

Potential Therapeutic Molecular Targets for Nasopharyngeal Carcinoma

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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- κ B) 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- κ B and activator protein-1 (AP-1) (334). NF- κ B is critically involved in tumor progression through transcriptional regulation of invasion related factors, such as MMP-9 and VEGF (3). NF- κ B overexpression can protect cancer cells against apoptosis induced by death receptors, thereby promoting the proliferation of cancer cells. Furthermore, constitutive activation of NF- κ B has been detected in various tumor cells (224). The involvement of the MAPK pathways in NF- κ B 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- κ B 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 (*ITG α 6*) 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- κ B, 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 G₂/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 (*oriP*), 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 *oriP*-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 *oriP* 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-1 α , has been observed in EBNA1-expressing NPC cells (222). EBNA1 also induces EBV-encoded RNA (EBER) expression

through the induction of EBV-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- κ B 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 G₂/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 Ca²⁺ 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-G₂/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 (Thr⁵⁶⁷) 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 Thr⁵⁶⁷ (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 KKHU100, KKHU-M156 and KKHU-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- κ B, 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- κ B activity *via* the inhibition of inhibitory protein IkappaB α 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- κ B 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 YUZA Z6 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 $\Delta Np63$ 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-1 β 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 β 1 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 Ca²⁺-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- κ B 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

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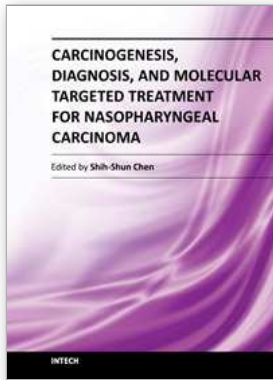
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