11

Potential Therapeutic Molecular Targets for Nasopharyngeal Carcinoma

Shih-Shun Chen
Department of Medical Laboratory Science and Biotechnology, Central Taiwan University of Science and Technology, Taichung, Taiwan

1. Introduction

Nasopharyngeal carcinoma (NPC) is the leading cause of death in Southeast Asian populations, especially among Chinese people (338). The specific type of NPC is defined by the World Health Organization and classified histologically as either type I (keratinizing squamous cell carcinoma), type II (non-keratinizing squamous cell carcinoma), or type III (undifferentiated carcinoma) (263). Etiologic factors associated with NPC development are classified according to three determinants, including genetic susceptibility, Epstein-Barr virus (EBV) infection, and environmental exposure to carcinogens (45, 337). Evidence has indicated that EBV infection is implicated in the development of type II and III and is observed particularly in Asia (50, 61, 205, 230). EBV infection is generally not detected in type I NPC patients, especially in non-endemic areas (221, 342). Potential risk factors significantly associated with the initiation and development of type I NPC are cigarette smoking and alcohol consumption (35, 225, 295, 301). However, increasing evidence indicates that EBV appears to be the predominant risk factor associated with the initiation and development of NPC, regardless of histological type (17, 20, 300). In particular, EBV infection is an important event in the early stage of the NPC carcinogenesis process before tumor formation (101). Clinically, NPC exhibits a high incidence of lymph node spread and distant metastasis that is correlated with a poor prognosis, even when employing radiation therapy and chemotherapy (43, 260, 326). In the search for new substances with anti-tumoral effects, many natural compounds from dietary plants, such as herb and fruit extracts, have been shown to inhibit NPC proliferation, invasion, metastasis, and angiogenesis both *in vitro* and *in vivo*. This review summarizes the molecular mechanisms of EBV infection in NPC development as well as the role of natural compounds in the regulation of multiple cellular pathways and their clinical importance for the prevention and treatment of NPC.

2. The molecular mechanisms of EBV infection and the effects on NPC growth and metastasis

Virus binding to the surface of a target cell is a major determinant of cellular tropism and is a critical step in viral pathogenesis. This early event initiates the virus replication cycle by the attachment of the virus to specific receptor (s) and leads to the release of the viral genome into the cytoplasm of the target cell. It is believed that EBV infection is initiated by

the interaction of the viral envelope glycoprotein gp350 with the complement receptor 2 (CR2/CD21) of the primary B cell surface membrane (11, 70, 219). The inefficient infection of epithelial cells by EBV is ascribed mainly to the lack of CD21 expression (17). RNA transcripts of the *CD21* gene have been found in the tonsillar epithelial cells of healthy patients by real-time quantitative polymerase chain reaction (PCR), although CD21 protein is not detected in these cells (125). A recent study has demonstrated that EBV-binding to the surface CD21 protein of CD11b-positive memory B cells (but not CD11b-negative naïve B cells) triggers co-capping of virus and integrins on B cells and activation of the adhesion molecules, which can induce the conjugation of EBV-loaded B cells and epithelial cells *via* the capped adhesion molecules while providing efficient virus transfer from B cells to infect epithelial cells (264). Memory B cells are regarded as professional antigen-presenting cells capable of priming T cells, which are responsible for the secretory IgA response and protective humoral immunity to virus. The anatomical localization of memory B cells from human tonsils preferentially colonize the tonsil epithelium, which is a potential site of viral entry, implying that transfer infection of normal epithelial cells may contribute to the EBV-induced tumorigenesis (191). Immunohistochemical analysis of CD21 in samples derived from healthy patients, non-tumoral nasopharyngeal mucosa patients, and NPC patients of different histological types with EBV infection has demonstrated a loss of CD21 expression in all NPC samples analyzed after EBV infection (18). A study of CD21 expression using a sensitive ribonuclease protection assay has demonstrated that a weak transcription signal of the *CD21* gene can be detected in the transplanted EBV-associated NPC tumors of nude mice, thereby suggesting that CD21 is expressed at low levels in EBV-positive NPC cells (11). These data suggest that EBV-induced immunophenotypic modulation of CD21 expression may be associated with NPC malignancy (18).

During EBV latency, NPC cells express a well-defined set of latent genes, including latent membrane proteins (LMP1, LMP2A, and LMP2B) and EBV-determined nuclear antigens (EBNA1 and EBNA2) (16, 84, 323). LMP1, an integral membrane protein encoded by the *BNLF1* gene (115), is the major transforming protein of the virus based on its ability to alter the phenotypic properties of epithelial cells and induce the expression of matrix metalloproteinase 9 (MMP-9), which is thought to contribute to tumor progression, invasiveness, and metastasis of NPC (58, 138, 334). Although low levels of LMP1 protein expression have been detected in NPC biopsies (68, 335), the *LMP1* gene transcripts detected by RT-PCR are present in approximately 95% of nasopharyngeal swab specimens from NPC patients (183). Expression of the *LMP1* gene was especially observed in early stage NPCs and pre-invasive lesions but not in late stage NPCs, therefore suggesting that its expression may initiate the development and progression of NPC (230). When the *LMP1* gene was expressed at high levels, it was toxic to human B-lymphoid cell lines, mouse embryonic fibroblast BALB/3T3 cells, a human osteosarcoma 143/EBNA-1 cell line expressing the EBV *EBNA-1* gene, and the human Larynx carcinoma HEp-2 cell line (93). Stable low-level expression of LMP1 is closely associated with the induction of anchorage-dependent growth and an invasive phenotype in mouse epithelial cells (294). Results have shown that LMP1-derived LALLFWL peptides are able to inhibit the proliferation of T cells and the cytotoxic function of NK cells (63). Studies have also indicated that EBV-infected NPC cells can use the exosome pathway for viral immune escape (134, 140). Moreover, LMP1 was shown to colocalize with the major histocompatibility complex (MHC) class II and be presented on the exosome (71). LMP1-containing exosomes derived from an EBV-positive lymphoblastoid

cell line (LCL) were also capable of reducing T cell proliferation (71). LMP1 exerts immunosuppressive activity and can modulate the cytotoxic effects of innate immune cells, which are thought to allow cancer cells to evade the immune system (297). Exposure of cells to exosomes containing LMP1 prepared from EBV-infected NPC cells leads to the activation of the extracellular signal-regulated protein kinase (ERK) and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathways in epithelial, endothelial, and fibroblast cells. Moreover, the data presented showed that LMP1 could also induce epidermal growth factor receptor (EGFR) expression in EBV-negative epithelial cells and that purified exosomes from treated cells contained high levels of EGFR (207). Incorporation of cancer cell-secreted EGFR-containing membrane microvesicles by endothelial cells can induce the endothelial cell expression of EGFR and lead to the activation of the mitogen-activated protein kinase (MAPK) and Akt pathways as well as subsequent increased expression of vascular endothelial growth factor (VEGF) (4). These results support the concept that LMP1 plays a role in the modulation of the tumor microenvironment and immune evasion of EBV.

LMP1 also displays pleiotropic effects on the induction of the cell surface adhesion molecule CD23 (303), upregulation of the anti-apoptotic genes *Bcl-2* and *A20* (99, 149), and stimulation of interleukin-6 (IL-6) and -8 production (64, 65). LMP1 operates as a constitutively activated tumor necrosis factor receptor (TNFR) by functionally mimicking CD40, thereby utilizing TNFR-associated factor (TRAF) adaptor proteins to induce signaling pathways in a ligand-independent manner (241). LMP1-regulated IL-6 production in epithelial cells, which is regulated *via* a nuclear factor-kappa B (NF-κB) pathway involving TRAF, is similar to those mediated by the CD40 (65). IL-6 production and cell survival have also been shown to be regulated by p38 MAPK activity in LMP1-expressing epithelial cells (59, 64). Recent studies have demonstrated that activation of the p38 MAPK signaling pathway can promote LMP1 expression, suggesting that LMP1 upregulation by p38 MAPK signaling may contribute to cell survival during the early stage of EBV infection (126). Moreover, LMP1 expression has a significant anti-differentiation effect on human epithelial cells by inducing CD40, CD54, IL-6, and IL-8 expression (57). The serum levels of IL-6 are usually found to be elevated in NPC patients (46). The role that IL-6 plays in the regulation of the growth and invasion of cancer cells has been well demonstrated in various cancer cells such as human melanoma (194), human ductal breast carcinoma (253), renal cell carcinoma (289), ovarian carcinoma cells (243), human oral squamous carcinoma cells (270), head and neck cancer cells (281), human chondrosarcoma cells (286), and human pancreatic cancer cells (112). Ectopic expression of LMP1 in epithelial cells has been shown to result in increased MMP-9 expression (334). The promoter region of MMP-9 contains various *cis*-acting elements, including potential binding sites for NF-κB and activator protein-1 (AP-1) (334). NF-κB is critically involved in tumor progression through transcriptional regulation of invasion related factors, such as MMP-9 and VEGF (3). NF-κB overexpression can protect cancer cells against apoptosis induced by death receptors, thereby promoting the proliferation of cancer cells. Furthermore, constitutive activation of NF-κB has been detected in various tumor cells (224). The involvement of the MAPK pathways in NF-κB activation has been demonstrated to play an important role in tumorigenesis (60). Furthermore, p38 MAPK activity has been reported to be associated with anti-apoptosis (220), cell proliferation (103), and cancer invasion (271). Collectively, the regulation of IL-6 and MMP-9 production *via* the LMP1-TRAF-p38-MAPK-NF-κB pathway may have implications for the tumorigenesis and metastasis of NPC.

Dissociation or dissemination of cells from primary cancer to distant organs has been characterized by the loss of function or expression of epithelial cell adhesion molecules (148, 162). E-cadherin is a homophilic adhesion molecule expressed predominantly in epithelial tissues, which acts as an invasion suppressor and was found to be downregulated in most carcinomas (48). Reduced expression of E-cadherin has been observed in the advanced stages of NPC, therefore suggesting its association with cancer metastasis and poor prognosis (347). Significantly decreased expression levels of E-cadherin regulated by LMP1 have been shown to be associated with a higher invasive capability in human epithelial cells (67). LMP1 induces the downregulation of E-*cadherin* gene expression in NPC cell lines, which was shown by activation of DNA methyltransferases (292). The recent generation of transgenic mice has demonstrated that LMP1 overexpression antagonizes Wingless (WNT)/β-catenin signaling through inhibition of the Wilms' tumor gene on the X chromosome (WTX) and subsequent promotion of epithelial dysplasia of the nasopharynx and oropharynx but not tumorigenesis; downregulation of E-cadherin expression was also observed in these mice (240). The study has indicated that a reduction in WTX expression caused by LMP1 is associated with epithelial dysplasia *via* regulation of the WNT/β-catenin pathway and E-cadherin expression.

LMP1 also has effects on inhibition of p53-mediated apoptosis in stable epithelial cells expressing the *A20* gene (78). Another study has indicated that LMP1 can activate MAPK kinases to modulate p53 phosphorylation (167). The *p53* gene mutation rate was significantly lower in NPC than in other cancers (192, 238, 282). Dominant-negative mutations in the DNA-binding domain of the *p53* gene are rarely detected in NPC (107). An immunohistochemical study has shown significant p53 overexpression in approximately 82% of primary nasopharyngeal biopsy specimens (2). These results indicate that inhibition of p53-mediated apoptosis by LMP1 was probably responsible for p53 overexpression and the lack of *p53* gene mutations in EBV-positive NPC.

The *LMP2* transcription unit generates two alternatively spliced mRNAs that encode two functionally distinct proteins, LMP2A and LMP2B, which differ at their amino terminus (336). Only LMP2A has a 119-amino-acid amino-terminal cytoplasmic domain (79). This domain contains eight tyrosine residues with two of the tyrosines forming an immunoreceptor tyrosine-based activation motif (24, 193, 248). Immunohistochemical analysis of paraffin-embedded NPC biopsy samples with the LMP2A monoclonal antibody has shown that LMP2A mainly localizes to the tumor cell membrane and is expressed in invasive tumor front cells (142). Amino-terminal tyrosine phosphorylation of LMP2A has been shown to be necessary for association with Lyn and Syk protein-tyrosine kinases (210). In addition, tyrosine phosphorylation of LMP2A in epithelial cells can be triggered by cell adhesion to extracellular matrix proteins *via* the C-terminal Src kinase (257). *LMP2A* mRNA has been detected in all NPC specimens (21), whereas protein expression could be detected in only approximately 46% of these specimens (102). Stable expression of LMP2A in squamous epithelial cells was shown to promote cell spreading and migration in the extracellular matrix that required tyrosine kinase activity (5). Similarly, using primary epithelial cells from tonsil tissue that overexpress LMP2A, an increase in cell invasion and extracellular matrix receptor integrin-α-6 (ITGα6) has been demonstrated, therefore suggesting that LMP2 expression may contribute to the invasive process of NPC cells (233). Functional studies have indicated that LMP2 can induce the activation of PI3K/Akt, Syk

tyrosine kinase, NF-κB, signal transducer and activators of transcription (STAT), and β-catenin pathways, thereby resulting in the inhibition of cell differentiation and the induction of cell migration in epithelial cells (196, 212, 256, 279, 284). A recent report has demonstrated that the ectopic expression of LMP2A in NPC cells induces epithelial-mesenchymal transition and increases the self-renewal capacity of cancer stem-like cells, which supports the concept that LMP2A functions as a potential inducer of tumor initiation and cellular invasiveness in NPC cells (142).

EBNA1 is a DNA-binding nuclear phosphoprotein that consists of two major functional domains, a carboxy-terminal DNA-binding domain and an amino-terminal chromosome tethering domain (159, 305). Both domains are separated by a glycine-alanine repeat sequence (GAr) that has been identified as a *cis*-acting inhibitor of MHC-class I-restricted antigen presentation (161). It has been recently shown that the GAr suppresses the presentation of MHC-class I-restricted antigen through the entire mRNA direct targeting of the mRNA translation initiation process (7). These results suggest that EBNA1 interferes with virus-encoded protein presentation by the MHC-class I-restricted pathway. Furthermore, EBNA1 expression is able to induce growth inhibition by inducing G_2/M phase arrest in human squamous epithelial cell lines (but not epithelial cell lines of glandular origin) (128). These results further indicate that the induction of the cytotoxicity effects in human squamous epithelial cells by EBNA1 is associated with EBNA1 degradation and processing. This leads to the endogenous degradation of EBNA1 in human squamous epithelial cells resulting from a specific cytotoxic T lymphocyte response (128), which suggests the possibility of the efficient EBV infection in malignant squamous epithelial cells but not in normal epithelial cells.

The dimerization and DNA-binding domains of EBNA1 have previously been shown to be located at the carboxy-terminal domain, amino acids 459 to 487 (36). The DNA-binding domain is essential for EBNA1 binding to the origin of plasmid replication (*ori*P), which is required for the replication and maintenance of the episomal EBV genome (237). The phosphorylation of EBNA1 is crucial for its transcriptional activity and the stability of EBV plasmids in virus-infected cells (62). The formation of the *ori*P-EBNA1 complex is also required for transactivation of the EBV C promoter (Cp), which is involved in the rearrangement of chromatin structure induced by EBNA1 (339). Moreover, recruitment of the histone H2B deubiquitylating complex to the *ori*P can be regulated by EBNA1 (254). EBNA1 has also been reported to upregulate LMP1 promoter activity (81). The effect of EBNA1 in promoting tumorigenesis has been found to increase genomic instability and DNA damage by inducing production of reactive oxygen species (ROS) (89). Stable complex formation between EBNA1 and the nucleosome assembly proteins, NAP1 and TAF-I, can affect cellular DNA replication (309). The EBNA1 portion of the EBNA1-binding protein 2 complex was shown to promote its interaction with mitotic chromosomes (218). A recent study has demonstrated that high-level expression of the EBNA1 protein in NPC cells interferes with mitotic segregation (275).

EBNA1 enhances the activity of the AP-1 transcription factor by binding to the promoter regions of c-Jun and activating transcription factor 2 (222). Elevated expression of the AP-1 targets IL-8, VEGF, and hypoxia-inducible factor-1alpha, has been observed in EBNA1-expressing NPC cells (222). EBNA1 also induces EBV-encoded RNA (EBER) expression

through the induction of EBER-associated cellular transcription factors, ATF-2 and c-Myc, in an EBV-infected human adenocarcinoma cell line derived from nasopharynx (226). EBNA1 expression also influences the expression of genes involved in the dysregulation of oncogenic pathways in epithelial 293 cell lines (25) and decreases the expression levels and nuclear localization of phosphate-NF-κB in NPC cell lines (296). Survivin is a member of the family of inhibitors of apoptosis protein (IAP). It is expressed in a number of human cancer cells but not in normal adult tissue (6). The anti-apoptotic function of survivin involves its ability to block the activity of caspase-3 and caspase-7 (269, 285). Dysregulation of survivin expression in NPC cells affects cell viability and induces apoptosis (266, 333). More recent studies have demonstrated that EBNA1 forms a complex with SP1 or SP1-like protein at the *cis*-element of the survivin promoter and thereby regulates survivin expression. Results have further demonstrated an increase in resistance to apoptosis through upregulation of survivin expression by EBNA1 (197). Thus, EBNA1 may regulate multiple cellular signaling pathways to control cell proliferation and survival, thereby promoting the development of NPC.

EBNA2 is a nuclear phosphoprotein lacking sequence-specific DNA-binding activity. It was found to associate with the chromatin and nuclear matrix (32) and has been identified previously as a transcriptional regulator of the expression of cellular and EBV genes including *AML-2* (*RUNX3*), *CD21*, *CD23*, c-*MYC*, *EBI-1*, *Hes-1*, *LMP1*, and *LMP2A* (19, 44, 51, 80, 85, 130, 152, 255, 278, 303, 304). Their mechanism of regulation is suggested by the binding of EBNA2 with cellular transcription factors RBPJ, CBF-2/AUF1 or Spi-1/PU.1 to specific response elements of each promoter (137). Recent work has demonstrated that human endogenous retrovirus K nuclear protein NP9 can bind to EBNA2 and negatively regulate the EBNA2-mediated activation of the EBV viral C- and LMP2A promoters (88). The carboxy-terminal acidic activation domain of EBNA2 is required for direct interaction with the CSL family of DNA-binding protein (CBF1) and participates in EBNA2-mediated gene transcription (306). EBNA2 has been shown to be able to functionally replace the intracellular region of Notch in the regulation of gene expression of B cells by targeting CBF1 and localizing the coactivators p300, PCAF, and CBP to the promoter (109, 122, 250, 280, 306, 321). In normal cells, CBF-1 is bound by Notch to regulate the expression of cellular genes involved in cell proliferation (14, 187). Lee *et al.* have demonstrated that like Notch, EBNA2 can block orphan nuclear receptor Nur77-mediated apoptosis through interaction between its amino acids 123–147 conserved domain and Nur77 (158). Although Notch signaling functions have been linked to a variety of cellular processes such as adhesion, differentiation, cell proliferation, apoptosis, epithelial to mesenchymal transition, migration, and angiogenesis, Notch can also function as an oncogene or a tumor suppressor in cancer development (14). The biological effect of Notch signaling depends on the type and fate of the cell (244). An immunocytochemical study of NPC biopsies using antibodies against the activated form of Notch1 and Hes-1 have demonstrated that Notch signaling is activated in human primary NPC cells (345). High expression levels of both Notch and Notch ligand (Jagged1) were detected in human head and neck and breast cancer samples, and patients harboring these tumors showed poor prognosis (174, 246). Recent studies have indicated that activation of Notch signaling contributes to the survival and proliferation of several types of cancer entities, such as human non-small cell lung cancer (40), human tongue carcinoma (343), human leukemia cells (164), human gastric cancer (332), and human colon adenocarcinoma (247). These findings suggest that EBNA2 mimics the effects of Notch,

thereby upregulating Notch signaling activity to maintain cell proliferation and survival of NPC.

3. The inhibitory mechanisms of natural compounds against NPC survival and metastasis signaling

The prognosis of NPC is based on the size of the tumor and the spread of the cancer to the lymph nodes or to other organs. Traditionally, this type of cancer is treated either with surgery, radiotherapy, chemotherapy, immunotherapy, or other methods. The main treatment of NPC is radiotherapy, usually given in combination with chemotherapy drugs (315). However, NPC exhibits a high incidence of lymph node spread and distant metastasis that is correlated with a poor prognosis, even during the use of radiation therapy and chemotherapy (43, 260, 326). The currently available chemotherapy agents for cancer treatment are usually toxic to normal cells, often resulting in adverse side effects such as temporary hair loss, nausea and vomiting. The use of chemopreventative agents is now regarded as a promising strategy against cancer development (10). Cancer development and progression is a complex process that involves the dysregulation of multiple signaling pathways and molecular changes. These events may contribute to tumor growth, invasion, metastasis, and immune evasion (27). In the search for new substances with anti-tumoral effects, many natural, dietary, or synthetic substances have been shown to inhibit carcinogenesis *in vitro* and *in vivo* through the targeting of specific proteins or modulating signal transduction pathways (133).

Aloe-emodin (AE; 1,8-dihydroxy-3-(hydroxymethyl)-anthraquinone), which is isolated from the rhizomes of *Rheum palmatum*, has been shown to inhibit cell growth and induce apoptosis *in vitro* in several cancer cell lines, such as human cervical carcinoma HeLa (91), rat C6 glioma carcinoma (209), human hepatoma HepG2 (147, 180), human neuroblastoma SJ-N-KP and SK-N-BE(2c) (232), human lung squamous carcinoma CH27 (155), and human lung non-small cell carcinoma H460 cell lines (331). Animal studies using severe combined immune deficiency (SCID) mice have shown that AE selectively inhibited the growth of human neuroectodermal tumors but not normal fibroblasts and hematopoietic progenitor cells (231). The results of a recent *in vitro* study have shown that high concentrations (up to 100 μM) of AE exhibit low cytotoxicity in normal human fibroblasts WI-38, Detroit 551, and MRC-5 cells (178), which are consistent with evidence provided by other reports in other normal cells including the proximal tubule-derived opossum kidney OK cell line, the human keratinocyte HACAT cell line, the human airway epithelial BEAS-2B cell line (195), and rat primary astrocytes (209). AE also inhibited the proliferation of both human umbilical vein endothelial and bovine aortic endothelial cells (28). These results suggest that the effect of AE is highly specific for cancer cells and endothelial cells, thereby supporting the concept that AE could be a potent cancer chemotherapeutic and anti-angiogenic agent. Apoptosis is a physiological mechanism involved in the elimination of malignant or cancer cells without eliciting damage to normal cells or surrounding tissues. Thus, the induction of apoptosis exclusively in target cells is an attractive approach for anticancer therapy (133). It is now recognized that the mitochondria play a crucial role in the regulation of cell death, which seems to be the main target for apoptosis induction in response to a variety of stress stimuli, such as growth factor withdrawal and chemopreventative components (133). Bcl-2 and Bcl-X_L have been well characterized as important regulators of apoptosis in response to a wide

range of stimuli, including chemopreventative components (1, 272). In addition, the ability of Bcl-2 and Bcl-X_L to suppress the mitochondrial-mediated pathway of apoptosis is well known (86, 87, 310). Overexpression of either Bcl-2 or Bcl-X_L in tumor cells has been shown to be associated with poor prognosis in many human cancers (52) and contributes to the development of resistance to chemotherapy and radiation treatment (127, 261). Although EBV LMP1 can block apoptosis in B cells by upregulating Bcl-2 expression (99), knockdown of *Bcl-X_L* by siRNA has been shown to induce apoptosis in NPC cells (166), thereby suggesting that Bcl-X_L is an important effector of resistance to apoptosis in NPC cells. A recent *in vitro* NPC cell study has shown that increasing levels of cyclin B1 bound to cyclin-dependent kinase 2 contributes to 60 μM AE-induced G_2/M phase cell cycle arrest (178). AE (60 μM)-induced apoptosis of NPC-TW076 and NPC-TW039 cells was mediated by elevated Bax and decreased Bcl-X_L expression, which was confirmed by ectopic expression of Bcl-X_L, although it was not observed in Bcl-2 or small interfering RNA (siRNA)-mediated attenuation of Bax suppressing AE-induced apoptotic cell death (178). The reduction of mitochondrial membrane potential and the increase in cellular Ca^{2+} content, ROS production, and apoptosis induced by AE were attenuated by treatment with either cyclosporin A or the caspase-8 inhibitor Z-IETD-FMK. Further analysis has shown that suppression of caspase-8 with the specific inhibitor Z-IETD-FMK inhibited AE-induced activation of Bax, the cleavage of Bid, the translocation of tBid to the mitochondria, and the release of cytochrome *c*, apoptosis-inducing factor and endonuclease G from the mitochondria, and subsequent apoptosis. These results indicate that caspase-8-mediated activation of the mitochondrial death pathway plays a critical role in 60 μM AE-induced apoptosis of NPC cells (178). A more recent investigation has revealed that 40 μM AE significantly inhibits NPC cell growth through cell cycle arrest at the S-G_2/M phase, which is associated with increased levels of cyclin B1 bound to Cdk1 but not the apoptotic process (179). Gene silencing of MMP-2 mediated by siRNA inhibits NPC cell invasion, thereby demonstrating the involvement of MMP-2 in the NPC invasion process (179). Using siRNA against p38 MAPK, the p38 MAPK inhibitor SB203580, NF-κB inhibitors N-*p*-tosyl-$_L$-phenylalanine chloromethyl ketone and pyrrolidine dithiocarbamate, transient ectopic expression of wild type NF-κB, a MMP-2 promoter activity assay, and an NF-κB-dependent reporter assay it has been further demonstrated that 40 μM AE inhibits the invasion of NPC cells by reducing the expression of MMP-2, likely through the inhibition of the p38 MAPK-NF-κB pathway, and that NF-κB activity is involved in regulating the expression of MMP-2 and VEGF through the p38 MAPK-dependent pathway (179). The reason that NPC cells are more sensitive to 60 μM than 40 μM AE for the induction of apoptosis remains unclear. AE was found to induce DNA single-strand breaks and nuclear condensation through the generation of ROS, leading to apoptosis in the human lung non-small cell carcinoma H460 cell line (156). Previous studies have also reported that the release of the nuclear protein nucleophosmin from the nucleus to the cytosol is associated with AE-induced cell apoptosis (157). These observations led to the speculation that nuclear DNA might be a target of AE during AE-induced apoptotic cell death. The results from another group have shown that AE displayed an affinity for nuclear DNA; disrupted chromatin structure and DNA template function were detected in susceptible cell lines upon treatment with a high dose of AE (214). The participation of ROS in cancer cell apoptosis stimulated by chemotherapeutic agents through the induction of DNA damage has been investigated for several decades (154). Oxidative damage to DNA is a result of the interaction of DNA with ROS. AE contains

a quinone structure that was predicted to have the ability to induce ROS production, which may play a role in the induction of cancer cell apoptosis (156). Consistent with the data presented by Lee *et al*. (156), an increase in intracellular ROS levels was observed when apoptosis was induced in NPC cells using 60 μM AE (178). However, apoptosis, DNA damage, and increases in ROS levels were not detected in the same cells treated with 40 μM AE, therefore suggesting that different concentrations of AE could differentially modulate the expression of cellular genes that are involved in cell growth, apoptosis, and cell invasion in different types of cancer cells (179).

Berberine (2,3-Methylenedioxy-9,10-dimethoxyprotoberberine chloride), is an isoquinoline plant alkaloid isolated from the roots, rhizomes, and stem bark of *Hydrastis Canadensis*, *Coptis chinensis*, *Berberis aquifolium*, *Berberis vulgaris*, *Berberis aristata*, and *Berberis thunbergii* (143). It is traditionally used in China to treat gastrointestinal diseases such as dysentery and diarrhea. Clinical studies conducted in 1985 and 1987 have shown that berberine is considered to be a non-toxic alkaloid and is useful for the treatment of bacterial diarrhea (136, 242). Berberine also has anti-fungal (76), anti-human immunodeficiency virus (HIV) infection (53), and anti-protozoan properties (131). Berberine-induced apoptosis of cancer cells likely involves the enhanced activities of the mitochondria-dependent signaling events or Fas/FasL signaling as implied by the loss of mitochondrial membrane potential ($\Delta\psi_m$) and the release of cytochrome *c* in human colonic carcinoma SW620 (118), promonocytic U937 (121), leukemia HL-60 (169), and oral cancer HSC-3 cell lines (170); the decrease of Bcl-X_L and Bcl-2 expression in human epidermoid carcinoma A431 cell lines (204); and the generation of ROS and activation of FasL in human colonic carcinoma SW620 cell lines (111). Other signaling pathways have also been shown to be required for berberine-induced apoptosis, including the JNK/p38 MAPK (111), p53-dependent ATF3 (235), ER stress (172), and NF-κB pathways (227). In addition to apoptosis induction, berberine has also shown potent anti-angiogenic effects on the inhibition of tumor-induced angiogenesis and MMP-1, -2, and -9 expression (313). Berberine inhibits the invasion of human lung cancer A549 cells *in vitro* by decreasing the production of the urokinase-plasminogen activator and MMP-2 (234). The inhibition of cell invasion by berberine through downregulation of MMP-2 and -9 expression was also observed in human breast cancer MDA-MB-231 (139), gastric cancer SNU-5 (173), glioma U-87 (184), and tongue squamous carcinoma SSC-4 cell lines (106). Moreover, oral administration of berberine in mice significantly inhibited the spontaneous mediastinal lymph node metastasis of Lewis lung carcinoma into the lung parenchyma (211). In NPC cells, berberine inhibits the intracranial invasion of tumors in nude mice injected with NPC 5-8F cells through the induction of NM23-H1 expression (190). Other investigations have also found that berberine exerts a potent *in vitro* anti-invasive effect on the NPC 5-8F cell line through the reduction of filopodia formation (287). Significant inhibition of tumor metastasis to the lymph nodes and a decrease in Ezrin phosphorylation at threonine 567 (Thr^{567}) in metastatic samples were observed in nude mice injected *via* intravenous (tail vein) injection with NPC 5-8F cell lines and treated with berberine. The authors further demonstrated that berberine-induced reduction in filopodia formation was associated with decreased Rho kinase-mediated Ezrin phosphorylation at Thr^{567} (287).

Curcumin (1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a polyphenol isolated from the rhizomes of *Curcuma longa*, which has demonstrated low toxicity in

humans (299). It has been shown to inhibit cell growth and induce apoptosis *in vitro* in several cancer cell lines, such as breast cancer; human basal cell carcinoma BCC-1/KMC (123); biliary cancer KKU100, KKU-M156 and KKU-M213 (239); colon cancer HT-29 and HCT116 (124, 129, 314); esophageal adenocarcinoma OE33 (95); hepatoma HepG2 (26, 124, 308); myeloid leukemia U937 and HL60 (252); liposarcoma SW872 (307); lung adenocarcinoma A549 (38, 39, 340, 341); lung squamous carcinoma H520 (258); medulloblastoma MED (8); neuroblastoma Lan-5, SK-N-SH, and Kelly (77); esophageal cancer OE21 and OE33 (223); prostate carcinoma PC3 (105); salivary adenoid cystic carcinoma SACC-83 (283); and small cell lung cancer NCI-H446 and PC-9 cell lines (249, 322, 328). *In vitro* cell culture studies have shown that curcumin can also suppress the migration and invasion of human cancer cell lines, such as breast carcinoma MDA-MB-231 and MDA-MB-468 (217, 277); colon cancer HCT116 (213, 311); gastric cancer BGC823 (23); glioblastoma A-172, MZ-18, MZ-54, MZ-256, and MZ-304 (259); hepatocellular carcinoma SK-Hep-1 (175); lung adenocarcinoma A549 and CL1-5 (33, 182); medulloblastoma MED (8, 34); and prostate cancer PC-3 cell lines (100). Animal studies using SCID mice have shown that curcumin selectively inhibits the growth of human breast, colon, gastric, liver, ovarian, and brain cancers but not normal tissues (144). Curcumin also induces apoptosis and cell growth arrest in cancer cells by modulating the expression of cell cycle regulatory factors, inhibiting the transcriptional regulation of NF-κB, and activating the activities of caspases (144). In addition, curcumin blocks angiogenesis and metastasis by modulating the signaling pathways involved in the expression of growth factors and cell adhesion molecules (144). Although the anti-cancer mechanisms of curcumin that are involved in the modulation of signal transducer and activator pathways to interrupt the process of carcinogenesis are diverse (144, 317), it exhibits potential as an anti-cancer chemotherapeutic agent for the treatment of many human cancers. Curcumin's inhibitory effect on NPC cell migration has been demonstrated to increase the expression of E-cadherin (320). Conversely, curcumin exerts an apoptotic effect on NPC cells through the decrease in the relative ratio of Bcl-2 to Bax, dysfunction of the mitochondria, cytochrome *c* release, and the activation of caspase-9 and caspase-3, therefore indicating that the mitochondrial death pathway is involved in the curcumin-induced apoptosis of NPC cells (145).

Epigallocatechin gallate (EGCG), also known as epigallocatechin 3-gallate, is a polyphenol isolated from green tea leaves (329). EGCG has been reported to possess several biochemical and pharmacological properties, which include anti-HIV and HCV infection activity (49, 94, 318, 325), reduction of Sjögren's syndrome in murine models (83, 110), prevention of Alzheimer's and Parkinson's diseases (203), anti-obesity effects on mice and humans (41, 319), anti-oxidant activity (75, 104, 293, 348), and anti-neoplastic activity (135, 262). The cancer-preventive effects of EGCG have been proposed to suppress the transformative, hyperproliferative, and inflammatory processes that are involved in carcinogenesis (288). The anti-oxidant activity of EGCG is thought to play an important role in the induction of apoptotic signaling pathways in cancer cells (104, 151), such as human hepatoma Hepa1c1c7 (151), cervical cancer HeLa (274), chondrosarcoma (330), lung cancer H1299 (165), and glioblastoma T98G and U87MG cell lines (56). EGCG displays anti-oxidant activity due to the presence of phenolic groups in the molecule that are sensitive to oxidation (151, 215). However, the molecular targets of EGCG in the inhibition of cancer growth, metastasis, and angiogenesis are diverse. EGCG also affects various signaling pathways (273). Yan *et al*. have showed that EGCG inhibits the growth of NPC CNE-LMP1 cell lines by suppressing

LMP-1-induced NF-κB activity *via* the inhibition of inhibitory protein IkappaBα phosphorylation (327). LMP-1-promoted activator protein-1 (AP-1) transcriptional activity, the nuclear translocation of JNK, the phosphorylation of c-Jun, promoter activity and phosphorylation of EGFR, and cyclin D expression in NPC CNE-LMP1 cell lines were also suppressed by EGCG (327, 346), thereby suggesting that EGCG suppresses LMP-1-mediated NPC cell growth through the inhibition of AP-1 and NF-κB signaling pathways.

Osajin (5-hydroxy-3-(4-hydroxyphenyl)-8,8-dimethyl-6-(3-methylbut-2-enyl) pyrano[2,3-h]chromen-4-one;5-Hydroxy-3-(4-hydroxyphenyl)-8,8-dimethyl-6-(3-methyl-2-butenyl)-4H,8H-benzo[1,2-b:3,4-b']dipyran-4-one) is a prenylated isoflavone originally isolated from the fruit of *Maclura pomifera* (302). The biological activity of osajin is thought to have anti-oxidant properties that can attenuate the myocardial dysfunction provoked by ischemia reperfusion in rats (72). It has been shown to inhibit the growth of six types of human cancer cell lines *in vitro*, including renal carcinoma ACHN, lung adenocarcinoma NCI-H23, prostate cancer PC-3, breast cancer MDA-MB-231, melanoma LOX-IMVI, and colon carcinoma HCT-15 cell lines (276). Osajin has demonstrated low toxicity in human hepatocytes compared with human cancer cell lines (276). However, the mechanism of growth inhibition in human cancer cells by osajin is not clear. A recent study has shown that the activation of the death receptor Fas/FasL, mitochondrial death, and endoplasmic reticulum (ER) stress signaling pathways are involved in the apoptosis of NPC cells induced by osajin (114).

Resveratrol (3,4,5-trihydroxy-trans-stilbene), a polyphenol phytoalexin, is widely present in foods such as grapes, berries, peanuts, and other plant sources. It has been shown to possess diverse biochemical and physiological functions, including anti-aging (9), anti-platelet aggregation (201, 312), anti-inflammatory (268), cardioprotection (15, 116, 119), and estrogenic properties (160). Experimental results from animal models have revealed that the anti-inflammatory properties of resveratrol control the development of arthritis (66), pancreatitis (198, 199), and colitis (153). Although resveratrol is a poor ROS scavenger *in vitro*, it behaves as a potent anti-oxidant due to its ability to increase the synthesis of nitric oxide *in vivo* (22, 54, 96, 324). During the last decade, resveratrol has been shown to have strong anti-carcinogenic activity in a wide range of human cancer cell lines, such as anaplastic large-cell lymphoma SR-786 (141), breast cancer MCF-7 and MDA-MB231 (267), chronic myeloid leukemia K562 (132), colon cancer HT-29 (298), diffuse large B cell lymphoma DLBCL (117), glioblastoma A172 and T98G (171), glioma U87 (69), hepatocellular carcinoma Huh-7 (168), leukemia HL-60 (163), leukemic monocyte lymphoma U937 (90), lung adenocarcinoma ASTC-a-1 (344), medullary thyroid cancer (291), melanoma YUZAZ6 and M14 (290), neuroblastoma B65 (236), non-small cell lung cancer A549 (188, 189), and prostate cancer LNCaP cell lines (37). Resveratrol also been shown to suppress the growth of cancer *in vivo* such as colon (55, 316), hepatocellular (13), lung (200), mammary (31), and skin cancer (82). *In vitro* and *in vivo* studies have led to several clinical trials to evaluate resveratrol's potential for cancer chemoprevention and chemotherapy, including the prevention and treatment of colon cancer (12, 228, 229). The anti-cancer activity of resveratrol has been attributed to the induction of apoptotic cell death *via* its anti-proliferation and anti-invasion properties (216, 228). Its mechanism of action and molecular targets are diverse (216, 228). In human NPC TWP4 cells, treatment with resveratrol induced apoptosis and was associated with the induction of multiple apoptotic pathways, including

death receptor, mitochondria, and ER stress pathways (113). Chow *et al.* have suggested that ΔNp63 is a molecular target of resveratrol-induced apoptosis in NPC-TW076 and NPC-TW039 cell lines (47).

Rhein (4, 5-dihydroxyanthraquinone-2-carboxylic acid), a major constituent in the rhizome of *rhubarb*, shows anti-oxidant and free radical scavenging effects similar to AE, which has been shown to play an important role in the inhibition of carcinogenesis (202). In addition to the inhibitory effects on the process of hepatic fibrosis in rats (92), synthesis of aggrecan and tissue inhibitor of metalloproteinases-1 in cultured human chondrocytes (251), activation of the MEK/ERK pathway induced by IL-1β in chondrocytes cultured in hypoxia (206), and fungal infection of plants (349), rhein also protects the dysfunction of human umbilical endothelium ECV-304 cell lines induced by transforming growth factor β1 through the inhibition of plasminogen activator inhibitor-1 (350). *In vivo* experimental results have shown that rhein has the ability to suppress the growth of tumor cells in rat liver (208). The anti-angiogenic property of rhein has been characterized in a zebrafish model (97, 98). Interestingly, rhein lysinate showed a synergistic increase in the anti-tumor activity of Taxol in mice (185, 186). It has also been shown to influence cell growth and apoptosis in several human cancer cell lines such as cervical cancer Ca Ski (120), colon adenocarcinoma CaCo-2 (245), glioma U-373MG (74), hepatocellular carcinoma BEL-7402 (265), hepatoblastoma HepG2 (146), lung cancer A549 (108), promyelocytic leukemia HL-60 (181), and human tongue SSC-4 cancer cell lines (42, 150). Moreover, rhein can inhibit the uptake and glycolysis of glucose and protein synthesis in cancer cells (29, 30, 73). Although it has been reported that increased expression of p53, p21, and CD96 may be responsible for the apoptosis of human hepatoblastoma HepG2 cell lines induced by rhein in a similar manner to AE (146), the molecular mechanisms by which rhein influences cell growth and apoptosis of cancer cells differ from AE. In NPC-TW076 and -TW039 cells, rhein induces apoptotic cell death *via* the ER stress and Ca^{2+}-dependent mitochondrial death pathways. The induction of ER stress by rhein correlated with the augmented expression of glucose-regulated protein 78, PKR-like ER kinase, activating transcription factor 6 and CCAAT/enhancer-binding protein homologous protein as well as the cleavage of procaspase-12 (176). In addition, NPC cells exposed to rhein have demonstrated a dramatic increase in mitochondrial dysfunction, including the loss of $\Delta\psi_m$ and the release of cytochrome *c* and apoptosis-inducing factor (176). Lin *et al*. have further demonstrated that rhein inhibits the invasion of NPC cells by suppressing the expression of MMP-9 and VEGF *via* the NF-κB signaling pathway (177).

4. Conclusion

Although numerous studies have attempted to define the initiation and development of NPC, the exact mechanism remains controversial. The understanding of the signaling pathways and regulatory mechanisms leading to NPC carcinogenesis will provide sufficient information for the identification of potent chemopreventive agents against NPC. Based on the studies discussed here, there is strong evidence that the anti-NPC activities of AE, berberine, curcumin, osajin, resveratrol, and rhein involve the inhibition of cell growth and metastasis as well as the induction of apoptosis through modulation of multiple signaling pathways and molecular factors. Further studies should attempt to analyze other active components or chemotherapeutic agents and integrate with *in vivo* studies and clinical trials to evaluate the applicability of these natural compounds in NPC prevention and treatment.

5. References

[1] Adams, J. M., and S. Cory. 2007. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene 26:1324-37.

[2] Agaoglu, F. Y., Y. Dizdar, O. Dogan, C. Alatli, I. Ayan, N. Savci, S. Tas, N. Dalay, and M. Altun. 2004. P53 overexpression in nasopharyngeal carcinoma. In Vivo 18:555-60.

[3] Aggarwal, B. B. 2004. Nuclear factor-kappaB: the enemy within. Cancer Cell 6:203-8.

[4] Al-Nedawi, K., B. Meehan, R. S. Kerbel, A. C. Allison, and J. Rak. 2009. Endothelial expression of autocrine VEGF upon the uptake of tumor-derived microvesicles containing oncogenic EGFR. Proc Natl Acad Sci U S A 106:3794-9.

[5] Allen, M. D., L. S. Young, and C. W. Dawson. 2005. The Epstein-Barr virus-encoded LMP2A and LMP2B proteins promote epithelial cell spreading and motility. J Virol 79:1789-802.

[6] Altieri, D. C. 2008. New wirings in the survivin networks. Oncogene 27:6276-84.

[7] Apcher, S., C. Daskalogianni, B. Manoury, and R. Fahraeus. 2010. Epstein Barr virus-encoded EBNA1 interference with MHC class I antigen presentation reveals a close correlation between mRNA translation initiation and antigen presentation. PLoS Pathog 6:e1001151.

[8] Bangaru, M. L., S. Chen, J. Woodliff, and S. Kansra. 2010. Curcumin (diferuloylmethane) induces apoptosis and blocks migration of human medulloblastoma cells. Anticancer Res 30:499-504.

[9] Baur, J. A., K. J. Pearson, N. L. Price, H. A. Jamieson, C. Lerin, A. Kalra, V. V. Prabhu, J. S. Allard, G. Lopez-Lluch, K. Lewis, P. J. Pistell, S. Poosala, K. G. Becker, O. Boss, D. Gwinn, M. Wang, S. Ramaswamy, K. W. Fishbein, R. G. Spencer, E. G. Lakatta, D. Le Couteur, R. J. Shaw, P. Navas, P. Puigserver, D. K. Ingram, R. de Cabo, and D. A. Sinclair. 2006. Resveratrol improves health and survival of mice on a high-calorie diet. Nature 444:337-42.

[10] Benner, S. E., and W. K. Hong. 1993. Clinical chemoprevention: developing a cancer prevention strategy. J Natl Cancer Inst 85:1446-7.

[11] Billaud, M., P. Busson, D. Huang, N. Mueller-Lantzch, G. Rousselet, O. Pavlish, H. Wakasugi, J. M. Seigneurin, T. Tursz, and G. M. Lenoir. 1989. Epstein-Barr virus (EBV)-containing nasopharyngeal carcinoma cells express the B-cell activation antigen blast2/CD23 and low levels of the EBV receptor CR2. J Virol 63:4121-8.

[12] Bishayee, A. 2009. Cancer prevention and treatment with resveratrol: from rodent studies to clinical trials. Cancer Prev Res (Phila) 2:409-18.

[13] Bishayee, A., and N. Dhir. 2009. Resveratrol-mediated chemoprevention of diethylnitrosamine-initiated hepatocarcinogenesis: inhibition of cell proliferation and induction of apoptosis. Chem Biol Interact 179:131-44.

[14] Bolos, V., J. Grego-Bessa, and J. L. de la Pompa. 2007. Notch signaling in development and cancer. Endocr Rev 28:339-63.

[15] Bradamante, S., L. Barenghi, F. Piccinini, A. A. Bertelli, R. De Jonge, P. Beemster, and J. W. De Jong. 2003. Resveratrol provides late-phase cardioprotection by means of a nitric oxide- and adenosine-mediated mechanism. Eur J Pharmacol 465:115-23.

[16] Brooks, L., Q. Y. Yao, A. B. Rickinson, and L. S. Young. 1992. Epstein-Barr virus latent gene transcription in nasopharyngeal carcinoma cells: coexpression of EBNA1, LMP1, and LMP2 transcripts. J Virol 66:2689-97.

[17] Burgos, J. S. 2005. Involvement of the Epstein-Barr virus in the nasopharyngeal carcinoma pathogenesis. Med Oncol 22:113-21.

[18] Burgos, J. S., and F. J. Vera-Sempere. 2000. Immunohistochemical absence of CD21 membrane receptor in nasopharyngeal carcinoma cells infected by Epstein-Barr virus in Spanish patients. Laryngoscope 110:2081-4.

[19] Burgstahler, R., B. Kempkes, K. Steube, and M. Lipp. 1995. Expression of the chemokine receptor BLR2/EBI1 is specifically transactivated by Epstein-Barr virus nuclear antigen 2. Biochem Biophys Res Commun 215:737-43.

[20] Busson, P., C. Keryer, T. Ooka, and M. Corbex. 2004. EBV-associated nasopharyngeal carcinomas: from epidemiology to virus-targeting strategies. Trends Microbiol 12:356-60.

[21] Busson, P., R. McCoy, R. Sadler, K. Gilligan, T. Tursz, and N. Raab-Traub. 1992. Consistent transcription of the Epstein-Barr virus LMP2 gene in nasopharyngeal carcinoma. J Virol 66:3257-62.

[22] Cadenas, S., and G. Barja. 1999. Resveratrol, melatonin, vitamin E, and PBN protect against renal oxidative DNA damage induced by the kidney carcinogen KBrO3. Free Radic Biol Med 26:1531-7.

[23] Cai, X. Z., J. Wang, X. D. Li, G. L. Wang, F. N. Liu, M. S. Cheng, and F. Li. 2009. Curcumin suppresses proliferation and invasion in human gastric cancer cells by downregulation of PAK1 activity and cyclin D1 expression. Cancer Biol Ther 8:1360-8.

[24] Cambier, J. C. 1995. New nomenclature for the Reth motif (or ARH1/TAM/ARAM/YXXL). Immunol Today 16:110.

[25] Canaan, A., I. Haviv, A. E. Urban, V. P. Schulz, S. Hartman, Z. Zhang, D. Palejev, A. B. Deisseroth, J. Lacy, M. Snyder, M. Gerstein, and S. M. Weissman. 2009. EBNA1 regulates cellular gene expression by binding cellular promoters. Proc Natl Acad Sci U S A 106:22421-6.

[26] Cao, J., Y. Liu, L. Jia, H. M. Zhou, Y. Kong, G. Yang, L. P. Jiang, Q. J. Li, and L. F. Zhong. 2007. Curcumin induces apoptosis through mitochondrial hyperpolarization and mtDNA damage in human hepatoma G2 cells. Free Radic Biol Med 43:968-75.

[27] Carbone, M., and H. I. Pass. 2004. Multistep and multifactorial carcinogenesis: when does a contributing factor become a carcinogen? Semin Cancer Biol 14:399-405.

[28] Cardenas, C., A. R. Quesada, and M. A. Medina. 2006. Evaluation of the anti-angiogenic effect of aloe-emodin. Cell Mol Life Sci 63:3083-9.

[29] Castiglione, S., M. Fanciulli, T. Bruno, M. Evangelista, C. Del Carlo, M. G. Paggi, A. Chersi, and A. Floridi. 1993. Rhein inhibits glucose uptake in Ehrlich ascites tumor cells by alteration of membrane-associated functions. Anticancer Drugs 4:407-14.

[30] Castiglione, S., M. G. Paggi, A. Delpino, M. Zeuli, and A. Floridi. 1990. Inhibition of protein synthesis in neoplastic cells by rhein. Biochem Pharmacol 40:967-73.

[31] Chatterjee, M., S. Das, M. Janarthan, H. K. Ramachandran, and M. Chatterjee. 2011. Role of 5-lipoxygenase in resveratrol mediated suppression of 7,12-

dimethylbenz(alpha)anthracene-induced mammary carcinogenesis in rats. Eur J Pharmacol 668:99-106.

[32] Chau, C. M., and P. M. Lieberman. 2004. Dynamic chromatin boundaries delineate a latency control region of Epstein-Barr virus. J Virol 78:12308-19.

[33] Chen, H. W., J. Y. Lee, J. Y. Huang, C. C. Wang, W. J. Chen, S. F. Su, C. W. Huang, C. C. Ho, J. J. Chen, M. F. Tsai, S. L. Yu, and P. C. Yang. 2008. Curcumin inhibits lung cancer cell invasion and metastasis through the tumor suppressor HLJ1. Cancer Res 68:7428-38.

[34] Chen, H. W., S. L. Yu, J. J. Chen, H. N. Li, Y. C. Lin, P. L. Yao, H. Y. Chou, C. T. Chien, W. J. Chen, Y. T. Lee, and P. C. Yang. 2004. Anti-invasive gene expression profile of curcumin in lung adenocarcinoma based on a high throughput microarray analysis. Mol Pharmacol 65:99-110.

[35] Chen, L., L. Gallicchio, K. Boyd-Lindsley, X. G. Tao, K. A. Robinson, T. K. Lam, J. G. Herman, L. E. Caulfield, E. Guallar, and A. J. Alberg. 2009. Alcohol consumption and the risk of nasopharyngeal carcinoma: a systematic review. Nutr Cancer 61:1-15.

[36] Chen, M. R., J. M. Middeldorp, and S. D. Hayward. 1993. Separation of the complex DNA binding domain of EBNA-1 into DNA recognition and dimerization subdomains of novel structure. J Virol 67:4875-85.

[37] Chen, Q., S. Ganapathy, K. P. Singh, S. Shankar, and R. K. Srivastava. 2010. Resveratrol induces growth arrest and apoptosis through activation of FOXO transcription factors in prostate cancer cells. PLoS One 5:e15288.

[38] Chen, Q., Y. Wang, K. Xu, G. Lu, Z. Ying, L. Wu, J. Zhan, R. Fang, Y. Wu, and J. Zhou. 2010. Curcumin induces apoptosis in human lung adenocarcinoma A549 cells through a reactive oxygen species-dependent mitochondrial signaling pathway. Oncol Rep 23:397-403.

[39] Chen, Q. Y., J. G. Shi, Q. H. Yao, D. M. Jiao, Y. Y. Wang, H. Z. Hu, Y. Q. Wu, J. Song, J. Yan, and L. J. Wu. 2012. Lysosomal membrane permeabilization is involved in curcumin-induced apoptosis of A549 lung carcinoma cells. Mol Cell Biochem. 359:389-98.

[40] Chen, Y., D. Li, H. Liu, H. Xu, H. Zheng, F. Qian, W. Li, C. Zhao, Z. Wang, and X. Wang. 2011. Notch-1 signaling facilitates survivin expression in human non-small cell lung cancer cells. Cancer Biol Ther 11:14-21.

[41] Chen, Y. K., C. Cheung, K. R. Reuhl, A. B. Liu, M. J. Lee, Y. P. Lu, and C. S. Yang. 2011. Effects of Green Tea Polyphenol (-)-Epigallocatechin-3-gallate on a Newly Developed High-fat/Western-style Diet-induced Obesity and Metabolic Syndrome in Mice. J Agric Food Chem 59:11862-71.

[42] Chen, Y. Y., S. Y. Chiang, J. G. Lin, J. S. Yang, Y. S. Ma, C. L. Liao, T. Y. Lai, N. Y. Tang, and J. G. Chung. 2010. Emodin, aloe-emodin and rhein induced DNA damage and inhibited DNA repair gene expression in SCC-4 human tongue cancer cells. Anticancer Res 30:945-51.

[43] Cheng, S. H., J. J. Jian, S. Y. Tsai, K. L. Yen, N. M. Chu, K. Y. Chan, T. D. Tan, J. C. Cheng, S. Y. Leu, C. Y. Hsieh, and A. T. Huang. 2000. Long-term survival of

nasopharyngeal carcinoma following concomitant radiotherapy and chemotherapy. Int J Radiat Oncol Biol Phys 48:1323-30.

[44] Chiaramonte, R., E. Calzavara, A. Basile, P. Comi, and G. V. Sherbet. 2002. Notch signal transduction is not regulated by SEL1L in leukaemia and lymphoma cells in culture. Anticancer Res 22:4211-4.

[45] Chou, J., Y. C. Lin, J. Kim, L. You, Z. Xu, B. He, and D. M. Jablons. 2008. Nasopharyngeal carcinoma--review of the molecular mechanisms of tumorigenesis. Head Neck 30:946-63.

[46] Chow, K. C., S. H. Chiou, S. P. Ho, M. H. Tsai, C. L. Chen, L. S. Wang, and K. H. Chi. 2003. The elevated serum interleukin-6 correlates with the increased serum butyrate level in patients with nasopharyngeal carcinoma. Oncol Rep 10:813-9.

[47] Chow, S. E., J. S. Wang, S. F. Chuang, Y. L. Chang, W. K. Chu, W. S. Chen, and Y. W. Chen. 2010. Resveratrol-induced p53-independent apoptosis of human nasopharyngeal carcinoma cells is correlated with the downregulation of DeltaNp63. Cancer Gene Ther 17:872-82.

[48] Christofori, G., and H. Semb. 1999. The role of the cell-adhesion molecule E-cadherin as a tumour-suppressor gene. Trends Biochem Sci 24:73-6.

[49] Ciesek, S., T. von Hahn, C. C. Colpitts, L. M. Schang, M. Friesland, J. Steinmann, M. P. Manns, M. Ott, H. Wedemeyer, P. Meuleman, T. Pietschmann, and E. Steinmann. 2011. The green tea polyphenol epigallocatechin-3-gallate (EGCG) inhibits hepatitis C virus (HCV) entry. Hepatology 54:1947-55.

[50] Cohen, J. I. 2000. Epstein-Barr virus infection. N Engl J Med 343:481-92.

[51] Cordier-Bussat, M., M. Billaud, A. Calender, and G. M. Lenoir. 1993. Epstein-Barr virus (EBV) nuclear-antigen-2-induced up-regulation of CD21 and CD23 molecules is dependent on a permissive cellular context. Int J Cancer 53:153-60.

[52] Cory, S., and J. M. Adams. 2002. The Bcl2 family: regulators of the cellular life-or-death switch. Nat Rev Cancer 2:647-56.

[53] Cos, P., T. De Bruyne, N. Hermans, S. Apers, D. V. Berghe, and A. J. Vlietinck. 2004. Proanthocyanidins in health care: current and new trends. Curr Med Chem 11:1345-59.

[54] Csiszar, A., N. Labinskyy, S. Olson, J. T. Pinto, S. Gupte, J. M. Wu, F. Hu, P. Ballabh, A. Podlutsky, G. Losonczy, R. de Cabo, R. Mathew, M. S. Wolin, and Z. Ungvari. 2009. Resveratrol prevents monocrotaline-induced pulmonary hypertension in rats. Hypertension 54:668-75.

[55] Cui, X., Y. Jin, A. B. Hofseth, E. Pena, J. Habiger, A. Chumanevich, D. Poudyal, M. Nagarkatti, P. S. Nagarkatti, U. P. Singh, and L. J. Hofseth. 2010. Resveratrol suppresses colitis and colon cancer associated with colitis. Cancer Prev Res (Phila) 3:549-59.

[56] Das, A., N. L. Banik, and S. K. Ray. 2010. Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes. Cancer 116:164-76.

[57] Dawson, C. W., A. G. Eliopoulos, S. M. Blake, R. Barker, and L. S. Young. 2000. Identification of functional differences between prototype Epstein-Barr virus-

encoded LMP1 and a nasopharyngeal carcinoma-derived LMP1 in human epithelial cells. Virology 272:204-17.

[58] Dawson, C. W., A. B. Rickinson, and L. S. Young. 1990. Epstein-Barr virus latent membrane protein inhibits human epithelial cell differentiation. Nature 344:777-80.

[59] Dawson, C. W., G. Tramountanis, A. G. Eliopoulos, and L. S. Young. 2003. Epstein-Barr virus latent membrane protein 1 (LMP1) activates the phosphatidylinositol 3-kinase/Akt pathway to promote cell survival and induce actin filament remodeling. J Biol Chem 278:3694-704.

[60] Dhillon, A. S., S. Hagan, O. Rath, and W. Kolch. 2007. MAP kinase signalling pathways in cancer. Oncogene 26:3279-90.

[61] Dickson, R. I., and A. D. Flores. 1985. Nasopharyngeal carcinoma: an evaluation of 134 patients treated between 1971-1980. Laryngoscope 95:276-83.

[62] Duellman, S. J., K. L. Thompson, J. J. Coon, and R. R. Burgess. 2009. Phosphorylation sites of Epstein-Barr virus EBNA1 regulate its function. J Gen Virol 90:2251-9.

[63] Dukers, D. F., P. Meij, M. B. Vervoort, W. Vos, R. J. Scheper, C. J. Meijer, E. Bloemena, and J. M. Middeldorp. 2000. Direct immunosuppressive effects of EBV-encoded latent membrane protein 1. J Immunol 165:663-70.

[64] Eliopoulos, A. G., N. J. Gallagher, S. M. Blake, C. W. Dawson, and L. S. Young. 1999. Activation of the p38 mitogen-activated protein kinase pathway by Epstein-Barr virus-encoded latent membrane protein 1 coregulates interleukin-6 and interleukin-8 production. J Biol Chem 274:16085-96.

[65] Eliopoulos, A. G., M. Stack, C. W. Dawson, K. M. Kaye, L. Hodgkin, S. Sihota, M. Rowe, and L. S. Young. 1997. Epstein-Barr virus-encoded LMP1 and CD40 mediate IL-6 production in epithelial cells via an NF-kappaB pathway involving TNF receptor-associated factors. Oncogene 14:2899-916.

[66] Elmali, N., O. Baysal, A. Harma, I. Esenkaya, and B. Mizrak. 2007. Effects of resveratrol in inflammatory arthritis. Inflammation 30:1-6.

[67] Fahraeus, R., W. Chen, P. Trivedi, G. Klein, and B. Obrink. 1992. Decreased expression of E-cadherin and increased invasive capacity in EBV-LMP-transfected human epithelial and murine adenocarcinoma cells. Int J Cancer 52:834-8.

[68] Fahraeus, R., H. L. Fu, I. Ernberg, J. Finke, M. Rowe, G. Klein, K. Falk, E. Nilsson, M. Yadav, P. Busson, and et al. 1988. Expression of Epstein-Barr virus-encoded proteins in nasopharyngeal carcinoma. Int J Cancer 42:329-38.

[69] Filippi-Chiela, E. C., E. S. Villodre, L. L. Zamin, and G. Lenz. 2011. Autophagy interplay with apoptosis and cell cycle regulation in the growth inhibiting effect of resveratrol in glioma cells. PLoS One 6:e20849.

[70] Fingeroth, J. D., J. J. Weis, T. F. Tedder, J. L. Strominger, P. A. Biro, and D. T. Fearon. 1984. Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. Proc Natl Acad Sci U S A 81:4510-4.

[71] Flanagan, J., J. Middeldorp, and T. Sculley. 2003. Localization of the Epstein-Barr virus protein LMP 1 to exosomes. J Gen Virol 84:1871-9.

[72] Florian, T., J. Necas, L. Bartosikova, J. Klusakova, V. Suchy, E. B. Naggara, E. Janostikova, and T. Bartosik. 2006. Effects of prenylated isoflavones osajin and

pomiferin in premedication on heart ischemia-reperfusion. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub 150:93-100.

[73] Floridi, A., S. Castiglione, C. Bianchi, and A. Mancini. 1990. Effect of rhein on the glucose metabolism of Ehrlich ascites tumor cells. Biochem Pharmacol 40:217-22.

[74] Floridi, A., F. P. Gentile, T. Bruno, S. Castiglione, M. Zeuli, and M. Benassi. 1990. Growth inhibition by rhein and lonidamine of human glioma cells in vitro. Anticancer Res 10:1633-6.

[75] Frei, B., and J. V. Higdon. 2003. Antioxidant activity of tea polyphenols in vivo: evidence from animal studies. J Nutr 133:3275S-84S.

[76] Freile, M. L., F. Giannini, G. Pucci, A. Sturniolo, L. Rodero, O. Pucci, V. Balzareti, and R. D. Enriz. 2003. Antimicrobial activity of aqueous extracts and of berberine isolated from Berberis heterophylla. Fitoterapia 74:702-5.

[77] Freudlsperger, C., J. Greten, and U. Schumacher. 2008. Curcumin induces apoptosis in human neuroblastoma cells via inhibition of NFkappaB. Anticancer Res 28:209-14.

[78] Fries, K. L., W. E. Miller, and N. Raab-Traub. 1996. Epstein-Barr virus latent membrane protein 1 blocks p53-mediated apoptosis through the induction of the A20 gene. J Virol 70:8653-9.

[79] Fruehling, S., R. Swart, K. M. Dolwick, E. Kremmer, and R. Longnecker. 1998. Tyrosine 112 of latent membrane protein 2A is essential for protein tyrosine kinase loading and regulation of Epstein-Barr virus latency. J Virol 72:7796-806.

[80] Fujiwara, S., Y. Nitadori, H. Nakamura, T. Nagaishi, and Y. Ono. 1999. Epstein-barr virus (EBV) nuclear protein 2-induced disruption of EBV latency in the Burkitt's lymphoma cell line Akata: analysis by tetracycline-regulated expression. J Virol 73:5214-9.

[81] Gahn, T. A., and B. Sugden. 1995. An EBNA-1-dependent enhancer acts from a distance of 10 kilobase pairs to increase expression of the Epstein-Barr virus LMP gene. J Virol 69:2633-6.

[82] George, J., M. Singh, A. K. Srivastava, K. Bhui, P. Roy, P. K. Chaturvedi, and Y. Shukla. 2011. Resveratrol and Black Tea Polyphenol Combination Synergistically Suppress Mouse Skin Tumors Growth by Inhibition of Activated MAPKs and p53. PLoS One 6:e23395.

[83] Gillespie, K., I. Kodani, D. P. Dickinson, K. U. Ogbureke, A. M. Camba, M. Wu, S. Looney, T. C. Chu, H. Qin, F. Bisch, M. Sharawy, G. S. Schuster, and S. D. Hsu. 2008. Effects of oral consumption of the green tea polyphenol EGCG in a murine model for human Sjogren's syndrome, an autoimmune disease. Life Sci 83:581-8.

[84] Glickman, J. N., J. G. Howe, and J. A. Steitz. 1988. Structural analyses of EBER1 and EBER2 ribonucleoprotein particles present in Epstein-Barr virus-infected cells. J Virol 62:902-11.

[85] Gordadze, A. V., C. W. Onunwor, R. Peng, D. Poston, E. Kremmer, and P. D. Ling. 2004. EBNA2 amino acids 3 to 30 are required for induction of LMP-1 and immortalization maintenance. J Virol 78:3919-29.

[86] Green, D. R., and J. C. Reed. 1998. Mitochondria and apoptosis. Science 281:1309-12.

[87] Gross, A., J. M. McDonnell, and S. J. Korsmeyer. 1999. BCL-2 family members and the mitochondria in apoptosis. Genes Dev 13:1899-911.

[88] Gross, H., S. Barth, T. Pfuhl, V. Willnecker, A. Spurk, V. Gurtsevitch, M. Sauter, B. Hu, E. Noessner, N. Mueller-Lantzsch, E. Kremmer, and F. A. Grasser. 2011. The NP9 protein encoded by the human endogenous retrovirus HERV-K(HML-2) negatively regulates gene activation of the Epstein-Barr virus nuclear antigen 2 (EBNA2). Int J Cancer 129:1105-15.

[89] Gruhne, B., R. Sompallae, D. Marescotti, S. A. Kamranvar, S. Gastaldello, and M. G. Masucci. 2009. The Epstein-Barr virus nuclear antigen-1 promotes genomic instability via induction of reactive oxygen species. Proc Natl Acad Sci U S A 106:2313-8.

[90] Guha, P., A. Dey, R. Sen, M. Chatterjee, S. Chattopadhyay, and S. K. Bandyopadhyay. 2011. Intracellular GSH depletion triggered mitochondrial Bax translocation to accomplish resveratrol-induced apoptosis in the U937 cell line. J Pharmacol Exp Ther 336:206-14.

[91] Guo, J. M., B. X. Xiao, Q. Liu, S. Zhang, D. H. Liu, and Z. H. Gong. 2007. Anticancer effect of aloe-emodin on cervical cancer cells involves G2/M arrest and induction of differentiation. Acta Pharmacol Sin 28:1991-5.

[92] Guo, M. Z., X. S. Li, D. M. Shen, X. Q. Guan, H. R. Xu, and J. Gao. 2003. [Effect of Rhein on the development of hepatic fibrosis in rats]. Zhonghua Gan Zang Bing Za Zhi 11:26-9.

[93] Hammerschmidt, W., B. Sugden, and V. R. Baichwal. 1989. The transforming domain alone of the latent membrane protein of Epstein-Barr virus is toxic to cells when expressed at high levels. J Virol 63:2469-75.

[94] Hamza, A., and C. G. Zhan. 2006. How can (-)-epigallocatechin gallate from green tea prevent HIV-1 infection? Mechanistic insights from computational modeling and the implication for rational design of anti-HIV-1 entry inhibitors. J Phys Chem B 110:2910-7.

[95] Hartojo, W., A. L. Silvers, D. G. Thomas, C. W. Seder, L. Lin, H. Rao, Z. Wang, J. K. Greenson, T. J. Giordano, M. B. Orringer, A. Rehemtulla, M. S. Bhojani, D. G. Beer, and A. C. Chang. 2010. Curcumin promotes apoptosis, increases chemosensitivity, and inhibits nuclear factor kappaB in esophageal adenocarcinoma. Transl Oncol 3:99-108.

[96] Hattori, R., H. Otani, N. Maulik, and D. K. Das. 2002. Pharmacological preconditioning with resveratrol: role of nitric oxide. Am J Physiol Heart Circ Physiol 282:H1988-95.

[97] He, Z. H., M. F. He, S. C. Ma, and P. P. But. 2009. Anti-angiogenic effects of rhubarb and its anthraquinone derivatives. J Ethnopharmacol 121:313-7.

[98] He, Z. H., R. Zhou, M. F. He, C. B. Lau, G. G. Yue, W. Ge, and P. P. But. 2011. Anti-angiogenic effect and mechanism of rhein from Rhizoma Rhei. Phytomedicine 18:470-8.

[99] Henderson, S., M. Rowe, C. Gregory, D. Croom-Carter, F. Wang, R. Longnecker, E. Kieff, and A. Rickinson. 1991. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. Cell 65:1107-15.

[100] Herman, J. G., H. L. Stadelman, and C. E. Roselli. 2009. Curcumin blocks CCL2-induced adhesion, motility and invasion, in part, through down-regulation of CCL2 expression and proteolytic activity. Int J Oncol 34:1319-27.

[101] Herrmann, K., and G. Niedobitek. 2003. Epstein-Barr virus-associated carcinomas: facts and fiction. J Pathol 199:140-5.

[102] Heussinger, N., M. Buttner, G. Ott, E. Brachtel, B. Z. Pilch, E. Kremmer, and G. Niedobitek. 2004. Expression of the Epstein-Barr virus (EBV)-encoded latent membrane protein 2A (LMP2A) in EBV-associated nasopharyngeal carcinoma. J Pathol 203:696-9.

[103] Hideshima, T., M. Akiyama, T. Hayashi, P. Richardson, R. Schlossman, D. Chauhan, and K. C. Anderson. 2003. Targeting p38 MAPK inhibits multiple myeloma cell growth in the bone marrow milieu. Blood 101:703-5.

[104] Higdon, J. V., and B. Frei. 2003. Tea catechins and polyphenols: health effects, metabolism, and antioxidant functions. Crit Rev Food Sci Nutr 43:89-143.

[105] Hilchie, A. L., S. J. Furlong, K. Sutton, A. Richardson, M. R. Robichaud, C. A. Giacomantonio, N. D. Ridgway, and D. W. Hoskin. 2010. Curcumin-induced apoptosis in PC3 prostate carcinoma cells is caspase-independent and involves cellular ceramide accumulation and damage to mitochondria. Nutr Cancer 62:379-89.

[106] Ho, Y. T., J. S. Yang, T. C. Li, J. J. Lin, J. G. Lin, K. C. Lai, C. Y. Ma, W. G. Wood, and J. G. Chung. 2009. Berberine suppresses in vitro migration and invasion of human SCC-4 tongue squamous cancer cells through the inhibitions of FAK, IKK, NF-kappaB, u-PA and MMP-2 and -9. Cancer Lett 279:155-62.

[107] Hoe, S. L., E. S. Lee, A. S. Khoo, and S. C. Peh. 2009. p53 and nasopharyngeal carcinoma: a Malaysian study. Pathology 41:561-5.

[108] Hsia, T. C., J. S. Yang, G. W. Chen, T. H. Chiu, H. F. Lu, M. D. Yang, F. S. Yu, K. C. Liu, K. C. Lai, C. C. Lin, and J. G. Chung. 2009. The roles of endoplasmic reticulum stress and Ca2+ on rhein-induced apoptosis in A-549 human lung cancer cells. Anticancer Res 29:309-18.

[109] Hsieh, J. J., and S. D. Hayward. 1995. Masking of the CBF1/RBPJ kappa transcriptional repression domain by Epstein-Barr virus EBNA2. Science 268:560-3.

[110] Hsu, S. D., D. P. Dickinson, H. Qin, J. Borke, K. U. Ogbureke, J. N. Winger, A. M. Camba, W. B. Bollag, H. J. Stoppler, M. M. Sharawy, and G. S. Schuster. 2007. Green tea polyphenols reduce autoimmune symptoms in a murine model for human Sjogren's syndrome and protect human salivary acinar cells from TNF-alpha-induced cytotoxicity. Autoimmunity 40:138-47.

[111] Hsu, W. H., Y. S. Hsieh, H. C. Kuo, C. Y. Teng, H. I. Huang, C. J. Wang, S. F. Yang, Y. S. Liou, and W. H. Kuo. 2007. Berberine induces apoptosis in SW620 human colonic carcinoma cells through generation of reactive oxygen species and activation of JNK/p38 MAPK and FasL. Arch Toxicol 81:719-28.

[112] Huang, C., G. Yang, T. Jiang, G. Zhu, H. Li, and Z. Qiu. 2011. The effects and mechanisms of blockage of STAT3 signaling pathway on IL-6 inducing EMT in human pancreatic cancer cells in vitro. Neoplasma 58:396-405.

[113] Huang, T. T., H. C. Lin, C. C. Chen, C. C. Lu, C. F. Wei, T. S. Wu, F. G. Liu, and H. C. Lai. 2011. Resveratrol induces apoptosis of human nasopharyngeal carcinoma cells via activation of multiple apoptotic pathways. J Cell Physiol 226:720-8.

[114] Huang, T. T., F. G. Liu, C. F. Wei, C. C. Lu, C. C. Chen, H. C. Lin, D. M. Ojcius, and H. C. Lai. 2011. Activation of multiple apoptotic pathways in human nasopharyngeal carcinoma cells by the prenylated isoflavone, osajin. PLoS One 6:e18308.

[115] Hudson, G. S., P. J. Farrell, and B. G. Barrell. 1985. Two related but differentially expressed potential membrane proteins encoded by the EcoRI Dhet region of Epstein-Barr virus B95-8. J Virol 53:528-35.

[116] Hung, L. M., M. J. Su, and J. K. Chen. 2004. Resveratrol protects myocardial ischemia-reperfusion injury through both NO-dependent and NO-independent mechanisms. Free Radic Biol Med 36:774-81.

[117] Hussain, A. R., S. Uddin, R. Bu, O. S. Khan, S. O. Ahmed, M. Ahmed, and K. S. Al-Kuraya. 2011. Resveratrol Suppresses Constitutive Activation of AKT via Generation of ROS and Induces Apoptosis in Diffuse Large B Cell Lymphoma Cell Lines. PLoS One 6:e24703.

[118] Hwang, J. M., H. C. Kuo, T. H. Tseng, J. Y. Liu, and C. Y. Chu. 2006. Berberine induces apoptosis through a mitochondria/caspases pathway in human hepatoma cells. Arch Toxicol 80:62-73.

[119] Imamura, G., A. A. Bertelli, A. Bertelli, H. Otani, N. Maulik, and D. K. Das. 2002. Pharmacological preconditioning with resveratrol: an insight with iNOS knockout mice. Am J Physiol Heart Circ Physiol 282:H1996-2003.

[120] Ip, S. W., Y. S. Weng, S. Y. Lin, D. Mei, N. Y. Tang, C. C. Su, and J. G. Chung. 2007. The role of Ca+2 on rhein-induced apoptosis in human cervical cancer Ca Ski cells. Anticancer Res 27:379-89.

[121] Jantova, S., L. Cipak, and S. Letasiova. 2007. Berberine induces apoptosis through a mitochondrial/caspase pathway in human promonocytic U937 cells. Toxicol In Vitro 21:25-31.

[122] Jarriault, S., C. Brou, F. Logeat, E. H. Schroeter, R. Kopan, and A. Israel. 1995. Signalling downstream of activated mammalian Notch. Nature 377:355-8.

[123] Jee, S. H., S. C. Shen, C. R. Tseng, H. C. Chiu, and M. L. Kuo. 1998. Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells. J Invest Dermatol 111:656-61.

[124] Jiang, M. C., H. F. Yang-Yen, J. J. Yen, and J. K. Lin. 1996. Curcumin induces apoptosis in immortalized NIH 3T3 and malignant cancer cell lines. Nutr Cancer 26:111-20.

[125] Jiang, R., X. Gu, C. O. Nathan, and L. Hutt-Fletcher. 2008. Laser-capture microdissection of oropharyngeal epithelium indicates restriction of Epstein-Barr virus receptor/CD21 mRNA to tonsil epithelial cells. J Oral Pathol Med 37:626-33.

[126] Johansson, P., A. Jansson, U. Ruetschi, and L. Rymo. 2010. The p38 signaling pathway upregulates expression of the Epstein-Barr virus LMP1 oncogene. J Virol 84:2787-97.

[127] Johnstone, R. W., A. A. Ruefli, and S. W. Lowe. 2002. Apoptosis: a link between cancer genetics and chemotherapy. Cell 108:153-64.

[128] Jones, R. J., L. J. Smith, C. W. Dawson, T. Haigh, N. W. Blake, and L. S. Young. 2003. Epstein-Barr virus nuclear antigen 1 (EBNA1) induced cytotoxicity in epithelial cells is associated with EBNA1 degradation and processing. Virology 313:663-76.

[129] Jung, K. H., and J. W. Park. 2011. Suppression of mitochondrial NADP(+)-dependent isocitrate dehydrogenase activity enhances curcumin-induced apoptosis in HCT116 cells. Free Radic Res 45:431-8.

[130] Kaiser, C., G. Laux, D. Eick, N. Jochner, G. W. Bornkamm, and B. Kempkes. 1999. The proto-oncogene c-myc is a direct target gene of Epstein-Barr virus nuclear antigen 2. J Virol 73:4481-4.

[131] Kaneda, Y., M. Torii, T. Tanaka, and M. Aikawa. 1991. In vitro effects of berberine sulphate on the growth and structure of Entamoeba histolytica, Giardia lamblia and Trichomonas vaginalis. Ann Trop Med Parasitol 85:417-25.

[132] Kartal, M., G. Saydam, F. Sahin, and Y. Baran. 2011. Resveratrol triggers apoptosis through regulating ceramide metabolizing genes in human K562 chronic myeloid leukemia cells. Nutr Cancer 63:637-44.

[133] Kelloff, G. J. 2000. Perspectives on cancer chemoprevention research and drug development. Adv Cancer Res 78:199-334.

[134] Keryer-Bibens, C., C. Pioche-Durieu, C. Villemant, S. Souquere, N. Nishi, M. Hirashima, J. Middeldorp, and P. Busson. 2006. Exosomes released by EBV-infected nasopharyngeal carcinoma cells convey the viral latent membrane protein 1 and the immunomodulatory protein galectin 9. BMC Cancer 6:283.

[135] Khan, N., F. Afaq, M. Saleem, N. Ahmad, and H. Mukhtar. 2006. Targeting multiple signaling pathways by green tea polyphenol (-)-epigallocatechin-3-gallate. Cancer Res 66:2500-5.

[136] Khin Maung, U., K. Myo, W. Nyunt Nyunt, K. Aye, and U. Tin. 1985. Clinical trial of berberine in acute watery diarrhoea. Br Med J (Clin Res Ed) 291:1601-5.

[137] Kieff, E., and A. E. Rickinson. 2007. Epstein-Barr virus and its replication. Fields Virology 2:2603–2654.

[138] Kim, K. R., T. Yoshizaki, H. Miyamori, K. Hasegawa, T. Horikawa, M. Furukawa, S. Harada, M. Seiki, and H. Sato. 2000. Transformation of Madin-Darby canine kidney (MDCK) epithelial cells by Epstein-Barr virus latent membrane protein 1 (LMP1) induces expression of Ets1 and invasive growth. Oncogene 19:1764-71.

[139] Kim, S., J. H. Choi, J. B. Kim, S. J. Nam, J. H. Yang, J. H. Kim, and J. E. Lee. 2008. Berberine suppresses TNF-alpha-induced MMP-9 and cell invasion through inhibition of AP-1 activity in MDA-MB-231 human breast cancer cells. Molecules 13:2975-85.

[140] Klibi, J., T. Niki, A. Riedel, C. Pioche-Durieu, S. Souquere, E. Rubinstein, S. Le Moulec, J. Guigay, M. Hirashima, F. Guemira, D. Adhikary, J. Mautner, and P. Busson. 2009. Blood diffusion and Th1-suppressive effects of galectin-9-containing exosomes released by Epstein-Barr virus-infected nasopharyngeal carcinoma cells. Blood 113:1957-66.

[141] Ko, Y. C., C. L. Chang, H. F. Chien, C. H. Wu, and L. I. Lin. 2011. Resveratrol enhances the expression of death receptor Fas/CD95 and induces differentiation and apoptosis in anaplastic large-cell lymphoma cells. Cancer Lett 309:46-53.

[142] Kong, Q. L., L. J. Hu, J. Y. Cao, Y. J. Huang, L. H. Xu, Y. Liang, D. Xiong, S. Guan, B. H. Guo, H. Q. Mai, Q. Y. Chen, X. Zhang, M. Z. Li, J. Y. Shao, C. N. Qian, Y. F. Xia, L. B. Song, Y. X. Zeng, and M. S. Zeng. 2010. Epstein-Barr virus-encoded LMP2A induces an epithelial-mesenchymal transition and increases the number of side population stem-like cancer cells in nasopharyngeal carcinoma. PLoS Pathog 6:e1000940.

[143] Kulkarni, S. K., and A. Dhir. 2010. Berberine: a plant alkaloid with therapeutic potential for central nervous system disorders. Phytother Res 24:317-24.

[144] Kunnumakkara, A. B., P. Anand, and B. B. Aggarwal. 2008. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. Cancer Lett 269:199-225.

[145] Kuo, C. L., S. Y. Wu, S. W. Ip, P. P. Wu, C. S. Yu, J. S. Yang, P. Y. Chen, S. H. Wu, and J. G. Chung. 2011. Apoptotic death in curcumin-treated NPC-TW 076 human nasopharyngeal carcinoma cells is mediated through the ROS, mitochondrial depolarization and caspase-3-dependent signaling responses. Int J Oncol 39:319-28.

[146] Kuo, P. L., Y. L. Hsu, L. T. Ng, and C. C. Lin. 2004. Rhein inhibits the growth and induces the apoptosis of Hep G2 cells. Planta Med 70:12-6.

[147] Kuo, P. L., T. C. Lin, and C. C. Lin. 2002. The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathway in human hepatoma cell lines. Life Sci 71:1879-92.

[148] Lafrenie, R. M., M. R. Buchanan, and F. W. Orr. 1993. Adhesion molecules and their role in cancer metastasis. Cell Biophys 23:3-89.

[149] Laherty, C. D., H. M. Hu, A. W. Opipari, F. Wang, and V. M. Dixit. 1992. The Epstein-Barr virus LMP1 gene product induces A20 zinc finger protein expression by activating nuclear factor kappa B. J Biol Chem 267:24157-60.

[150] Lai, W. W., J. S. Yang, K. C. Lai, C. L. Kuo, C. K. Hsu, C. K. Wang, C. Y. Chang, J. J. Lin, N. Y. Tang, P. Y. Chen, W. W. Huang, and J. G. Chung. 2009. Rhein induced apoptosis through the endoplasmic reticulum stress, caspase- and mitochondria-dependent pathways in SCC-4 human tongue squamous cancer cells. In Vivo 23:309-16.

[151] Lambert, J. D., and R. J. Elias. 2010. The antioxidant and pro-oxidant activities of green tea polyphenols: a role in cancer prevention. Arch Biochem Biophys 501:65-72.

[152] Larcher, C., B. Kempkes, E. Kremmer, W. M. Prodinger, M. Pawlita, G. W. Bornkamm, and M. P. Dierich. 1995. Expression of Epstein-Barr virus nuclear antigen-2 (EBNA2) induces CD21/CR2 on B and T cell lines and shedding of soluble CD21. Eur J Immunol 25:1713-9.

[153] Larrosa, M., M. J. Yanez-Gascon, M. V. Selma, A. Gonzalez-Sarrias, S. Toti, J. J. Ceron, F. Tomas-Barberan, P. Dolara, and J. C. Espin. 2009. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. J Agric Food Chem 57:2211-20.

[154] Lau, A. T., Y. Wang, and J. F. Chiu. 2008. Reactive oxygen species: current knowledge and applications in cancer research and therapeutic. J Cell Biochem 104:657-67.

[155] Lee, H. Z., S. L. Hsu, M. C. Liu, and C. H. Wu. 2001. Effects and mechanisms of aloe-emodin on cell death in human lung squamous cell carcinoma. Eur J Pharmacol 431:287-95.

[156] Lee, H. Z., C. J. Lin, W. H. Yang, W. C. Leung, and S. P. Chang. 2006. Aloe-emodin induced DNA damage through generation of reactive oxygen species in human lung carcinoma cells. Cancer Lett 239:55-63.

[157] Lee, H. Z., C. H. Wu, and S. P. Chang. 2005. Release of nucleophosmin from the nucleus: Involvement in aloe-emodin-induced human lung non small carcinoma cell apoptosis. Int J Cancer 113:971-6.

[158] Lee, J. M., K. H. Lee, M. Weidner, B. A. Osborne, and S. D. Hayward. 2002. Epstein-Barr virus EBNA2 blocks Nur77- mediated apoptosis. Proc Natl Acad Sci U S A 99:11878-83.

[159] Leight, E. R., and B. Sugden. 2000. EBNA-1: a protein pivotal to latent infection by Epstein-Barr virus. Rev Med Virol 10:83-100.

[160] Levenson, A. S., B. D. Gehm, S. T. Pearce, J. Horiguchi, L. A. Simons, J. E. Ward, 3rd, J. L. Jameson, and V. C. Jordan. 2003. Resveratrol acts as an estrogen receptor (ER) agonist in breast cancer cells stably transfected with ER alpha. Int J Cancer 104:587-96.

[161] Levitskaya, J., M. Coram, V. Levitsky, S. Imreh, P. M. Steigerwald-Mullen, G. Klein, M. G. Kurilla, and M. G. Masucci. 1995. Inhibition of antigen processing by the internal repeat region of the Epstein-Barr virus nuclear antigen-1. Nature 375:685-8.

[162] Li, D. M., and Y. M. Feng. 2011. Signaling mechanism of cell adhesion molecules in breast cancer metastasis: potential therapeutic targets. Breast Cancer Res Treat 128:7-21.

[163] Li, G., S. He, L. Chang, H. Lu, H. Zhang, H. Zhang, and J. Chiu. 2011. GADD45alpha and annexin A1 are involved in the apoptosis of HL-60 induced by resveratrol. Phytomedicine 18:704-9.

[164] Li, G. H., Y. Z. Fan, X. W. Liu, B. F. Zhang, D. D. Yin, F. He, S. Y. Huang, Z. J. Kang, H. Xu, Q. Liu, Y. L. Wu, X. L. Niu, L. Zhang, L. Liu, M. W. Hao, H. Han, and Y. M. Liang. 2010. Notch signaling maintains proliferation and survival of the HL60 human promyelocytic leukemia cell line and promotes the phosphorylation of the Rb protein. Mol Cell Biochem 340:7-14.

[165] Li, G. X., Y. K. Chen, Z. Hou, H. Xiao, H. Jin, G. Lu, M. J. Lee, B. Liu, F. Guan, Z. Yang, A. Yu, and C. S. Yang. 2010. Pro-oxidative activities and dose-response relationship of (-)-epigallocatechin-3-gallate in the inhibition of lung cancer cell growth: a comparative study in vivo and in vitro. Carcinogenesis 31:902-10.

[166] Li, J. X., K. Y. Zhou, K. R. Cai, T. Liang, X. D. Tang, and Y. F. Zhang. 2005. [Knockdown of bcl-xL expression with RNA interference induces nasopharyngeal carcinoma cells apoptosis]. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 40:347-51.

[167] Li, L., L. Guo, Y. Tao, S. Zhou, Z. Wang, W. Luo, D. Hu, Z. Li, L. Xiao, M. Tang, W. Yi, S. W. Tsao, and Y. Cao. 2007. Latent membrane protein 1 of Epstein-Barr virus regulates p53 phosphorylation through MAP kinases. Cancer Lett 255:219-31.

[168] Liao, P. C., L. T. Ng, L. T. Lin, C. D. Richardson, G. H. Wang, and C. C. Lin. 2010. Resveratrol arrests cell cycle and induces apoptosis in human hepatocellular carcinoma Huh-7 cells. J Med Food 13:1415-23.

[169] Lin, C. C., S. T. Kao, G. W. Chen, H. C. Ho, and J. G. Chung. 2006. Apoptosis of human leukemia HL-60 cells and murine leukemia WEHI-3 cells induced by berberine through the activation of caspase-3. Anticancer Res 26:227-42.

[170] Lin, C. C., J. S. Yang, J. T. Chen, S. Fan, F. S. Yu, J. L. Yang, C. C. Lu, M. C. Kao, A. C. Huang, H. F. Lu, and J. G. Chung. 2007. Berberine induces apoptosis in human HSC-3 oral cancer cells via simultaneous activation of the death receptor-mediated and mitochondrial pathway. Anticancer Res 27:3371-8.

[171] Lin, H., W. Xiong, X. Zhang, B. Liu, W. Zhang, Y. Zhang, J. Cheng, and H. Huang. 2011. Notch-1 activation-dependent p53 restoration contributes to resveratrol-induced apoptosis in glioblastoma cells. Oncol Rep 26:925-30.

[172] Lin, J. P., J. S. Yang, N. W. Chang, T. H. Chiu, C. C. Su, K. W. Lu, Y. T. Ho, C. C. Yeh, D. Mei, H. J. Lin, and J. G. Chung. 2007. GADD153 mediates berberine-induced apoptosis in human cervical cancer Ca ski cells. Anticancer Res 27:3379-86.

[173] Lin, J. P., J. S. Yang, C. C. Wu, S. S. Lin, W. T. Hsieh, M. L. Lin, F. S. Yu, C. S. Yu, G. W. Chen, Y. H. Chang, and J. G. Chung. 2008. Berberine induced down-regulation of matrix metalloproteinase-1, -2 and -9 in human gastric cancer cells (SNU-5) in vitro. In Vivo 22:223-30.

[174] Lin, J. T., M. K. Chen, K. T. Yeh, C. S. Chang, T. H. Chang, C. Y. Lin, Y. C. Wu, B. W. Su, K. D. Lee, and P. J. Chang. 2010. Association of high levels of Jagged-1 and Notch-1 expression with poor prognosis in head and neck cancer. Ann Surg Oncol 17:2976-83.

[175] Lin, L. I., Y. F. Ke, Y. C. Ko, and J. K. Lin. 1998. Curcumin inhibits SK-Hep-1 hepatocellular carcinoma cell invasion in vitro and suppresses matrix metalloproteinase-9 secretion. Oncology 55:349-53.

[176] Lin, M. L., S. S. Chen, Y. C. Lu, R. Y. Liang, Y. T. Ho, C. Y. Yang, and J. G. Chung. 2007. Rhein induces apoptosis through induction of endoplasmic reticulum stress and Ca2+-dependent mitochondrial death pathway in human nasopharyngeal carcinoma cells. Anticancer Res 27:3313-22.

[177] Lin, M. L., J. G. Chung, Y. C. Lu, C. Y. Yang, and S. S. Chen. 2009. Rhein inhibits invasion and migration of human nasopharyngeal carcinoma cells in vitro by down-regulation of matrix metalloproteinases-9 and vascular endothelial growth factor. Oral Oncol 45:531-7.

[178] Lin, M. L., Y. C. Lu, J. G. Chung, Y. C. Li, S. G. Wang, G. S. N, C. Y. Wu, H. L. Su, and S. S. Chen. 2010. Aloe-emodin induces apoptosis of human nasopharyngeal carcinoma cells via caspase-8-mediated activation of the mitochondrial death pathway. Cancer Lett 291:46-58.

[179] Lin, M. L., Y. C. Lu, J. G. Chung, S. G. Wang, H. T. Lin, S. E. Kang, C. H. Tang, J. L. Ko, and S. S. Chen. 2010. Down-regulation of MMP-2 through the p38 MAPK-NF-kappaB-dependent pathway by aloe-emodin leads to inhibition of nasopharyngeal carcinoma cell invasion. Mol Carcinog 49:783-97.

[180] Lin, M. L., Y. C. Lu, H. L. Su, H. T. Lin, C. C. Lee, S. E. Kang, T. C. Lai, J. G. Chung, and S. S. Chen. 2011. Destabilization of CARP mRNAs by aloe-emodin contributes to caspase-8-mediated p53-independent apoptosis of human carcinoma cells. J Cell Biochem 112:1176-91.

[181] Lin, S., M. Fujii, and D. X. Hou. 2003. Rhein induces apoptosis in HL-60 cells via reactive oxygen species-independent mitochondrial death pathway. Arch Biochem Biophys 418:99-107.

[182] Lin, S. S., K. C. Lai, S. C. Hsu, J. S. Yang, C. L. Kuo, J. P. Lin, Y. S. Ma, C. C. Wu, and J. G. Chung. 2009. Curcumin inhibits the migration and invasion of human A549 lung cancer cells through the inhibition of matrix metalloproteinase-2 and -9 and Vascular Endothelial Growth Factor (VEGF). Cancer Lett 285:127-33.

[183] Lin, S. Y., N. M. Tsang, S. C. Kao, Y. L. Hsieh, Y. P. Chen, C. S. Tsai, T. T. Kuo, S. P. Hao, I. H. Chen, and J. H. Hong. 2001. Presence of Epstein-Barr virus latent membrane protein 1 gene in the nasopharyngeal swabs from patients with nasopharyngeal carcinoma. Head Neck 23:194-200.

[184] Lin, T. H., H. C. Kuo, F. P. Chou, and F. J. Lu. 2008. Berberine enhances inhibition of glioma tumor cell migration and invasiveness mediated by arsenic trioxide. BMC Cancer 8:58.

[185] Lin, Y. J., and Y. S. Zhen. 2009. Rhein lysinate suppresses the growth of breast cancer cells and potentiates the inhibitory effect of Taxol in athymic mice. Anticancer Drugs 20:65-72.

[186] Lin, Y. J., Y. Z. Zhen, B. Y. Shang, and Y. S. Zhen. 2009. Rhein lysinate suppresses the growth of tumor cells and increases the anti-tumor activity of Taxol in mice. Am J Chin Med 37:923-31.

[187] Liu, J. P., L. Cassar, A. Pinto, and H. Li. 2006. Mechanisms of cell immortalization mediated by EB viral activation of telomerase in nasopharyngeal carcinoma. Cell Res 16:809-17.

[188] Liu, P. L., J. R. Tsai, A. L. Charles, J. J. Hwang, S. H. Chou, Y. H. Ping, F. Y. Lin, Y. L. Chen, C. Y. Hung, W. C. Chen, Y. H. Chen, and I. W. Chong. 2010. Resveratrol inhibits human lung adenocarcinoma cell metastasis by suppressing heme oxygenase 1-mediated nuclear factor-kappaB pathway and subsequently downregulating expression of matrix metalloproteinases. Mol Nutr Food Res 54 Suppl 2:S196-204.

[189] Liu, P. L., J. R. Tsai, C. C. Chiu, J. J. Hwang, S. H. Chou, C. K. Wang, S. J. Wu, Y. L. Chen, W. C. Chen, Y. H. Chen, and I. W. Chong. 2010. Decreased expression of thrombomodulin is correlated with tumor cell invasiveness and poor prognosis in nonsmall cell lung cancer. Mol Carcinog 49:874-81.

[190] Liu, S. J., Y. M. Sun, D. F. Tian, Y. C. He, L. Zeng, Y. He, C. Q. Ling, and S. H. Sun. 2008. Downregulated NM23-H1 expression is associated with intracranial invasion of nasopharyngeal carcinoma. Br J Cancer 98:363-9.

[191] Liu, Y. J., C. Barthelemy, O. de Bouteiller, C. Arpin, I. Durand, and J. Banchereau. 1995. Memory B cells from human tonsils colonize mucosal epithelium and directly present antigen to T cells by rapid up-regulation of B7-1 and B7-2. Immunity 2:239-48.

[192] Lo, K. W., and D. P. Huang. 2002. Genetic and epigenetic changes in nasopharyngeal carcinoma. Semin Cancer Biol 12:451-62.

[193] Longnecker, R., B. Druker, T. M. Roberts, and E. Kieff. 1991. An Epstein-Barr virus protein associated with cell growth transformation interacts with a tyrosine kinase. J Virol 65:3681-92.

[194] Lu, C., C. Sheehan, J. W. Rak, C. A. Chambers, N. Hozumi, and R. S. Kerbel. 1996. Endogenous interleukin 6 can function as an in vivo growth- stimulatory factor for advanced-stage human melanoma cells. Clin Cancer Res 2:1417-25.

[195] Lu, G. D., H. M. Shen, M. C. Chung, and C. N. Ong. 2007. Critical role of oxidative stress and sustained JNK activation in aloe-emodin-mediated apoptotic cell death in human hepatoma cells. Carcinogenesis 28:1937-45.

[196] Lu, J., W. H. Lin, S. Y. Chen, R. Longnecker, S. C. Tsai, C. L. Chen, and C. H. Tsai. 2006. Syk tyrosine kinase mediates Epstein-Barr virus latent membrane protein 2A-induced cell migration in epithelial cells. J Biol Chem 281:8806-14.

[197] Lu, J., M. Murakami, S. C. Verma, Q. Cai, S. Haldar, R. Kaul, M. A. Wasik, J. Middeldorp, and E. S. Robertson. 2011. Epstein-Barr Virus nuclear antigen 1 (EBNA1) confers resistance to apoptosis in EBV-positive B-lymphoma cells through up-regulation of survivin. Virology 410:64-75.

[198] Ma, Q., M. Zhang, Z. Wang, Z. Ma, and H. Sha. 2011. The beneficial effect of resveratrol on severe acute pancreatitis. Ann N Y Acad Sci 1215:96-102.

[199] Ma, Z. H., Q. Y. Ma, L. C. Wang, H. C. Sha, S. L. Wu, and M. Zhang. 2005. Effect of resveratrol on peritoneal macrophages in rats with severe acute pancreatitis. Inflamm Res 54:522-7.

[200] Malhotra, A., P. Nair, and D. K. Dhawan. 2010. Modulatory effects of curcumin and resveratrol on lung carcinogenesis in mice. Phytother Res 24:1271-7.

[201] Malinowska, J., and B. Olas. 2011. Response of blood platelets to resveratrol during a model of hyperhomocysteinemia. Platelets 22:277-83.

[202] Malterud, K. E., T. L. Farbrot, A. E. Huse, and R. B. Sund. 1993. Antioxidant and radical scavenging effects of anthraquinones and anthrones. Pharmacology 47 Suppl 1:77-85.

[203] Mandel, S. A., T. Amit, O. Weinreb, L. Reznichenko, and M. B. Youdim. 2008. Simultaneous manipulation of multiple brain targets by green tea catechins: a potential neuroprotective strategy for Alzheimer and Parkinson diseases. CNS Neurosci Ther 14:352-65.

[204] Mantena, S. K., S. D. Sharma, and S. K. Katiyar. 2006. Berberine inhibits growth, induces G1 arrest and apoptosis in human epidermoid carcinoma A431 cells by regulating Cdki-Cdk-cyclin cascade, disruption of mitochondrial membrane potential and cleavage of caspase 3 and PARP. Carcinogenesis 27:2018-27.

[205] Marks, J. E., J. L. Phillips, and H. R. Menck. 1998. The National Cancer Data Base report on the relationship of race and national origin to the histology of nasopharyngeal carcinoma. Cancer 83:582-8.

[206] Martin, G., P. Bogdanowicz, F. Domagala, H. Ficheux, and J. P. Pujol. 2003. Rhein inhibits interleukin-1 beta-induced activation of MEK/ERK pathway and DNA binding of NF-kappa B and AP-1 in chondrocytes cultured in hypoxia: a potential

mechanism for its disease-modifying effect in osteoarthritis. Inflammation 27:233-46.

[207] Meckes, D. G., Jr., K. H. Shair, A. R. Marquitz, C. P. Kung, R. H. Edwards, and N. Raab-Traub. 2010. Human tumor virus utilizes exosomes for intercellular communication. Proc Natl Acad Sci U S A 107:20370-5.

[208] Miccadei, S., R. Pulselli, and A. Floridi. 1993. Effect of lonidamine and rhein on the phosphorylation potential generated by respiring rat liver mitochondria. Anticancer Res 13:1507-10.

[209] Mijatovic, S., D. Maksimovic-Ivanic, J. Radovic, D. Miljkovic, L. Harhaji, O. Vuckovic, S. Stosic-Grujicic, M. Mostarica Stojkovic, and V. Trajkovic. 2005. Anti-glioma action of aloe emodin: the role of ERK inhibition. Cell Mol Life Sci 62:589-98.

[210] Miller, C. L., A. L. Burkhardt, J. H. Lee, B. Stealey, R. Longnecker, J. B. Bolen, and E. Kieff. 1995. Integral membrane protein 2 of Epstein-Barr virus regulates reactivation from latency through dominant negative effects on protein-tyrosine kinases. Immunity 2:155-66.

[211] Mitani, N., K. Murakami, T. Yamaura, T. Ikeda, and I. Saiki. 2001. Inhibitory effect of berberine on the mediastinal lymph node metastasis produced by orthotopic implantation of Lewis lung carcinoma. Cancer Lett 165:35-42.

[212] Morrison, J. A., A. J. Klingelhutz, and N. Raab-Traub. 2003. Epstein-Barr virus latent membrane protein 2A activates beta-catenin signaling in epithelial cells. J Virol 77:12276-84.

[213] Mudduluru, G., J. N. George-William, S. Muppala, I. A. Asangani, R. Kumarswamy, L. D. Nelson, and H. Allgayer. 2011. Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer. Biosci Rep 31:185-97.

[214] Mueller, S. O., and H. Stopper. 1999. Characterization of the genotoxicity of anthraquinones in mammalian cells. Biochim Biophys Acta 1428:406-14.

[215] Mukhtar, H., and N. Ahmad. 2000. Tea polyphenols: prevention of cancer and optimizing health. Am J Clin Nutr 71:1698S-702S; discussion 1703S-4S.

[216] Namasivayam, N. 2011. Chemoprevention in experimental animals. Ann N Y Acad Sci 1215:60-71.

[217] Narasimhan, M., and S. Ammanamanchi. 2008. Curcumin blocks RON tyrosine kinase-mediated invasion of breast carcinoma cells. Cancer Res 68:5185-92.

[218] Nayyar, V. K., K. Shire, and L. Frappier. 2009. Mitotic chromosome interactions of Epstein-Barr nuclear antigen 1 (EBNA1) and human EBNA1-binding protein 2 (EBP2). J Cell Sci 122:4341-50.

[219] Nemerow, G. R., R. Wolfert, M. E. McNaughton, and N. R. Cooper. 1985. Identification and characterization of the Epstein-Barr virus receptor on human B lymphocytes and its relationship to the C3d complement receptor (CR2). J Virol 55:347-51.

[220] Nemoto, S., J. Xiang, S. Huang, and A. Lin. 1998. Induction of apoptosis by SB202190 through inhibition of p38beta mitogen-activated protein kinase. J Biol Chem 273:16415-20.

[221] Niedobitek, G., M. L. Hansmann, H. Herbst, L. S. Young, D. Dienemann, C. A. Hartmann, T. Finn, S. Pitteroff, A. Welt, I. Anagnostopoulos, and et al. 1991. Epstein-Barr virus and carcinomas: undifferentiated carcinomas but not squamous

cell carcinomas of the nasopharynx are regularly associated with the virus. J Pathol 165:17-24.

[222] O'Neil, J. D., T. J. Owen, V. H. Wood, K. L. Date, R. Valentine, M. B. Chukwuma, J. R. Arrand, C. W. Dawson, and L. S. Young. 2008. Epstein-Barr virus-encoded EBNA1 modulates the AP-1 transcription factor pathway in nasopharyngeal carcinoma cells and enhances angiogenesis in vitro. J Gen Virol 89:2833-42.

[223] O'Sullivan-Coyne, G., G. C. O'Sullivan, T. R. O'Donovan, K. Piwocka, and S. L. McKenna. 2009. Curcumin induces apoptosis-independent death in oesophageal cancer cells. Br J Cancer 101:1585-95.

[224] Orlowski, R. Z., and A. S. Baldwin, Jr. 2002. NF-kappaB as a therapeutic target in cancer. Trends Mol Med 8:385-9.

[225] Ou, S. H., J. A. Zell, A. Ziogas, and H. Anton-Culver. 2007. Epidemiology of nasopharyngeal carcinoma in the United States: improved survival of Chinese patients within the keratinizing squamous cell carcinoma histology. Ann Oncol 18:29-35.

[226] Owen, T. J., J. D. O'Neil, C. W. Dawson, C. Hu, X. Chen, Y. Yao, V. H. Wood, L. E. Mitchell, R. J. White, L. S. Young, and J. R. Arrand. 2010. Epstein-Barr virus-encoded EBNA1 enhances RNA polymerase III-dependent EBER expression through induction of EBER-associated cellular transcription factors. Mol Cancer 9:241.

[227] Pandey, M. K., B. Sung, A. B. Kunnumakkara, G. Sethi, M. M. Chaturvedi, and B. B. Aggarwal. 2008. Berberine modifies cysteine 179 of IkappaBalpha kinase, suppresses nuclear factor-kappaB-regulated antiapoptotic gene products, and potentiates apoptosis. Cancer Res 68:5370-9.

[228] Patel, K. R., V. A. Brown, D. J. Jones, R. G. Britton, D. Hemingway, A. S. Miller, K. P. West, T. D. Booth, M. Perloff, J. A. Crowell, D. E. Brenner, W. P. Steward, A. J. Gescher, and K. Brown. 2010. Clinical pharmacology of resveratrol and its metabolites in colorectal cancer patients. Cancer Res 70:7392-9.

[229] Patel, K. R., E. Scott, V. A. Brown, A. J. Gescher, W. P. Steward, and K. Brown. 2011. Clinical trials of resveratrol. Ann N Y Acad Sci 1215:161-9.

[230] Pathmanathan, R., U. Prasad, R. Sadler, K. Flynn, and N. Raab-Traub. 1995. Clonal proliferations of cells infected with Epstein-Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. N Engl J Med 333:693-8.

[231] Pecere, T., M. V. Gazzola, C. Mucignat, C. Parolin, F. D. Vecchia, A. Cavaggioni, G. Basso, A. Diaspro, B. Salvato, M. Carli, and G. Palu. 2000. Aloe-emodin is a new type of anticancer agent with selective activity against neuroectodermal tumors. Cancer Res 60:2800-4.

[232] Pecere, T., F. Sarinella, C. Salata, B. Gatto, A. Bet, F. Dalla Vecchia, A. Diaspro, M. Carli, M. Palumbo, and G. Palu. 2003. Involvement of p53 in specific anti-neuroectodermal tumor activity of aloe-emodin. Int J Cancer 106:836-47.

[233] Pegtel, D. M., A. Subramanian, T. S. Sheen, C. H. Tsai, T. R. Golub, and D. A. Thorley-Lawson. 2005. Epstein-Barr-virus-encoded LMP2A induces primary epithelial cell migration and invasion: possible role in nasopharyngeal carcinoma metastasis. J Virol 79:15430-42.

[234] Peng, P. L., Y. S. Hsieh, C. J. Wang, J. L. Hsu, and F. P. Chou. 2006. Inhibitory effect of berberine on the invasion of human lung cancer cells via decreased productions of urokinase-plasminogen activator and matrix metalloproteinase-2. Toxicol Appl Pharmacol 214:8-15.

[235] Piyanuch, R., M. Sukhthankar, G. Wandee, and S. J. Baek. 2007. Berberine, a natural isoquinoline alkaloid, induces NAG-1 and ATF3 expression in human colorectal cancer cells. Cancer Lett 258:230-40.

[236] Pizarro, J. G., E. Verdaguer, V. Ancrenaz, F. Junyent, F. Sureda, M. Pallas, J. Folch, and A. Camins. 2011. Resveratrol inhibits proliferation and promotes apoptosis of neuroblastoma cells: role of sirtuin 1. Neurochem Res 36:187-94.

[237] Polvino-Bodnar, M., and P. A. Schaffer. 1992. DNA binding activity is required for EBNA 1-dependent transcriptional activation and DNA replication. Virology 187:591-603.

[238] Porter, M. J., J. K. Field, J. C. Lee, S. F. Leung, D. Lo, and C. A. Van Hasselt. 1994. Detection of the tumour suppressor gene p53 in nasopharyngeal carcinoma in Hong Kong Chinese. Anticancer Res 14:1357-60.

[239] Prakobwong, S., S. C. Gupta, J. H. Kim, B. Sung, P. Pinlaor, Y. Hiraku, S. Wongkham, B. Sripa, S. Pinlaor, and B. B. Aggarwal. 2011. Curcumin suppresses proliferation and induces apoptosis in human biliary cancer cells through modulation of multiple cell signaling pathways. Carcinogenesis 32:1372-80.

[240] QingLing, Z., Y. LiNa, L. Li, W. Shuang, Y. YuFang, D. Yi, J. Divakaran, L. Xin, and D. YanQing. 2011. LMP1 antagonizes WNT/beta-catenin signalling through inhibition of WTX and promotes nasopharyngeal dysplasia but not tumourigenesis in LMP1(B95-8) transgenic mice. J Pathol 223:574-83.

[241] Raab-Traub, N. 2002. Epstein-Barr virus in the pathogenesis of NPC. Semin Cancer Biol 12:431-41.

[242] Rabbani, G. H., T. Butler, J. Knight, S. C. Sanyal, and K. Alam. 1987. Randomized controlled trial of berberine sulfate therapy for diarrhea due to enterotoxigenic Escherichia coli and Vibrio cholerae. J Infect Dis 155:979-84.

[243] Rabinovich, A., L. Medina, B. Piura, S. Segal, and M. Huleihel. 2007. Regulation of ovarian carcinoma SKOV-3 cell proliferation and secretion of MMPs by autocrine IL-6. Anticancer Res 27:267-72.

[244] Radtke, F., and K. Raj. 2003. The role of Notch in tumorigenesis: oncogene or tumour suppressor? Nat Rev Cancer 3:756-67.

[245] Raimondi, F., P. Santoro, L. Maiuri, M. Londei, S. Annunziata, F. Ciccimarra, and A. Rubino. 2002. Reactive nitrogen species modulate the effects of rhein, an active component of senna laxatives, on human epithelium in vitro. J Pediatr Gastroenterol Nutr 34:529-34.

[246] Reedijk, M., S. Odorcic, L. Chang, H. Zhang, N. Miller, D. R. McCready, G. Lockwood, and S. E. Egan. 2005. High-level coexpression of JAG1 and NOTCH1 is observed in human breast cancer and is associated with poor overall survival. Cancer Res 65:8530-7.

[247] Reedijk, M., S. Odorcic, H. Zhang, R. Chetty, C. Tennert, B. C. Dickson, G. Lockwood, S. Gallinger, and S. E. Egan. 2008. Activation of Notch signaling in human colon adenocarcinoma. Int J Oncol 33:1223-9.

[248] Reth, M. 1989. Antigen receptor tail clue. Nature 338:383-4.

[249] Saha, A., T. Kuzuhara, N. Echigo, A. Fujii, M. Suganuma, and H. Fujiki. 2010. Apoptosis of human lung cancer cells by curcumin mediated through up-regulation of "growth arrest and DNA damage inducible genes 45 and 153". Biol Pharm Bull 33:1291-9.

[250] Sakai, T., Y. Taniguchi, K. Tamura, S. Minoguchi, T. Fukuhara, L. J. Strobl, U. Zimber-Strobl, G. W. Bornkamm, and T. Honjo. 1998. Functional replacement of the intracellular region of the Notch1 receptor by Epstein-Barr virus nuclear antigen 2. J Virol 72:6034-9.

[251] Sanchez, C., M. Mathy-Hartert, M. A. Deberg, H. Ficheux, J. Y. Reginster, and Y. E. Henrotin. 2003. Effects of rhein on human articular chondrocytes in alginate beads. Biochem Pharmacol 65:377-88.

[252] Sanchez, Y., G. P. Simon, E. Calvino, E. de Blas, and P. Aller. 2010. Curcumin stimulates reactive oxygen species production and potentiates apoptosis induction by the antitumor drugs arsenic trioxide and lonidamine in human myeloid leukemia cell lines. J Pharmacol Exp Ther 335:114-23.

[253] Sansone, P., G. Storci, S. Tavolari, T. Guarnieri, C. Giovannini, M. Taffurelli, C. Ceccarelli, D. Santini, P. Paterini, K. B. Marcu, P. Chieco, and M. Bonafe. 2007. IL-6 triggers malignant features in mammospheres from human ductal breast carcinoma and normal mammary gland. J Clin Invest 117:3988-4002.

[254] Sarkari, F., T. Sanchez-Alcaraz, S. Wang, M. N. Holowaty, Y. Sheng, and L. Frappier. 2009. EBNA1-mediated recruitment of a histone H2B deubiquitylating complex to the Epstein-Barr virus latent origin of DNA replication. PLoS Pathog 5:e1000624.

[255] Schlee, M., T. Krug, O. Gires, R. Zeidler, W. Hammerschmidt, R. Mailhammer, G. Laux, G. Sauer, J. Lovric, and G. W. Bornkamm. 2004. Identification of Epstein-Barr virus (EBV) nuclear antigen 2 (EBNA2) target proteins by proteome analysis: activation of EBNA2 in conditionally immortalized B cells reflects early events after infection of primary B cells by EBV. J Virol 78:3941-52.

[256] Scholle, F., K. M. Bendt, and N. Raab-Traub. 2000. Epstein-Barr virus LMP2A transforms epithelial cells, inhibits cell differentiation, and activates Akt. J Virol 74:10681-9.

[257] Scholle, F., R. Longnecker, and N. Raab-Traub. 1999. Epithelial cell adhesion to extracellular matrix proteins induces tyrosine phosphorylation of the Epstein-Barr virus latent membrane protein 2: a role for C-terminal Src kinase. J Virol 73:4767-75.

[258] Sen, S., H. Sharma, and N. Singh. 2005. Curcumin enhances Vinorelbine mediated apoptosis in NSCLC cells by the mitochondrial pathway. Biochem Biophys Res Commun 331:1245-52.

[259] Senft, C., M. Polacin, M. Priester, V. Seifert, D. Kogel, and J. Weissenberger. 2010. The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas. BMC Cancer 10:491.

[260] Sham, J. S., D. Choy, and P. H. Choi. 1990. Nasopharyngeal carcinoma: the significance of neck node involvement in relation to the pattern of distant failure. Br J Radiol 63:108-13.

[261] Shangary, S., and D. E. Johnson. 2003. Recent advances in the development of anticancer agents targeting cell death inhibitors in the Bcl-2 protein family. Leukemia 17:1470-81.

[262] Shankar, S., S. Ganapathy, S. R. Hingorani, and R. K. Srivastava. 2008. EGCG inhibits growth, invasion, angiogenesis and metastasis of pancreatic cancer. Front Biosci 13:440-52.

[263] Shanmugaratnam, K., and L. H. Sobin. 1993. The World Health Organization histological classification of tumours of the upper respiratory tract and ear. A commentary on the second edition. Cancer 71:2689-97.

[264] Shannon-Lowe, C., and M. Rowe. 2011. Epstein-Barr virus infection of polarized epithelial cells via the basolateral surface by memory B cell-mediated transfer infection. PLoS Pathog 7:e1001338.

[265] Shi, P., Z. Huang, and G. Chen. 2008. Rhein induces apoptosis and cell cycle arrest in human hepatocellular carcinoma BEL-7402 cells. Am J Chin Med 36:805-13.

[266] Shi, W., C. Bastianutto, A. Li, B. Perez-Ordonez, R. Ng, K. Y. Chow, W. Zhang, I. Jurisica, K. W. Lo, A. Bayley, J. Kim, B. O'Sullivan, L. Siu, E. Chen, and F. F. Liu. 2006. Multiple dysregulated pathways in nasopharyngeal carcinoma revealed by gene expression profiling. Int J Cancer 119:2467-75.

[267] Shi, Y., S. Yang, S. Troup, X. Lu, S. Callaghan, D. S. Park, Y. Xing, and X. Yang. 2011. Resveratrol induces apoptosis in breast cancer cells by E2F1-mediated up-regulation of ASPP1. Oncol Rep 25:1713-9.

[268] Shigematsu, S., S. Ishida, M. Hara, N. Takahashi, H. Yoshimatsu, T. Sakata, and R. J. Korthuis. 2003. Resveratrol, a red wine constituent polyphenol, prevents superoxide-dependent inflammatory responses induced by ischemia/reperfusion, platelet-activating factor, or oxidants. Free Radic Biol Med 34:810-7.

[269] Shin, S., B. J. Sung, Y. S. Cho, H. J. Kim, N. C. Ha, J. I. Hwang, C. W. Chung, Y. K. Jung, and B. H. Oh. 2001. An anti-apoptotic protein human survivin is a direct inhibitor of caspase-3 and -7. Biochemistry 40:1117-23.

[270] Shinriki, S., H. Jono, M. Ueda, K. Ota, T. Ota, T. Sueyoshi, Y. Oike, M. Ibusuki, A. Hiraki, H. Nakayama, M. Shinohara, and Y. Ando. 2011. Interleukin-6 signalling regulates vascular endothelial growth factor-C synthesis and lymphangiogenesis in human oral squamous cell carcinoma. J Pathol 225:142-50.

[271] Simon, C., H. Goepfert, and D. Boyd. 1998. Inhibition of the p38 mitogen-activated protein kinase by SB 203580 blocks PMA-induced Mr 92,000 type IV collagenase secretion and in vitro invasion. Cancer Res 58:1135-9.

[272] Simonian, P. L., D. A. Grillot, and G. Nunez. 1997. Bcl-2 and Bcl-XL can differentially block chemotherapy-induced cell death. Blood 90:1208-16.

[273] Singh, B. N., S. Shankar, and R. K. Srivastava. 2011. Green tea catechin, epigallocatechin-3-gallate (EGCG): Mechanisms, perspectives and clinical applications. Biochem Pharmacol 82:1807-21.

[274] Singh, M., R. Singh, K. Bhui, S. Tyagi, Z. Mahmood, and Y. Shukla. 2011. Tea polyphenols induce apoptosis through mitochondrial pathway and by inhibiting nuclear factor-kappaB and Akt activation in human cervical cancer cells. Oncol Res 19:245-57.

[275] Sivachandran, N., N. N. Thawe, and L. Frappier. 2011. Epstein-barr virus nuclear antigen 1 replication and segregation functions in nasopharyngeal carcinoma cell lines. J Virol 85:10425-30.

[276] Son, I. H., I. M. Chung, S. I. Lee, H. D. Yang, and H. I. Moon. 2007. Pomiferin, histone deacetylase inhibitor isolated from the fruits of Maclura pomifera. Bioorg Med Chem Lett 17:4753-5.

[277] Soung, Y. H., and J. Chung. 2011. Curcumin inhibition of the functional interaction between integrin alpha6beta4 and the epidermal growth factor receptor. Mol Cancer Ther 10:883-91.

[278] Spender, L. C., G. H. Cornish, A. Sullivan, and P. J. Farrell. 2002. Expression of transcription factor AML-2 (RUNX3, CBF(alpha)-3) is induced by Epstein-Barr virus EBNA-2 and correlates with the B-cell activation phenotype. J Virol 76:4919-27.

[279] Stewart, S., C. W. Dawson, K. Takada, J. Curnow, C. A. Moody, J. W. Sixbey, and L. S. Young. 2004. Epstein-Barr virus-encoded LMP2A regulates viral and cellular gene expression by modulation of the NF-kappaB transcription factor pathway. Proc Natl Acad Sci U S A 101:15730-5.

[280] Strobl, L. J., H. Hofelmayr, G. Marschall, M. Brielmeier, G. W. Bornkamm, and U. Zimber-Strobl. 2000. Activated Notch1 modulates gene expression in B cells similarly to Epstein-Barr viral nuclear antigen 2. J Virol 74:1727-35.

[281] Su, Y. W., T. X. Xie, D. Sano, and J. N. Myers. 2011. IL-6 stabilizes Twist and enhances tumor cell motility in head and neck cancer cells through activation of casein kinase 2. PLoS One 6:e19412.

[282] Sun, Y., G. Hegamyer, Y. J. Cheng, A. Hildesheim, J. Y. Chen, I. H. Chen, Y. Cao, K. T. Yao, and N. H. Colburn. 1992. An infrequent point mutation of the p53 gene in human nasopharyngeal carcinoma. Proc Natl Acad Sci U S A 89:6516-20.

[283] Sun, Z. J., G. Chen, W. Zhang, X. Hu, Y. Liu, Q. Zhou, L. X. Zhu, and Y. F. Zhao. 2010. Curcumin dually inhibits both mammalian target of rapamycin and nuclear factor-kappaB pathways through a crossed phosphatidylinositol 3-kinase/Akt/IkappaB kinase complex signaling axis in adenoid cystic carcinoma. Mol Pharmacol 79:106-18.

[284] Swart, R., I. K. Ruf, J. Sample, and R. Longnecker. 2000. Latent membrane protein 2A-mediated effects on the phosphatidylinositol 3-Kinase/Akt pathway. J Virol 74:10838-45.

[285] Tamm, I., Y. Wang, E. Sausville, D. A. Scudiero, N. Vigna, T. Oltersdorf, and J. C. Reed. 1998. IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. Cancer Res 58:5315-20.

[286] Tang, C. H., C. F. Chen, W. M. Chen, and Y. C. Fong. 2011. IL-6 increases MMP-13 expression and motility in human chondrosarcoma cells. J Biol Chem 286:11056-66.

[287] Tang, F., D. Wang, C. Duan, D. Huang, Y. Wu, Y. Chen, W. Wang, C. Xie, J. Meng, L. Wang, B. Wu, S. Liu, D. Tian, F. Zhu, Z. He, F. Deng, and Y. Cao. 2009. Berberine inhibits metastasis of nasopharyngeal carcinoma 5-8F cells by targeting Rho kinase-mediated Ezrin phosphorylation at threonine 567. J Biol Chem 284:27456-66.

[288] Thawonsuwan, J., V. Kiron, S. Satoh, A. Panigrahi, and V. Verlhac. 2010. Epigallocatechin-3-gallate (EGCG) affects the antioxidant and immune defense of the rainbow trout, Oncorhynchus mykiss. Fish Physiol Biochem 36:687-97.

[289] Thiounn, N., F. Pages, T. Flam, E. Tartour, V. Mosseri, M. Zerbib, P. Beuzeboc, L. Deneux, W. H. Fridman, and B. Debre. 1997. IL-6 is a survival prognostic factor in renal cell carcinoma. Immunol Lett 58:121-4.

[290] Trapp, V., B. Parmakhtiar, V. Papazian, L. Willmott, and J. P. Fruehauf. 2010. Anti-angiogenic effects of resveratrol mediated by decreased VEGF and increased TSP1 expression in melanoma-endothelial cell co-culture. Angiogenesis 13:305-15.

[291] Truong, M., M. R. Cook, S. N. Pinchot, M. Kunnimalaiyaan, and H. Chen. 2010. Resveratrol induces Notch2-mediated apoptosis and suppression of neuroendocrine markers in medullary thyroid cancer. Ann Surg Oncol 18:1506-11.

[292] Tsai, C. N., C. L. Tsai, K. P. Tse, H. Y. Chang, and Y. S. Chang. 2002. The Epstein-Barr virus oncogene product, latent membrane protein 1, induces the downregulation of E-cadherin gene expression via activation of DNA methyltransferases. Proc Natl Acad Sci U S A 99:10084-9.

[293] Tsai, P. Y., S. M. Ka, J. M. Chang, H. C. Chen, H. A. Shui, C. Y. Li, K. F. Hua, W. L. Chang, J. J. Huang, S. S. Yang, and A. Chen. 2011. Epigallocatechin-3-gallate prevents lupus nephritis development in mice via enhancing the Nrf2 antioxidant pathway and inhibiting NLRP3 inflammasome activation. Free Radic Biol Med 51:744-54.

[294] Tsao, S. W., X. Wang, Y. Liu, Y. C. Cheung, H. Feng, Z. Zheng, N. Wong, P. W. Yuen, A. K. Lo, Y. C. Wong, and D. P. Huang. 2002. Establishment of two immortalized nasopharyngeal epithelial cell lines using SV40 large T and HPV16E6/E7 viral oncogenes. Biochim Biophys Acta 1590:150-8.

[295] Tse, L. A., I. T. Yu, O. W. Mang, and S. L. Wong. 2006. Incidence rate trends of histological subtypes of nasopharyngeal carcinoma in Hong Kong. Br J Cancer 95:1269-73.

[296] Valentine, R., C. W. Dawson, C. Hu, K. M. Shah, T. J. Owen, K. L. Date, S. P. Maia, J. Shao, J. R. Arrand, L. S. Young, and J. D. O'Neil. 2010. Epstein-Barr virus-encoded EBNA1 inhibits the canonical NF-kappaB pathway in carcinoma cells by inhibiting IKK phosphorylation. Mol Cancer 9:1.

[297] van Niel, G., I. Porto-Carreiro, S. Simoes, and G. Raposo. 2006. Exosomes: a common pathway for a specialized function. J Biochem 140:13-21.

[298] Vanamala, J., S. Radhakrishnan, L. Reddivari, V. B. Bhat, and A. Ptitsyn. 2011. Resveratrol suppresses human colon cancer cell proliferation and induces apoptosis via targeting the pentose phosphate and the talin-FAK signaling pathways-A proteomic approach. Proteome Sci 9:49.

[299] Vareed, S. K., M. Kakarala, M. T. Ruffin, J. A. Crowell, D. P. Normolle, Z. Djuric, and D. E. Brenner. 2008. Pharmacokinetics of curcumin conjugate metabolites in healthy human subjects. Cancer Epidemiol Biomarkers Prev 17:1411-7.

[300] Vasef, M. A., A. Ferlito, and L. M. Weiss. 1997. Nasopharyngeal carcinoma, with emphasis on its relationship to Epstein-Barr virus. Ann Otol Rhinol Laryngol 106:348-56.

[301] Vaughan, T. L., J. A. Shapiro, R. D. Burt, G. M. Swanson, M. Berwick, C. F. Lynch, and J. L. Lyon. 1996. Nasopharyngeal cancer in a low-risk population: defining risk factors by histological type. Cancer Epidemiol Biomarkers Prev 5:587-93.

[302] Vesela, D., R. Kubinova, J. Muselik, M. Zemlicka, and V. Suchy. 2004. Antioxidative and EROD activities of osajin and pomiferin. Fitoterapia 75:209-11.

[303] Wang, F., C. Gregory, C. Sample, M. Rowe, D. Liebowitz, R. Murray, A. Rickinson, and E. Kieff. 1990. Epstein-Barr virus latent membrane protein (LMP1) and nuclear proteins 2 and 3C are effectors of phenotypic changes in B lymphocytes: EBNA-2 and LMP1 cooperatively induce CD23. J Virol 64:2309-18.

[304] Wang, F., S. F. Tsang, M. G. Kurilla, J. I. Cohen, and E. Kieff. 1990. Epstein-Barr virus nuclear antigen 2 transactivates latent membrane protein LMP1. J Virol 64:3407-16.

[305] Wang, J., S. E. Lindner, E. R. Leight, and B. Sugden. 2006. Essential elements of a licensed, mammalian plasmid origin of DNA synthesis. Mol Cell Biol 26:1124-34.

[306] Wang, L., S. R. Grossman, and E. Kieff. 2000. Epstein-Barr virus nuclear protein 2 interacts with p300, CBP, and PCAF histone acetyltransferases in activation of the LMP1 promoter. Proc Natl Acad Sci U S A 97:430-5.

[307] Wang, L., L. Wang, R. Song, Y. Shen, Y. Sun, Y. Gu, Y. Shu, and Q. Xu. 2011. Targeting sarcoplasmic/endoplasmic reticulum Ca(2)+-ATPase 2 by curcumin induces ER stress-associated apoptosis for treating human liposarcoma. Mol Cancer Ther 10:461-71.

[308] Wang, M., Y. Ruan, Q. Chen, S. Li, Q. Wang, and J. Cai. 2011. Curcumin induced HepG2 cell apoptosis-associated mitochondrial membrane potential and intracellular free Ca(2+) concentration. Eur J Pharmacol 650:41-7.

[309] Wang, S., and L. Frappier. 2009. Nucleosome assembly proteins bind to Epstein-Barr virus nuclear antigen 1 and affect its functions in DNA replication and transcriptional activation. J Virol 83:11704-14.

[310] Wang, X. 2001. The expanding role of mitochondria in apoptosis. Genes Dev 15:2922-33.

[311] Wang, X., Q. Wang, K. L. Ives, and B. M. Evers. 2006. Curcumin inhibits neurotensin-mediated interleukin-8 production and migration of HCT116 human colon cancer cells. Clin Cancer Res 12:5346-55.

[312] Wang, Z., Y. Huang, J. Zou, K. Cao, Y. Xu, and J. M. Wu. 2002. Effects of red wine and wine polyphenol resveratrol on platelet aggregation in vivo and in vitro. Int J Mol Med 9:77-9.

[313] Wartenberg, M., P. Budde, M. De Marees, F. Grunheck, S. Y. Tsang, Y. Huang, Z. Y. Chen, J. Hescheler, and H. Sauer. 2003. Inhibition of tumor-induced angiogenesis and matrix-metalloproteinase expression in confrontation cultures of embryoid

bodies and tumor spheroids by plant ingredients used in traditional chinese medicine. Lab Invest 83:87-98.

[314] Watson, J. L., R. Hill, P. B. Yaffe, A. Greenshields, M. Walsh, P. W. Lee, C. A. Giacomantonio, and D. W. Hoskin. 2010. Curcumin causes superoxide anion production and p53-independent apoptosis in human colon cancer cells. Cancer Lett 297:1-8.

[315] Wei, W. I., and J. S. Sham. 2005. Nasopharyngeal carcinoma. Lancet 365:2041-54.

[316] Weng, Y. L., H. F. Liao, A. F. Li, J. C. Chang, and R. Y. Chiou. 2010. Oral administration of resveratrol in suppression of pulmonary metastasis of BALB/c mice challenged with CT26 colorectal adenocarcinoma cells. Mol Nutr Food Res 54:259-67.

[317] Wilken, R., M. S. Veena, M. B. Wang, and E. S. Srivatsan. 2011. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. Mol Cancer 10:12.

[318] Williamson, M. P., T. G. McCormick, C. L. Nance, and W. T. Shearer. 2006. Epigallocatechin gallate, the main polyphenol in green tea, binds to the T-cell receptor, CD4: Potential for HIV-1 therapy. J Allergy Clin Immunol 118:1369-74.

[319] Wolfram, S., Y. Wang, and F. Thielecke. 2006. Anti-obesity effects of green tea: from bedside to bench. Mol Nutr Food Res 50:176-87.

[320] Wong, T. S., W. S. Chan, C. H. Li, R. W. Liu, W. W. Tang, S. W. Tsao, R. K. Tsang, W. K. Ho, W. I. Wei, and J. Y. Chan. 2010. Curcumin alters the migratory phenotype of nasopharyngeal carcinoma cells through up-regulation of E-cadherin. Anticancer Res 30:2851-6.

[321] Wu, L., J. C. Aster, S. C. Blacklow, R. Lake, S. Artavanis-Tsakonas, and J. D. Griffin. 2000. MAML1, a human homologue of Drosophila mastermind, is a transcriptional co-activator for NOTCH receptors. Nat Genet 26:484-9.

[322] Wu, S. H., L. W. Hang, J. S. Yang, H. Y. Chen, H. Y. Lin, J. H. Chiang, C. C. Lu, J. L. Yang, T. Y. Lai, Y. C. Ko, and J. G. Chung. 2010. Curcumin induces apoptosis in human non-small cell lung cancer NCI-H460 cells through ER stress and caspase cascade- and mitochondria-dependent pathways. Anticancer Res 30:2125-33.

[323] Wu, T. C., R. B. Mann, J. I. Epstein, E. MacMahon, W. A. Lee, P. Charache, S. D. Hayward, R. J. Kurman, G. S. Hayward, and R. F. Ambinder. 1991. Abundant expression of EBER1 small nuclear RNA in nasopharyngeal carcinoma. A morphologically distinctive target for detection of Epstein-Barr virus in formalin-fixed paraffin-embedded carcinoma specimens. Am J Pathol 138:1461-9.

[324] Xia, N., A. Daiber, A. Habermeier, E. I. Closs, T. Thum, G. Spanier, Q. Lu, M. Oelze, M. Torzewski, K. J. Lackner, T. Munzel, U. Forstermann, and H. Li. 2010. Resveratrol reverses endothelial nitric-oxide synthase uncoupling in apolipoprotein E knockout mice. J Pharmacol Exp Ther 335:149-54.

[325] Yamaguchi, K., M. Honda, H. Ikigai, Y. Hara, and T. Shimamura. 2002. Inhibitory effects of (-)-epigallocatechin gallate on the life cycle of human immunodeficiency virus type 1 (HIV-1). Antiviral Res 53:19-34.

[326] Yamashita, S., M. Kondo, and S. Hashimoto. 1985. Squamous cell carcinoma of the nasopharynx. An analysis of failure patterns after radiation therapy. Acta Radiol Oncol 24:315-20.

[327] Yan, Z., T. Yong-Guang, L. Fei-Jun, T. Fa-Qing, T. Min, and C. Ya. 2004. Interference effect of epigallocatechin-3-gallate on targets of nuclear factor kappaB signal transduction pathways activated by EB virus encoded latent membrane protein 1. Int J Biochem Cell Biol 36:1473-81.

[328] Yang, C. L., Y. G. Ma, Y. X. Xue, Y. Y. Liu, H. Xie, and G. R. Qiu. 2011. Curcumin Induces Small Cell Lung Cancer NCI-H446 Cell Apoptosis via the Reactive Oxygen Species-Mediated Mitochondrial Pathway and Not the Cell Death Receptor Pathway. DNA Cell Biol Jun 28. [Epub ahead of print]

[329] Yang, C. S., J. Y. Chung, G. Yang, S. K. Chhabra, and M. J. Lee. 2000. Tea and tea polyphenols in cancer prevention. J Nutr 130:472S-478S.

[330] Yang, W. H., Y. C. Fong, C. Y. Lee, T. R. Jin, J. T. Tzen, T. M. Li, and C. H. Tang. 2011. Epigallocatechin-3-gallate induces cell apoptosis of human chondrosarcoma cells through apoptosis signal-regulating kinase 1 pathway. J Cell Biochem 112:1601-11.

[331] Yeh, F. T., C. H. Wu, and H. Z. Lee. 2003. Signaling pathway for aloe-emodin-induced apoptosis in human H460 lung nonsmall carcinoma cell. Int J Cancer 106:26-33.

[332] Yeh, T. S., C. W. Wu, K. W. Hsu, W. J. Liao, M. C. Yang, A. F. Li, A. M. Wang, M. L. Kuo, and C. W. Chi. 2009. The activated Notch1 signal pathway is associated with gastric cancer progression through cyclooxygenase-2. Cancer Res 69:5039-48.

[333] Yip, K. W., W. Shi, M. Pintilie, J. D. Martin, J. D. Mocanu, D. Wong, C. MacMillan, P. Gullane, B. O'Sullivan, C. Bastianutto, and F. F. Liu. 2006. Prognostic significance of the Epstein-Barr virus, p53, Bcl-2, and survivin in nasopharyngeal cancer. Clin Cancer Res 12:5726-32.

[334] Yoshizaki, T., H. Sato, M. Furukawa, and J. S. Pagano. 1998. The expression of matrix metalloproteinase 9 is enhanced by Epstein-Barr virus latent membrane protein 1. Proc Natl Acad Sci U S A 95:3621-6.

[335] Young, L. S., C. W. Dawson, D. Clark, H. Rupani, P. Busson, T. Tursz, A. Johnson, and A. B. Rickinson. 1988. Epstein-Barr virus gene expression in nasopharyngeal carcinoma. J Gen Virol 69 (Pt 5):1051-65.

[336] Young, L. S., and P. G. Murray. 2003. Epstein-Barr virus and oncogenesis: from latent genes to tumours. Oncogene 22:5108-21.

[337] Yu, M. C., J. H. Ho, R. K. Ross, and B. E. Henderson. 1981. Nasopharyngeal carcinoma in Chinese---salted fish or inhaled smoke? Prev Med 10:15-24.

[338] Yu, M. C., and J. M. Yuan. 2002. Epidemiology of nasopharyngeal carcinoma. Semin Cancer Biol 12:421-9.

[339] Zetterberg, H., C. Borestrom, T. Nilsson, and L. Rymo. 2004. Multiple EBNA1-binding sites within oriPI are required for EBNA1-dependent transactivation of the Epstein-Barr virus C promoter. Int J Oncol 25:693-6.

[340] Zhang, J., Y. Du, C. Wu, X. Ren, X. Ti, J. Shi, F. Zhao, and H. Yin. 2010. Curcumin promotes apoptosis in human lung adenocarcinoma cells through miR-186* signaling pathway. Oncol Rep 24:1217-23.

[341] Zhang, J., T. Zhang, X. Ti, J. Shi, C. Wu, X. Ren, and H. Yin. 2010. Curcumin promotes apoptosis in A549/DDP multidrug-resistant human lung adenocarcinoma cells through an miRNA signaling pathway. Biochem Biophys Res Commun 399:1-6.

[342] Zhang, J. X., H. L. Chen, Y. S. Zong, K. H. Chan, J. Nicholls, J. M. Middeldorp, J. S. Sham, B. E. Griffin, and M. H. Ng. 1998. Epstein-Barr virus expression within keratinizing nasopharyngeal carcinoma. J Med Virol 55:227-33.

[343] Zhang, T. H., H. C. Liu, L. J. Zhu, M. Chu, Y. J. Liang, L. Z. Liang, and G. Q. Liao. 2011. Activation of Notch signaling in human tongue carcinoma. J Oral Pathol Med 40:37-45.

[344] Zhang, W., X. Wang, and T. Chen. 2011. Resveratrol induces mitochondria-mediated AIF and to a lesser extent caspase-9-dependent apoptosis in human lung adenocarcinoma ASTC-a-1 cells. Mol Cell Biochem 354:29-37.

[345] Zhang, Y., J. Peng, H. Zhang, Y. Zhu, L. Wan, J. Chen, X. Chen, R. Lin, H. Li, X. Mao, and K. Jin. 2010. Notch1 signaling is activated in cells expressing embryonic stem cell proteins in human primary nasopharyngeal carcinoma. J Otolaryngol Head Neck Surg 39:157-66.

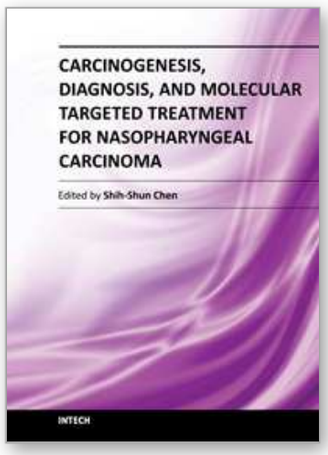
[346] Zhao, Y., H. Wang, X. R. Zhao, F. J. Luo, M. Tang, and Y. Cao. 2004. [Epigallocatechin-3-gallate interferes with EBV-encoding AP-1 signal transduction pathway]. Zhonghua Zhong Liu Za Zhi 26:393-7.

[347] Zheng, Z., J. Pan, B. Chu, Y. C. Wong, A. L. Cheung, and S. W. Tsao. 1999. Downregulation and abnormal expression of E-cadherin and beta-catenin in nasopharyngeal carcinoma: close association with advanced disease stage and lymph node metastasis. Hum Pathol 30:458-66.

[348] Zhong, Y., and F. Shahidi. 2011. Lipophilized epigallocatechin gallate (EGCG) derivatives as novel antioxidants. J Agric Food Chem 59:6526-33.

[349] Zhou, X., B. Song, L. Jin, D. Hu, C. Diao, G. Xu, Z. Zou, and S. Yang. 2006. Isolation and inhibitory activity against ERK phosphorylation of hydroxyanthraquinones from rhubarb. Bioorg Med Chem Lett 16:563-8.

[350] Zhu, J., Z. Liu, H. Huang, Z. Chen, and L. Li. 2003. Rhein inhibits transforming growth factor beta1 induced plasminogen activator inhibitor-1 in endothelial cells. Chin Med J (Engl) 116:354-9.



Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma

Edited by Dr. Shih-Shun Chen

ISBN 978-953-307-867-0
Hard cover, 246 pages
Publisher InTech
Published online 15, February, 2012
Published in print edition February, 2012

This book is a comprehensive treatise of the potential risk factors associated with NPC development, the tools employed in the diagnosis and detection of NPC, the concepts behind NPC patients who develop neuro-endocrine abnormalities and ear-related complications after radiotherapy and chemotherapy, the molecular mechanisms leading to NPC carcinogenesis, and the potential therapeutic molecular targets for NPC.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Shih-Shun Chen (2012). Potential Therapeutic Molecular Targets for Nasopharyngeal Carcinoma, Carcinogenesis, Diagnosis, and Molecular Targeted Treatment for Nasopharyngeal Carcinoma, Dr. Shih-Shun Chen (Ed.), ISBN: 978-953-307-867-0, InTech, Available from: http://www.intechopen.com/books/carcinogenesis-diagnosis-and-molecular-targeted-treatment-for-nasopharyngeal-carcinoma/potential-therapeutic-molecular-targets-for-nasopharyngeal-carcinoma

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen