*., **2015**, Oct 21.

[172] Patel, P.B.; Thakkar, V.R.; Patel, J.S. Cellular Effect of Curcumin

and Citral Combination on Breast Cancer Cells: Induction of Apoptosis and Cell Cycle Arrest. *J. Breast Cancer*, **2015**, *18*(3), 225-234.

[173] Li, F.; Chen, X.; Xu, B.; Zhou, H. Curcumin induces p53-independent necrosis in H1299 cells via a mitochondria-associated pathway. *Mol. Med. Rep*., **2015**, *12*(5), 7806-7814.

[174] Zhang, L.; Cheng, X.; Gao, Y.; Bao, J.; Guan, H.; Lu, R.; Yu, H.; Xu, Q.; Sun, Y. Induction of ROS-independent DNA damage by curcumin leads to G2/M cell cycle arrest and apoptosis in human papillary thyroid carcinoma BCPAP cells. *Food Funct*., **2015**, Oct 7.

[175] Khazaei Koohpar, Z.; Entezari, M.; Movafagh, A.; Hashemi, M. Anticancer Activity of Curcumin on Human Breast Adenocarcinoma: Role of Mcl-1 Gene. *Iran J. Cancer Prev.,* **2015**, *8*(3), e2331.

[176] Zhang, X.; Wang, R.; Chen, G.; Dejean, L.; Chen, Q.H. The Effects of Curcumin-based Compounds on Proliferation and Cell Death in Cervical Cancer Cells. *Anticancer Res*., **2015**, *35*(10), 5293-5298.

[177] Wu, L.; Guo, L.; Liang, Y.; Liu, X.; Jiang, L.; Wang, L. Curcumin suppresses stem-like traits of lung cancer cells via inhibiting the JAK2/STAT3 signaling pathway. *Oncol. Rep*., **2015**, *34*(6), 3311-3317.

[178] Jin,H.; Qiao, F.; Wang, Y.; Xu, Y.; Shang, Y. Curcumin inhibits cell proliferation and induces apoptosis of human non-small cell lung cancer cells through the upregulation of miR-192-5p and suppression of PI3K/Akt signaling pathway. *Oncol. Rep*., **2015**, *34*(5), 2782-2789.

[179] Díaz Osterman, C.J.; Gonda, A.; Stiff, T.; Sigaran, U.; Valenzuela, M.M.; Ferguson Bennit, H.R.; Moyron, R.B.; Khan, S.; Wall, N.R. Curcumin Induces Pancreatic Adenocarcinoma Cell Death Via Reduction of the Inhibitors of Apoptosis. *Pancreas*, **2015**, Sep 4.

[180] Yao, Q.; Lin, M.; Wang, Y.; Lai, Y.; Hu, J.; Fu, T.; Wang, L.; Lin, S.; Chen, L.; Guo, Y. Curcumin induces the apoptosis of A549 cells via oxidative stress and MAPK signaling pathways. *Int. J. Mol. Med*., **2015**, *36*(4), 1118-1126.

[181] Liao, H.; Wang, Z.; Deng, Z.; Ren, H.; Li, X. Curcumin inhibits lung cancer invasion and metastasis by attenuating GLUT1/MT1-MMP/MMP2 pathway. *Int. J. Clin. Exp. Med*., **2015**, *8*(6), 8948-8957.

[182] Cao, F.; Liu, T.; Xu, Y.; Xu, D.; Feng, S. Curcumin inhibits cell proliferation and promotes apoptosis in human osteoclastoma cell through MMP-9, NF-κB and JNK signaling pathways. *Int. J. Clin. Exp. Pathol.,* **2015**, 8(6), 6037-45.

[183] Zhao, Z.; Li, C.; Xi, H.; Gao, Y.; Xu, D. Curcumin induces apoptosis in pancreatic cancer cells through the induction of forkhead box O1 and inhibition of the PI3K/Akt pathway. *Mol. Med. Rep*., **2015**, *12*(4), 5415-5422.

[184] Taverna, S.; Giallombardo, M.; Pucci, M.; Flugy, A.; Manno, M.; Raccosta, S.; Rolfo, C.; De Leo, G.; Alessandro, R. Curcumin inhibits *in vitro* and *in vivo* chronic myelogenous leukemia cells growth: a possible role for exosomal disposal of miR-21. *Oncotarget*, **2015**, *6*(26), 21918-21933.

[185] Amin, A.R.; Haque, A.; Rahman, M.A.; Chen, Z.G.; Khuri, F.R.; Shin, D.M. Curcumin induces apoptosis of upper aerodigestive tract cancer cells by targeting multiple pathways. *PLoS One*, **2015**, *10*(4), e0124218.

[186] Wu, J.; Lu, W.Y.; Cui, L.L. Inhibitory effect of curcumin on invasion of skin squamous cell carcinoma A431 cells. *Asian Pac. J. Cancer Prev*., **2015**, *16*(7), 2813-2818.

[187] Park, M.J.; Kim, E.H.; Park, I.C.; Lee, H.C.; Woo, S.H.; Lee, J.Y.; Hong, Y.J.; Rhee, C.H.; Choi, S.H.; Shim, B.S.; Lee, S.H.; Hong, S.L. Curcumin inhibits cell cycle progression of immortalized human umbilical vein endothelial (ECV304) cells by up-regulating cyclin-dependent kinase inhibitor, p21WAF1/CIP1, p27KIP1 and p53. *Int. J. Oncol*., **2002**, *21*, 379-383.

[188] Liontas, A.; Yeger, H. Curcumin and resveratrol induce apoptosis and nuclear translocation and activation of p53 in human neuroblastoma. *Anticancer Res.,* **2004**, *24*, 987-998.

[189] Jaiswal, A.S.; Marlow, B.P.; Gupta, N.; Narayan, S. Beta-catenin-mediated transactivation and cell–cell adhesion pathways are important in curcumin (diferuylmethane)-induced growth arrest and apoptosis in colon cancer cells. *Oncogene*, **2002**, *21*, 8414-8427.

[190] Moragoda, L.; Jaszewski, R.; Majumdar, A.P. Curcumin induced modulation of cell cycle and apoptosis in gastric and colon cancer cells. *Anticancer Res*., **2001**, *21*, 873-878.

[191] Chen, H.; Zhang, Z.S.; Zhang, Y.L.; Zhou, D.Y. Curcumin inhibits cell proliferation by interfering with the cell cycle and inducing apoptosis in colon carcinoma cells. *Anticancer Res.,* **1999**, *19*, 3675-3680.

[192] Liu, E.; Wu, J.; Cao, W.; Zhang, J.; Liu, W.; Jiang, X.; Zhang, X. Curcumin induces G2/M cell cycle arrest in a p53-dependent manner and upregulates ING4 expression in human glioma. *J. Neurooncol*., **2007**, *85*(3), 263-270.

[193] Aggarwal, B.B.; Ichikawa, H. Molecular targets and anticancer potential of indole-3-carbinol and its derivatives. *Cell Cycle*, **2005**, *4*(9), 1201-1215.

[194] Brandi, G.; Paiardini, M.; Cervasi, B.; Fiorucci, C.; Filippone, P.; De Marco, C.; Zaffaroni, N.; Magnani, M. A new indole-3-carbinol tetrameric derivative inhibits cyclin-dependent kinase 6 expression, and induces G1 cell cycle arrest in both estrogen-dependent and estrogen-independent breast cancer cell lines. *Cancer Res*., **2003**, *63*(14), 4028-4036.

[195] Tsai, N.M.; Lin, S.Z.; Lee, C.C.; Chen, S.P.; Su, H.C.; Chang, W.L.; Harn, H.J. The antitumor effects of Angelica sinensis on malignant brain tumors *in vitro* and *in vivo*. *Clin. Cancer Res.,* **2005**, *11*(9), 3475-3484.

[196] Huang, G.C.; Chien, T.Y.; Chen, L.G.; Wang, C.C. Antitumor effects of zerumbone from Zingiber zerumbet in P-388D1 cells *in vitro* and *in vivo*. *Planta Med*., **2005**, *71*(3), 219-224.

[197] Bakshi, S.; Bergman, M.; Dovrat, S.; Grossman, S. Unique natural antioxidants (NAOs) and derived purified components inhibit cell cycle progression by downregulation of ppRb and E2F in human PC3 prostate cancer cells. *FEBS Lett*., **2004**, *573*(1-3), 31-37.

[198] Seo, B.R.; Lee, K.W.; Ha, J.; Park, H.J.; Choi, J.W.; Lee, K.T. Saucernetin-7 isolated from Saururus chinensis inhibits proliferation of human promyelocytic HL-60 leukemia cells via G0/G1 phase arrest and induction of differentiation. *Carcinogenesis*, **2004**, *25*(8), 1387-1394.

[199] Lee, J.H.; Kang, G.H.; Kim, K.C.; Kim, K.M.; Park, D.I.; Choi, B.T.; Kang, H.S.; Lee, Y.T.; Choi, Y.H. Tetrandrine-induced cell cycle arrest and apoptosis in A549 human lung carcinoma cells. *Int. J. Oncol*., **2002**, *21*(6), 1239-44.

[200] Hogan, F.S.; Krishnegowda, N.K.; Mikhailova, M.; Kahlenberg, M.S. Flavonoid, silibinin, inhibits proliferation and promotes cell-cycle arrest of human colon cancer. *J. Surg. Res*., **2007**, *143*(1), 58-65.

[201] Lee, S.J.; Kim, H.M.; Cho, Y.H.; Park, K.; Kim, E.J.; Jung, K.H.; Kim, C.H.; Kim, W.J.; Moon, S.K. Aqueous extract of Magnolia officinalis mediates proliferative capacity, p21WAF1 expression and TNF-alpha-induced NF-kappaB activity in human urinary bladder cancer 5637 cells; involvement of p38 MAP kinase. *Oncol. Rep*., **2007**, *18*(3), 729-736.

[202] Li, H.; Kapur, A.; Yang, J.X.; Srivastava, S.; McLeod, D.G.; Paredes-Guzman, J.F.; Daugsch, A.; Park, Y.K.; Rhim, J.S. Antiproliferation of human prostate cancer cells by ethanolic extracts of Brazilian propolis and its botanical origin. *Int. J. Oncol*., **2007**, *31*(3), 601-606.

[203] Lee, J.W.; Min, H.Y.; Han, A.R.; Chung, H.J.; Park, E.J.; Park, H.J.; Hong, J.Y.; Seo, E.K.; Lee, S.K. Growth inhibition and induction of G1 phase cell cycle arrest in human lung cancer cells by a phenylbutenoid dimer isolated from Zingiber cassumunar. *Biol. Pharm. Bull*., **2007**, *30*(8), 1561-1564.

[204] Liu, W.; Kato, M.; Akhand, A.A.; Hayakawa, A.; Takemura, M.; Yoshida, S.; Suzuki, H.; Nakashima, I. The herbal medicine shosaiko-to inhibits the growth of malignant melanoma cells by upregulating Fas-mediated apoptosis and arresting cell cycle through downregulation of cyclin dependent kinases. *Int. J. Oncol*., **1998**, *12*(6), 1321-1326.

[205] Sui, C.G.; Meng, F.D.; Li, Y.; Jiang, Y.H. Anti-proliferative activity of rosamultic acid is associated with induction of apoptosis, cell cycle arrest, inhibition of cell migration and caspase activation in human gastric cancer (SGC-7901) cells. *Phytomedicine*, **2015**, *22*(9), 796-806.

[206] Ionta, M.; Ferreira-Silva, G.A.; Niero, E.L.; Costa, É.D.; Martens, A.A.; Rosa, W.; Soares, M.G.; Machado-Santelli, G.M.; Lago, J.H.; Santos, M.H. 7-Epiclusianone, a Benzophenone Extracted from Garcinia brasiliensis (Clusiaceae), Induces Cell Cycle Arrest in G1/S Transition in A549 Cells. *Molecules*, **2015**, *20*(7), 12804-12816.

[207] Wu, P.F.; Chiu, C.C.; Chen, C.Y.; Wang, H.D. 7-Hydroxydehydronuciferine induces human melanoma death via triggering autophagy and apoptosis. *Exp. Dermatol*., **2015** Jul 14.

[208] Abaza, M.S.; Orabi, K.Y.; Al-Quattan, E.; Al-Attiyah, R.J. Growth inhibitory and chemo-sensitization effects of naringenin, a natural flavanone purified from Thymus vulgaris, on human breast and colorectal cancer. *Cancer Cell Int.,* **2015**, *15*, 46.

[209] Moskot, M.; Jakóbkiewicz-Banecka, J.; Smolińska, E.; Piotrowska, E.; Węgrzyn, G.; Gabig-Cimińska, M. Effects of flavonoids on expression of genes involved in cell cycle regulation and DNA replication in human fibroblasts. *Mol. Cell. Biochem*., 2015, *407*(1-2), 97-109.

[210] Weidner, C.; Rousseau, M.; Plauth, A.; Wowro, S.J.; Fischer, C.; Abdel-Aziz, H.; Sauer, S. Melissa officinalis extract induces apoptosis and inhibits proliferation in colon cancer cells through formation of reactive oxygen species. *Phytomedicine*, **2015**, *22*(2), 262-270.

[211] Peng, X.; Zhuang, D.D.; Guo, Q.S. Induction of S phase arrest and apoptosis by ethyl acetate extract from Tetrastigma hemsleyanum in human hepatoma HepG2 cells. *Tumour Biol.,* **2015**, *36*(4), 2541-2550.

[212] Su, C.C. Tanshinone IIA inhibits gastric carcinoma AGS cells through increasing p-p38, p-JNK and p53 but reducing p-ERK, CDC2 and cyclin B1 expression. *Anticancer Res.,* **2014**, *34*(12), 7097-7110.

[213] Zhang, M.; Sun, G.; Shen, A.; Liu, L.; Ding, J.; Peng, J. Patrinia scabiosaefolia inhibits the proliferation of colorectal cancer *in vitro* and *in vivo* via G1/S cell cycle arrest. *Oncol. Rep*., **2015**, *33*(2), 856-860.

[214] Xu, M.Y.; Kim, Y.S. Antitumor activity of glycyrol via induction of cell cycle arrest, apoptosis and defective autophagy. *Food Chem. Toxicol*., **2014**, *74*, 311-319.

[215] Unger, C.; Popescu, R.; Giessrigl, B.; Laimer, D.; Heider, S.; Seelinger, M.; Diaz, R.; Wallnöfer, B.; Egger, G.; Hassler, M.; Knöfler, M.; Saleh, L.; Sahin, E.; Grusch, M.; Fritzer-Szekeres, M.; Dolznig, H.; Frisch, R.; Kenner, L.; Kopp, B.; Krupitza, G. The dichloromethane extract of the ethnomedicinal plant Neurolaena lobata inhibits NPM/ ALK expression which is causal for anaplastic large cell lymphomagenesis. *Int. J. Oncol*., **2013**, 42(1), 338-348.

[216] Zhang, D.M.; Liu, J.S.; Tang, M.K.; Yiu, A.; Cao, H.H.; Jiang, L.; Chan, J.Y.; Tian, H.Y.; Fung, K.P.; Ye, W.C. Bufotalin from Venenum bufonis inhibits growth of multidrug resistant HepG2 cells through G2/M cell cycle arrest and apoptosis. *Eur. J. Pharmacol*., **2012**, *692*(1-3), 19-28.

[217] Unger, C.; Popescu, R.; Giessrigl, B.; Rarova, L.; Herbacek, I.; Seelinger, M.; Diaz, R.; Wallnöfer, B.; Fritzer-Szekeres, M.; Szekeres, T.; Frisch, R.; Doležal, K.; Strnad, M.; De Martin, R.; Grusch, M.; Kopp, B.; Krupitza, G. An apolar extract of Critonia morifolia inhibits c-Myc, cyclin D1, Cdc25A, Cdc25B, Cdc25C and Akt and induces apoptosis. *Int. J. Oncol*., **2012**, *40*(6), 2131-2139.

[218] Chen, H.S.; Liu, Y.; Lin, L.Q.; Zhao, J.L.; Zhang, C.P.; Jin, J.C.; Wang, L.; Bai, M.H.; Wang, Y.C.; Liu, M.; Shen, B.Z. Antiproliferative effect of an extract of the root of Polygonum multiflorum Thunb. on MCF-7 human breast cancer cells and the possible mechanisms. *Mol. Med. Rep*., **2011**, *4*(6), 1313-1319.

[219] Stark, N.; Gridling, M.; Madlener, S.; Bauer, S.; Lackner, A.; Popescu, R.; Diaz, R.; Tut, F.M.; Vo, T.P.; Vonach, C.; Giessrigl, B.; Saiko, P.; Grusch, M.; Fritzer-Szekeres, M.; Szekeres, T.; Kopp, B.; Frisch, R.; Krupitza, G. A polar extract of the Maya healing plant Anthurium schlechtendalii (Aracea) exhibits strong *in vitro* anticancer activity. *Int. J. Mol. Med*., **2009**, *24*(4), 513-521.

[220] Ozmen, A.; Madlener, S.; Bauer, S.; Krasteva, S.; Vonach, C.; Giessrigl, B.; Gridling, M.; Viola, K.; Stark, N.; Saiko, P.; Michel, B.; Fritzer-Szekeres, M.; Szekeres, T.; Askin-Celik, T.; Krenn, L.; Krupitza, G. *In vitro* anti-leukemic activity of the ethnopharmacological plant Scutellaria orientalis ssp. carica endemic to western Turkey. *Phytomedicine*, **2010**, *17*(1), 55-62.

[221] Hsieh, W.T.; Huang, K.Y.; Lin, H.Y.; Chung, J.G. Physalis angulata induced G2/M phase arrest in human breast cancer cells. *Food Chem. Toxicol.,* **2006**, 44(7), 974-983.

[222] Lu, M.C.; Yang, S.H.; Hwang, S.L.; Lu, Y.J.; Lin, Y.H.; Wang, S.R.; Wu, Y.C.; Lin, S.R. Induction of G2/M phase arrest by squamocin in chronic myeloid leukemia (K562) cells. *Life Sci.,* **2006**, *78*(20), 2378-2383.

[223] Aressy, B.; Ducommun, B. Cell cycle control by the CDC25 phosphatases. *Anticancer Agents Med. Chem*., **2008**, *8*, 818-824.

[224] Sadhu, K.; Reed, S.I.; Richardson, H.; Russell, P. Human homolog of fission yeast cdc25 mitotic inducer is expressed predominantly in G2. *Proc. Natl. Acad. Sci. U.S.A.,* **1990**, *87* (13), 5139-5143.

[225] Ferguson, A.M.; White, L.S.; Donovan, P.J.; Piwnica-Worms, H. Normal Cell Cycle and Checkpoint Responses in Mice and Cells Lacking CDC25B and CDC25C Protein Phosphatases. *Mol. Cell. Biol*., **2005**, *25* (7), 2853-60.

[226] Rudolph, J. Cdc25 phosphatases: structure, specificity and mechanisms. *Biochemistry*, **2007**, *46*(12), 3595-3604.

[227] Galaktionov, K.; Beach, D. Specific activation of cdc25 tyrosine phosphatases by B-type cyclins: evidence for multiple roles of mitotic cyclins. *Cell*, **1991**, *67*(6), 1181-1194.

[228] Kristjánsdóttir, K.; Rudolph, J. CDC25 phosphatases and cancer. *Chem. Biol.,* **2004**, *11* (8), 1043-1051.

[229] Galaktionov, K.; Lee, A.K.; Eckstein, J.; Draetta, G.; Meckler, J.; Loda, M.; Beach, D. CDC25 phosphatases as potential human oncogenes. *Science*, **1995**, *269*(5230), 1575-1577.

[230] Broggini, M.; Buraggi, G.; Brenna, A.; Riva, L.; Codegoni, A. M.;Torri, V.; Lissoni, A. A.; Mangioni, C.; D'Incalci, M. Cell cycle-related phosphatases CDC25A and B expression correlates with survival in ovarian cancer patients. *Anticancer Res.,* **2000**, *20*(6C), 4835-4840.

[231] Takemasa, I.; Yamamoto, H.; Sekimoto, M.; Ohue, M.; Noura, S.; Miyake, Y.; Matsumoto, T.; Aihara, T.; Tomita, N.; Tamaki, Y.; Sakita, I.; Kikkawa, N.; Matsuura, N.; Shiozaki, H.; Monden, M. Overexpression of CDC25B phosphatase as a novel marker of poor prognosis of human colorectal carcinoma. *Cancer Res*., **2000**, *60*(11), 3043-3050.

[232] Sasaki, H.; Yukiue, H.; Kobayashi, Y.; Tanahashi, M.; Moriyama, S.; Nakashima, Y.; Fukai, I.; Kiriyama, M.; Yamakawa, Y.; Fujii, Y. Expression of the cdc25B gene as a prognosis marker in non-small cell lung cancer. *Cancer Lett.,* **2001**, *173*(2), 187-192.

[233] Kudo, Y.; Yasui, W.; Ue, T.; Yamamoto, S.; Yokozaki, H.; Nikai, H.; Tahara, E. Overexpression of cyclin-dependent kinase-activating CDC25B phosphatase in human gastric carcinomas. *Jpn. J. Cancer Res*., **1997**, *88*(10), 947-952.

[234] Wu, W.; Fan, Y. H.; Kemp, B. L.; Walsh, G.; Mao, L. Overexpression of cdc25A and cdc25B is frequent in primary non-small cell lung cancer but is not associated with overexpression of c-myc. *Cancer Res*., **1998**, *58*(18), 4082-4085.

[235] Coqueret, O.; Berube, G.; Nepveu, A. The mammalian Cut homeodomain protein functions as a cell-cycle-dependent transcriptional repressor which downmodulates p21WAF1/CIP1/SDI1 in S phase. *EMBO J*., **1998**, *17*(16), 4680-4694.

[236] Boutros, R.; Lobjois, V.; Ducommun, B. CDC25 phosphatases in cancer cells: key players? Good targets? *Nat. Rev. Cancer*., **2007**, *7*, 495-507.

[237] Lavecchia, A.; Coluccia, A.; Giovanni, C. D.; Novellino, E. Cdc25B phosphatase inhibitors in cancer therapy: latest developments, trends and medicinal chemistry perspective. *Anticancer Agents Med. Chem*., **2008**, *8*, 843-856.

[238] Johansson, M.; Persson, J. L. Cancer Therapy: Targeting cell cycle regulators. *Anticancer Agents Med. Chem*., **2008**, *8*, 723-731.

[239] Prevost, G. P.; Brezak, M. C.; Goubin, F.; Mondesert, O.; Galcera, M. O.; Quaranta, M.; Alby, F.; Lavergne, O.; Ducommun, B. Inhibitors of the CDC25 phosphatases. *Progr. Cell Cycle Res.,* **2003**, *5*, 225-234.

[240] Nagle, A.; Hur, W.; Gray, N.S. Antimitotic agents of natural origin. *Curr. Drug Targets,* **2006**, *7*(3), 305-326

[241] Chen, W.Q.; Xu, B.; Mao, J.W.; Wei, F.X.; Li, M.; Liu, T.; Jin, X.B.; Zhang, L.R. Inhibitory effects of α-pinene on hepatoma carcinoma cell proliferation. *Asian Pac. J. Cancer Prev*., **2014**, *15*(7), 3293-3297.

[242] Neumann, J.; Boerries, M.; Köhler, R.; Giaisi, M.; Krammer, P.H.; Busch, H.; Li-Weber, M. The natural anticancer compound rocaglamide selectively inhibits the G1-S-phase transition in cancer cells through the ATM/ATR-mediated Chk1/2 cell cycle checkpoints. *Int. J. Cancer*, **2014**, *134*(8), 1991-2002.

[243] Meng, A.G.; Jiang, L.L. Induction of G2/M arrest by pseudolaric acid B is mediated by activation of the ATM signaling pathway. *Acta Pharmacol. Sin*., **2009**, *30*(4), 442-450.

[244] Yang, H.; Zheng, S.; Meijer, L.; Li, S.M.; Leclerc, S.; Yu, L.L.; Cheng, J.Q.; Zhang, S.Z. Screening the active constituents of Chinese medicinal herbs as potent inhibitors of Cdc25 tyrosine phosphatase, an activator of the mitosis-inducing p34cdc2 kinase. *J. Zhejiang Univ. Sci. B*., **2005**, *6*(7), 656-663.

[245] Cao, S.; Foster, C.; Brisson, M.; Lazo, J.S.; Kingston, D.G. Halenaquinone and xestoquinone derivatives, inhibitors of Cdc25B

phosphatase from a Xestospongia sp. *Bioorg. Med. Chem*., **2005**, *13*(4), 999-1003.

[246] Erdogan-Orhan, I.; Sener, B.; de Rosa, S.; Perez-Baz, J.; Lozach, O.; Leost, M.; Rakhilin, S.; Meijer, L. Polyprenyl-hydroquinones and -furans from three marine sponges inhibit the cell cycle regulating phosphatase CDC25A. *Nat. Prod. Res*., **2004**, *18*(1), 1-9.

[247] Rajeshkumar, N.V.; Joy, K.L.; Kuttan, G.; Ramsewak, R.S.; Nair, M.G.; Kuttan, R. Antitumour and anticarcinogenic activity of Phyllanthus amarus extract. *J. Ethnopharmacol.,* **2002**, *81*(1), 17-22.

[248] Loukaci, A.; Le Saout, I.; Samadi, M.; Leclerc, S.; Damiens, E.; Meijer, L.; Debitus, C.; Guyot, M. Coscinosulfate, a CDC25 phosphatase inhibitor from the sponge Coscinoderma mathewsi. *Bioorg. Med. Chem.,* **2001**, *9*(11), 3049-3054.

[249] Hirano, N.; Kohno, J.; Tsunoda, S.; Nishio, M.; Kishi, N.; Okuda, T.; Kawano, K.; Komatsubara, S.; Nakanishi, N. TMC-69, a new antitumor antibiotic with Cdc25A inhibitory activity, produced by Chrysosporium sp. TC1068. Taxonomy, fermentation and biological activities. *J. Antibiot. (Tokyo),* **2001**, *54*(5), 421-427.

[250] Dou, Q. P.; Li, B. Proteasome inhibitors as potential novel anticancer agents. *Drug Resist. Updat*., **1999**, *2*(4), 215-223.

[251] Lewin, B. Driving the cell cycle: M phase kinase, its partners, and substrates. *Cell*, **1990**, *61*(5), 743-752.

[252] Glotzer, M.; Murray, A. W.; Kirschner, M. W. Cyclin is degraded by the ubiquitin pathway. *Nature*, **1991**, *349*(6305), 132-138.

[253] Koff, A.; Giordano, A.; Desai, D.; Yamashita, K.; Harper, J. W.; Elledge, S.; Nishimoto, T.; Morgan, D. O.; Franza, B. R.; Roberts, J. M. Formation and activation of a cyclin E-cdk2 complex during the G1 phase of the human cell cycle. *Science*, **1992**, *257*(5077), 1689-1694.

[254] Won, K. A.; Reed, S. I. Activation of cyclin E/CDK2 is coupled to site-specific autophosphorylation and ubiquitin-dependent degradation of cyclin E. *EMBO J*., **1996**, *15*(16), 4182-4193.

[255] Omura, S.; Fujimoto, T.; Otoguro, K.; Matsuzaki, K.; Moriguchi, R.; Tanaka, H.; Sasaki, Y. Lactacystin, a novel microbial metabolite, induces neuritogenesis of neuroblastoma cells. *J. Antibiot. (Tokyo),* **1991**, *44*(1), 113-116.

[256] Fenteany, G.; Standaert, R. F.; Lane, W. S.; Choi, S.; Corey, E. J.; Schreiber, S. L. Inhibition of proteasome activities and subunit-specific amino-terminal threonine modification by lactacystin. *Science*, **1995**, *268*(5211), 726-731.

[257] Hanada, M.; Sugawara, K.; Kaneta, K.; Toda, S.; Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. Epoxomicin, a new antitumor agent of microbial origin. *J. Antibiot. (Tokyo),* **1992**, *45*(11), 1746-1752.

[258] Meng, L.; Mohan, R.; Kwok, B. H.; Elofsson, M.; Sin, N.; Crews, C. M. Epoxomicin, a potent and selective proteasome inhibitor, exhibits *in vivo* antiinflammatory activity. *Proc. Natl. Acad. Sci. U.S.A*., **1999**, *96*(18), 10403-10408.

[259] Meng, L.; Kwok, B. H.; Sin, N.; Crews, C. M. Eponemycin exerts its antitumor effect through the inhibition of proteasome function. *Cancer Res.,* **1999**, *59*(12), 2798-2801.

[260] Larsen, A. K.; Skladanowski, A.; Bojanowski, K. The roles of DNA topoisomerase II during the cell cycle. *Progr. Cell Cycle Res*., **1996**, *2*, 229-239.

[261] Champoux, J.J. DNA topoisomerases: structure, function, and mechanism. *Annu. Rev. Biochem*., **2001**, *70*, 369-413.

[262] Pommier, Y.; Leo, E.; Zhang, H.; Marchand, C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. *Chem. Biol*., **2010**, *17* (5), 421-433.

[263] Skladanowski, A.; Côme, M.G.; Sabisz, M.; Escargueil, A.E.; Larsen, A.K. Down-regulation of DNA topoisomerase IIalpha leads to prolonged cell cycle transit in G2 and early M phases and increased survival to microtubule-interacting agents. *Mol. Pharmacol.,* **2005**, 68(3), 625-634.

[264] Larsen, A.K.; Escargueil, A.E.; Skladanowski, A. Catalytic topoisomerase II inhibitors in cancer therapy. *Pharmacol. Ther.,* **2003**, *99*(2), 167-81.

[265] Escargueil, A.E.; Plisov, S.Y.; Skladanowski, A.; Borgne, A.; Meijer, L.; Gorbsky, G.J.; Larsen, A.K. Recruitment of cdc2 kinase by DNA topoisomerase II is coupled to chromatin remodeling. *FASEB J.,* **2001**, *15*(12), 2288-2290.

[266] Sørensen, B.S.; Jensen, P.B.; Sehested, M.; Jensen, P.S.; Kjeldsen, E.; Nielsen, O.F.; Alsner, J. Antagonistic effect of aclarubicin on camptothecin induced cytotoxicity: role of topoisomerase I. *Biochem. Pharmacol*., **1994**, *47*(11), 2105-2110.

[267] Bridewell, D. J.; Finlay, G. J.; Baguley, B. C. Differential actions of aclarubicin and doxorubicin: the role of topoisomerase I. *Oncol. Res*., **1997**, *9*(10), 535-542.

[268] Hajji, N.; Mateos, S.; Pastor, N.; Domínguez, I.; Cortés, F. Induction of genotoxic and cytotoxic damage by aclarubicin, a dual topoisomerase inhibitor. *Mutat. Res*., **2005**, *583*(1), 26-35.

[269] Gieseler, F.; Bauer, E.; Nuessler, V.; Clark, M.; Valsamas, S. Molecular effects of topoisomerase II inhibitors in AML cell lines: correlation of apoptosis with topoisomerase II activity but not with DNA damage. *Leukemia*, **1999**, *13*(11), 1859-63.

[270] González-Molleda, L.; Wang, Y.; Yuan, Y. Potent antiviral activity of topoisomerase I and II inhibitors against Kaposi's sarcoma-associated herpesvirus. *Antimicrob. Agents Chemother*., **2012**, *56*(2), 893-902.

[271] Haldane, A.; Finlay, G.J.; Baguley, B.C. A comparison of the effects of aphidicolin and other inhibitors on topoisomerase II-directed cytotoxic drugs. *Oncol Res*., **1993**, *5*(3), 133-138.

[272] Constantinou, A.; Henning-Chubb, C.; Huberman, E. Novobiocin- and phorbol-12-myristate-13-acetate-induced differentiation of human leukemia cells associated with a reduction in topoisomerase II activity. *Cancer Res*., **1989**, *49*(5), 1110-1117.

[273] Sudan, S.; Rupasinghe, H.P. Quercetin-3-O-glucoside induces human DNA topoisomerase II inhibition, cell cycle arrest and apoptosis in hepatocellular carcinoma cells. *Anticancer Res*., **2014**, *34*(4), 1691-1699.

[274] Howard, J.; Hyman, A.A. Microtubule polymerases and depolymerases. *Curr. Opin. Cell Biol.,* **2007**, *19* (1), 31-35.

[275] Desai, A.; Mitchison, T.J. Microtubule polymerization dynamics. *Annu. Rev.Cell Dev. Biol*., **1997**, *13*, 83-117.

[276] Nogales, E. Structural Insights into Microtubule Function. *Annu. Rev. Biochem*., **2000**, *69*, 277-302.

[277] Mitchison, T.; Kirschner, M. Dynamic instability of microtubule growth. *Nature*, **1984**, *312* (5991), 237-242.

[278] Parker, A.L.; Kavallaris, M.; McCarroll, J.A. Microtubules and their role in cellular stress in cancer. *Front Oncol*., **2014**, *4*, 153.

[279] Mandelkow, E.; Mandelkow, E.M. Microtubules and microtubule-associated proteins. *Curr. Opin. Cell Biol*., **1995**, *7* (1), 72–81.

[280] Yang, H.; Ganguly, A.; Cabral, F. Inhibition of Cell Migration and Cell Division Correlates with Distinct Effects of Microtubule Inhibiting Drugs. *J. Biol. Chem*., **2010**, *285* (42), 32242-32250.

[281] Ganguly, A.; Yang, H.; Cabral, F. Paclitaxel-dependent cell lines reveal a novel drug activity. *Mol. Cancer Ther*., **2010**, *9* (11), 2914-2923.

[282] Schiff, P. B.; Fant, J.; Horwitz, S. B. Promotion of microtubule assembly *in vitro* by taxol. *Nature*, **1979**, *277*(5698), 665-667.

[283] Gligorov, J.; Lotz, J. P. Preclinical pharmacology of the taxanes: implications of the differences. *Oncologist*, **2004**, *9*(Suppl. 2), 3-8.

[284] Shi, Q.; Chen, K.; Morris-Natschke, S. L.; Lee, K. H. Recent progress in the development of tubulin inhibitors as antimitotic antitumor agents. *Curr. Pharm. Des*., **1998**, *4*(3), 219-248.

[285] Jordan, A.; Hadfield, J.A.; Lawrence, N.J.; McGown, A.T. Tubulin as a target for anticancer drugs: agents, which interact with the mitotic spindle. *Med. Res. Rev*., **1998**, *18*(4), 259-296.

[286] Islam, M.N.; Iskander, M.N. Microtubulin binding sites as target for developing anticancer agents. *Mini-Rev. Med. Chem.,* **2004**, *4*(10), 1077-1010.

[287] Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. Epothilones, a new class of microtubule-stabilizing agents with a taxol-like mechanism of action. *Cancer Res*., **1995**, *55*(11), 2325-2333.

[288] Kowalski, R. J.; Giannakakou, P.; Hamel, E. Activities of the microtubule-stabilizing agents epothilones A and B with purified tubulin and in cells resistant to paclitaxel (Taxol(R). *J. Biol. Chem*., **1997**, *272*(4), 2534-2541.

[289] Altmann, K. H.; Wartmann, M.; O'Reilly, T. Epothilones and related structures - a new class of microtubule inhibitors with potent *in vivo* antitumor activity. *Biochim. Biophys. Acta*, **2000**, *1470*(3), M79-91.

[290] Chou, T. C.; Zhang, X. G.; Harris, C. R.; Kuduk, S. D.; Balog, A.; Savin, K. A.; Bertino, J. R.; Danishefsky, S. J. Desoxyepothilone B is curative against human tumor xenografts that are refractory to paclitaxel. *Proc. Natl. Acad. Sci. U.S.A*., **1998**, *95*(26), 15798-15802.

[291] Giannakakou, P.; Gussio, R.; Nogales, E.; Downing, K. H.; Zaharevitz, D.; Bollbuck, B.; Poy, G.; Sackett, D.; Nicolaou, K. C.; Fojo, T. A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations

in human cancer cells. *Proc. Natl. Acad. Sci. U.S.A*., **2000**, *97*(6), 2904-2909.

[292] Gerth, K.; Bedorf, N.; Hofle, G.; Irschik, H.; Reichenbach, H. Epothilons A and B: antifungal and cytotoxic compounds from Sorangium cellulosum (Myxobacteria). Production, physicochemical and biological properties. *J. Antibiot. (Tokyo),* **1996**, *49*(6), 560-563.

[293] Kolman, A. Activity of epothilones. *Curr. Opin. Invest. Drugs*., **2005**, *6*(6), 616-622.

[294] Dietzmann, A.; Kanakis, D.; Kirches, E.; Kropf, S.; Mawrin, C.; Dietzmann, K. Nanomolar concentrations of epothilone D inhibit the proliferation of glioma cells and severely affect their tubulin cytoskeleton. *J. Neurooncol.,* **2003**, *65*(2), 99-106.

[295] Chou, T. C.; O'Connor, O. A.; Tong, W. P.; Guan, Y.; Zhang, Z. G.; Stachel, S. J.; Lee, C.; Danishefsky, S. J. The synthesis, discovery, and development of a highly promising class of microtubule stabilization agents: curative effects of desoxyepothilones B and F against human tumor xenografts in nude mice. *Proc. Natl. Acad. Sci. U.S.A*., **2001**, *98*(14), 8113-8118.

[296] ter Haar, E.; Kowalski, R. J.; Hamel, E.; Lin, C. M.; Longley, R. E.; Gunasekera, S. P.; Rosenkranz, H. S.; Day, B. W. Discodermolide, a cytotoxic marine agent that stabilizes microtubules more potently than taxol. *Biochemistry*, **1996**, *35*(1), 243-250.

[297] Kowalski, R. J.; Giannakakou, P.; Gunasekera, S. P.; Longley, R. E.; Day, B. W.; Hamel, E. The microtubule-stabilizing agent discodermolide competitively inhibits the binding of paclitaxel (Taxol) to tubulin polymers, enhances tubulin nucleation reactions more potently than paclitaxel, and inhibits the growth of paclitaxel-resistant cells. *Mol. Pharmacol.,* **1997**, *52*(4), 613-622.

[298] Singh, R.; Sharma, M.; Joshi, P.; Rawat, D.S. Clinical status of anti-cancer agents derived from marine sources. *Anticancer Agents Med. Chem*., **2008**, *8*(6), 603-617.

[299] Pettit, G. R.; Singh, S. B.; Hamel, E.; Lin, C. M.; Alberts, D. S.; Garcia-Kendall, D. Isolation and structure of the strong cell growth and tubulin inhibitor combretastatin A-4. *Experientia*, **1989**, *45*(2), 209-211.

[300] Tozer, G. M.; Prise, V. E.; Wilson, J.; Locke, R. J.; Vojnovic, B.; Stratford, M. R.; Dennis, M. F.; Chaplin, D. J. Combretastatin A-4 phosphate as a tumor vascular-targeting agent: early effects in tumors and normal tissues. *Cancer Res*., **1999**, *59*(7), 1626-1634.

[301] Desbene, S.; Giorgi-Renault, S. Drugs that inhibit tubulin polymerization: the particular case of podophyllotoxin and analogues. *Curr. Med. Chem. Anticancer Agents*, **2002**, *2*(1), 71-90.

[302] Blokhin, A.V.; Yoo, H.D.; Geralds, R.S.; Nagle, D.G.; Gerwick, W.H.; Hamel, E. Characterization of the interaction of the marine cyanobacterial natural product curacin A with the colchicine site of tubulin and initial structure-activity studies with analogues. *Mol. Pharmacol*., **1995**, *48*(3), 523-531.

[303] Verdier-Pinard, P.; Lai, J.Y.; Yoo, H.D.; Yu, J.; Marquez, B.; Nagle, D.G.; Nambu, M.; White, J.D.; Falck, J.R.; Gerwick, W.H.; Day, B.W.; Hamel, E. Structure-activity analysis of the interaction of curacin A, the potent colchicine site antimitotic agent, with tubulin and effects of analogs on the growth of MCF-7 breast cancer cells. *Mol. Pharmacol*., **1998**, *53*(1), 62-76.

[304] Márquez, B.; Verdier-Pinard, P.; Hamel, E.; Gerwick, W.H. Curacin D, an antimitotic agent from the marine cyanobacterium Lyngbya majuscula. *Phytochemistry*, **1998**, 49(8), 2387-2389.

[305] Wipf, P.; Reeves, J. T.; Day, B. W. Chemistry and biology of curacin A. *Curr. Pharm. Des.,* **2004**, *10*(12), 1417-1437.

[306] Kavallaris, M.; Verrills, N.M.; Hill, B.T. Anticancer therapy with novel tubulin-interacting drugs. *Drug Resist. Updat.,* **2001**, 4(6), 392-401.

[307] Ngan, V. K.; Bellman, K.; Panda, D.; Hill, B. T.; Jordan, M. A.; Wilson, L. Novel actions of the antitumor drugs vinflunine and vinorelbine on microtubules. *Cancer Res*., **2000**, *60*(18), 5045-5051.

[308] Hill, B. T.; Fiebig, H. H.; Waud, W. R.; Poupon, M. F.; Colpaert, F.; Kruczynski, A. Superior *in vivo* experimental antitumour activity of vinflunine, relative to vinorelbine, in a panel of human tumour xenografts. *Eur. J. Cancer*, **1999**, *35*(3), 512-520.

[309] Howard, S. M.; Theologides, A.; Sheppard, J. R. Comparative effects of vindesine, vinblastine, and vincristine on mitotic arrest and hormonal response of L1210 leukemia cells. *Cancer Res*., **1980**, *40*(8 Pt 1), 2695-2700.

[310] Malawista, S. E.; Sato, H.; Bensch, K. G. Vinblastine and griseofulvin reversibly disrupt the living mitotic spindle. *Science,* **1968**, *160*(829), 770-772.

[311] Bruchovsky, N.; Owen, A. A.; Becker, A. J.; Till, J. E. Effects of vinblastine on the proliferative capacity of L cells and their progress through the division cycle. *Cancer Res*., **1965**, *25*(8), 1232-1237.

[312] Poncet, J. The dolastatins, a family of promising antineoplastic agents. *Curr. Pharm. Des.,* **1999**, *5*(3), 139-162.

[313] Bai, R.; Friedman, S.J.; Pettit, G.R.; Hamel, E. Dolastatin 15, a potent antimitotic depsipeptide derived from Dolabella auricularia. Interaction with tubulin and effects of cellular microtubules. *Biochem. Pharmacol*., **1992**, *43*(12), 2637-2645.

[314] Cruz-Monserrate, Z.; Mullaney, J.T.; Harran, P.G.; Pettit, G.R.; Hamel, E. Dolastatin 15 binds in the vinca domain of tubulin as demonstrated by Hummel-Dreyer chromatography. *Eur. J. Biochem*., **2003**, *270*(18), 3822-3828.

[315] Hu, Z.B.; Gignac, S.M.; Quentmeier, H.; Pettit, G.R.; Drexler, H.G. Effects of dolastatins on human B-lymphocytic leukemia cell lines. *Leuk. Res*., **1993**, *17*(4), 333-339.

[316] Beckwith, M.; Urba, W.J.; Longo, D.L. Growth inhibition of human lymphoma cell lines by the marine compounds, dolastatins 10 and 15. *J. Natl. Cancer Inst*., **1993**, 85(6), 483-488.

[317] Steube, K.G.; Grunicke, D.; Pietsch, T.; Gignac, S.M.; Pettit, G.R.; Drexler, H.G. Dolastatin 10 and dolastatin 15: effects of two natural peptides on growth and differentiation of leukemia cells. *Leukemia*, **1992**, *6*(10), 1048-1053.

[318] Vaishampayan, U.; Glode, M.; Du, W.; Kraft, A.; Hudes, G.; Wright, J.; Hussain, M. Phase II study of dolastatin-10 in patients with hormone-refractory metastatic prostate adenocarcinoma. *Clin. Cancer Res*., **2000**, *6*(11), 4205-4208.

[319] Sato, M.; Sagawa, M.; Nakazato, T.; Ikeda, Y.; Kizaki, M. A natural peptide, dolastatin 15, induces G2/M cell cycle arrest and apoptosis of human multiple myeloma cells. *Int. J. Oncol.,* **2007**, *30*(6), 1453-1459.

[320] Scherlach, K.; Partida-Martinez, L.P.; Dahse, H.M.; Hertweck, C. Antimitotic rhizoxin derivatives from a cultured bacterial endosymbiont of the rice pathogenic fungus Rhizopus microsporus. *J. Am. Chem. Soc.,* **2006**, *128*(35), 11529-11536.

[321] Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y. Rhizoxin binding to tubulin at the maytansine-binding site. *Biochim. Biophys. Acta*, **1987**, *926*(3), 215-223.

[322] Prota, A.E.; Bargsten, K.; Diaz, J.F.; Marsh, M.; Cuevas, C.; Liniger, M.; Neuhaus, C.; Andreu, J.M.; Altmann, K.H.; Steinmetz, M.O. A new tubulin-binding site and pharmacophore for microtubule-destabilizing anticancer drugs. *Proc. Natl. Acad. Sci.* U*.S.A*., **2014**, *111*(38), 13817-13821.

[323] Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, I.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. Rhizoxin, a macrocyclic lactone antibiotic, as a new antitumor agent against human and murine tumor cells and their vincristine-resistant sublines. *Cancer Res*., **1986**, 46, 381-385.

[324] Arioka, H.; Nishio, K.; Heike, Y.; Abe, S.; Saijo, N. *In vitro* and *in vivo* modulation by rhizoxin of non-P-glycoprotein-mediated vindesine resistance. *J. Cancer Res. Clin. Oncol*., **1997**, *123*(4), 195-200.

[325] Hendriks, H. R.; Plowman, J.; Berger, D. P.; Paull, K. D.; Fiebig, H. H.; Fodstad, O.; Dreef-van der Meulen, H. C.; Henrar, R. E.; Pinedo, H. M.; Schwartsmann, G. Preclinical antitumour activity and animal toxicology studies of rhizoxin, a novel tubulin-interacting agent. *Ann. Oncol.,* **1992**, *3*(9), 755-763.

[326] Kaplan, S.; Hanauske, A.R.; Pavlidis, N.; Bruntsch, U.; te Velde, A.; Wanders, J.; Heinrich, B.; Verweij, J. Single agent activity of rhizoxin in non-small-cell lung cancer: a phase II trial of the EORTC Early Clinical Trials Group. *Br. J. Cancer*, **1996**, *73*(3), 403-405.

[327] Pettit, R.K.; McAllister, S.C.; Pettit, G.R.; Herald, C.L.; Johnson, J.M.; Cichacz, Z.A. A broad-spectrum antifungal from the marine sponge Hyrtios erecta. *Int. J. Antimicrob. Agents*, **1997**, *9*(3), 147-152.

[328] Bai, R.; Cichacz, Z.A.; Herald, C.L.; Pettit, G.R.; Hamel, E. Spongistatin 1, a highly cytotoxic, sponge-derived, marine natural product that inhibits mitosis, microtubule assembly, and the binding of vinblastine to tubulin. *Mol. Pharmacol.,* **1993**, *44*(4), 757-766.

[329] Bai, R.; Taylor, G.F.; Cichacz, Z.A.; Herald, C.L.; Kepler, J.A.; Pettit, G.R.; Hamel, E. The spongistatins, potently cytotoxic inhibitors of tubulin polymerization, bind in a distinct region of the vinca domain. *Biochemistry*, **1995**, *34*(30), 9714-9721.

[330] Uckun, F. M.; Mao, C.; Jan, S. T.; Huang, H.; Vassilev, A. O.; Navara, C. S.; Narla, R. K. Spongistatins as tubulin targeting agents. *Curr. Pharm. Des.,* **2001**, 7(13), 1291-1296.

[331] Xu, Q.; Huang, K.C.; Tendyke, K.; Marsh, J.; Liu, J.; Qiu, D.; Littlefield, B.A.; Nomoto, K.; Atasoylu, O.; Risatti, C.A.; Sperry, J.B.; Smith, A.B. 3rd. *In vitro* and *in vivo* anticancer activity of (+)-spongistatin 1. *Anticancer Res.,* **2011**, *31*(9), 2773-2779.

[332] Rothmeier, A.S.; Schneiders, U.M.; Wiedmann, R.M.; Ischenko, I.; Bruns, C.J.; Rudy, A.; Zahler, S.; Vollmar, A.M. The marine compound spongistatin 1 targets pancreatic tumor progression and metastasis. *Int. J. Cancer*, **2010**, *127*(5), 1096-1105.

[333] Umezawa, H.; Takeuchi, T.; Iinuma, H.; Ito, M.; Ishizuka, M. A new antibiotic, calvatic acid. *J. Antibiot. (Tokyo),* **1975**, *28*(1), 87-90.

[334] Gadoni, E.; Gabriel, L.; Olivero, A.; Bocca, C.; Miglietta, A. Antimicrotubular effect of calvatic acid and of some related compounds. *Cell Biochem. Funct.,* 1995, 13(4), 231-238.

[335] Drewes, G.; Ebneth, A.; Mandelkow, E.M. MAPs, MARKs and microtubule dynamics. *Trends Biochem. Sci.,* **1998**, *23* (8), 307-311.

[336] Ookata, K.; Hisanaga, S.; Bulinski, J. C.; Murofushi, H.; Aizawa, H.; Itoh, T. J.; Hotani, H.; Okumura, E.; Tachibana, K.; Kishimoto, T. Cyclin B interaction with microtubule-associated protein 4 (MAP4) targets p34cdc2 kinase to microtubules and is a potential regulator of M-phase microtubule dynamics. *J. Cell Biol.,* **1995**, *128*(5), 849-862.

[337] Usui, T.; Kondoh, M.; Cui, C.B.; Mayumi, T.; Osada, H. Tryprostatin A, a specific and novel inhibitor of microtubule assembly. *Biochem. J*., **1998**, *333* (Pt. 3), 543-548.

[338] Meeran, S.M.; Katiyar, S.K. Cell cycle control as a basis for cancer chemoprevention through dietary agents. *Front. Biosci*., **2008**, *13*, 2191-2202.