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Resveratrol inhibits epithelial-mesenchymal transition in hepatocellular carcinoma

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Abstract

Hepatocellular carcinoma [HCC] is a brutally aggressive cancer that puts a tremendous amount of strain on both the medical systems and the drug regulatory organizations as well. It is believed that a crucial stage in the development of HCC is the epithelial-mesenchymal transition [EMT], which increases hepatocyte malignancy and is linked to invasion and metastasis. Resveratrol [RES] has been shown to reverse EMT in a number of cancer types. In order to further understand how RES influences EMT in HCC, we have chosen to concentrate on studying and summarizing the serine/threonine kinase [Akt]/glycogen synthesis kinase 3-beta [GSK3β]/Snail signaling pathway as one of the central pathways involved in activating EMT and tumorigenesis in this review.

Keywords
Hepatocellular carcinoma; epithelial-mesenchymal transition; resveratrol; Akt/GSK3β/Snail pathway

1. Introduction

Being the third most common cause of cancer-related deaths worldwide and the fifth most common cancer, hepatocellular carcinoma [HCC] is a significant health burden. In 2020, about 19 million new cancer cases were detected and almost 10 million cancer fatalities were reported [1-3]. Although hepatitis B and C virus-related underlying infections account for the majority of HCC cases [4, 5], other risk factors like alcohol abuse, obesity, and environmental variables also play a role in the disease etiology.

Among the major environmental variables that cause HCC is diethylnitrosamine [DEN], which is present in tobacco smoke, alcoholic beverages, occupational settings, agriculture chemicals and pharmaceutical products [6]. In addition to initiation of oxidative stress, DEN has also been found to be the primary cause of DNA damage that not only induces liver cell mutations, but also promotes postnecrotic hepatocellular proliferation [7, 8]. Given these conditions, DEN is a widely used model for HCC in animals such as rats and mice, that mimics the symptoms agonizing human beings [9, 10].

The genetic controls and biochemical mechanisms underlying the pathophysiology of HCC have been areas of intensive research [11, 12]. In many of these studies, activation of epithelial-mesenchymal transition [EMT] program has been suggested as the mechanism linked to acquisition of invasive phenotype and the subsequent systemic dissemination of the epithelial cancer cells [13].

Due to the high recurrence rates and development of adverse effects after therapy, as well as the fact that liver cancer is typically discovered at an advanced stage since the lack of symptoms during early stages of the disease, the current management of HCC is not satisfactory [14, 15]. Recently, a considerable attention has been paid to the use of natural polyphenols as a prophylactic and therapeutic remedy for liver cancer. They are multi-targeting, less expensive, and prevalent in whole foods with minimal to no negative effects [16, 17].

In this review, we provide a summary on the role of EMT in the different aspects of HCC and we suggest that targeting of EMT may pave the way to develop efficacious and safe therapies to overcome the disease.

2. BASIC CONCEPT OF EMT

Epithelial to mesenchymal transition [EMT] is the process during which, the epithelial cells miss their biosignatures and display mesenchymal cell phenotypic characteristics [18-22]. This is manifested by the loss of cell polarity, acquisition of invasive and migratory qualities and resistance to apoptosis [23]. An assortment of genetic and epigenetic alterations mediate both EMT and its opposite mesenchymal to epithelial to transition [MET] that are physiologically noticed during organ development and wound healing and are pathologically associated with tumor invasion and dissemination [24-26]. Activation of EMT is driven by a series of transcription factors [EMT-TFs] including members of the SNAIL, TWIST, and ZEB families restricting the formation of E-cadherin [27-30].

Transforming growth factor-beta [TGFβ], released by a variety of cell types in the tumor-associated stroma, is regarded as the primary inductor of EMT [31, 32]. TGFβ was found to have a dual role in tumor progression; in the early stages, TGFβ has an anti-tumorigenic impact increasing apoptosis and decreasing the growth whereas in the advanced stages, TGFβ has a pro-tumorigenic impact inducing EMT and boosting metastasis [33,

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34]. It exerts its effect via a combination of Smad-dependent and -independent mechanisms. Dependent of Smad activity, TβRs-mediated phosphorylation of R Smads fosters the production of high-mobility group A2 [HMGA2] to upregulate SNAIL1 transcription [35]. Independent of Smad activity, TβRII-mediated phosphorylation of Par6 promotes the dissociation of cell junction complexes [36]. Moreover, TGFβ acts in a context specific manner in co-operation with other pathways, including Hippo, WNT/β-catenin, mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK], and phosphoinositide 3‑kinase [PI3K]/Akt to enhance their functions [37-39].

3. EMT IN HCC: Akt/GSK3β/SNAIL PATHWAY

A previous work has established the crucial role of the Akt/GSK3β/Snail signaling pathway in hepatocarcinogenesis and EMT [40-43]. The serine/threonine kinase [Akt] is an important signaling kinase participating in a wide range of physiological and pathological processes including angiogenesis and cancer progression [44, 45], and is fundamentally linked to the initiation of EMT [Figure 1] [41, 46]. According to Alessi et al. [1996] [47], Akt activity depends on Ser473 phosphorylation. After being phosphorylated, Akt serves to inhibit particular enzymes by phosphorylation such as glycogen synthesis kinase3-β [GSK3β] [48-50]. GSK3β is a multitasking kinase engaged in many signaling pathways and biochemical attributes such as neurologic disorders, diabetes, and cancer. Phosphorylation of GSK3β occurs at two key regulatory sites, Tyr216 indicating its activation and Ser9 indicating its inactivation. GSK3β phosphorylates SNAIL leading to its inhibition by ubiquitination and degradation, while P-GSK3β leads to its stabilization and nuclear localization, ensuing induction of EMT [51-53]. SNAIL has been implicated in various developmental cell fate and cell survival processes and has been correlated with recurrence and poor prognosis in various tumors [54, 55]. It moves back and forth between the cytoplasm and nucleus, where it attaches to an E-box site in the promoter of the gene that codes for E-cadherin [56], prevents the transcription of E-cadherin and therefore leads to EMT [57-59]. It also controls a number of other EMT phenotypic traits including; increased expression of mesenchymal cell markers [vimentin, N-cadherin and fibronectin], decreased expression of epithelial markers [claudins, occludins and cytokeratins], obstruction of proliferation and protection from cell death [60]. Accordingly, blockade of Akt/GSK3β/SNAIL pathway could be a promising strategy, which aims at protecting hepatocytes from EMT, thus controlling HCC.

4. THERAPEUTIC INTERVENTIONS

Of the various phytochemicals tested for their beneficial health effects, resveratrol [RES] has drawn much attention [61-63]. Many plants, including grapes, mulberries and peanuts, produce RES in reaction to harmful circumstances like stress, UV irradiation, and fungal diseases [64-66]. Several studies have indicated that, mechanisms underlying the hepatoprotective potential of RES may be combinations of anti-oxidant, anti-inflammatory, antimutagenic, reversal of EMT, influence on the cell cycle and cell differentiation, induction of apoptosis and suppression of proliferation playing roles in the initiation and secondary modification stages of neoplastic development [67-72]. RES was able to suppress chemical-induced carcinogenesis, relying on its inhibitory action of CYP450 dependent oxidase

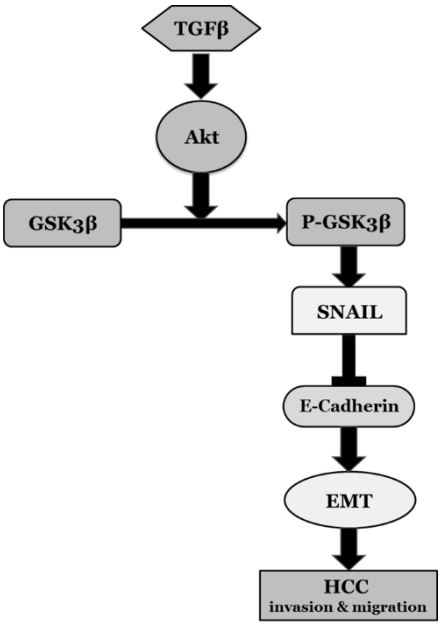

Figure 1. Role of Akt/GSK3β/Snail signaling pathway in the activation of EMT. Release of TGFβ up-regulated the Akt/GSK3β/Snail signaling cascade, promoting hepatocarcinogenesis.

detoxification and elimination by up-regulating catalase and superoxide dismutase activities [73, 74]. Besides, a previous study has evaluated the important role of RES in hindering the TGFβ /Smads signaling pathway and reducing the rate of lung and hepatic metastases in mice in an orthotopic mouse model of colorectal carcinoma [63]. In addition, RES blocked EMT, invasiveness and metastatic capacity of head and neck cancer cells by suppressing the expression of the EMT-related genes SLUG, ZEB1, E- and N-cadherin [75]. Similarly, RES prevented EMT that had been induced by the transcription factors SNAI1 and TWIST1 and also prevented the WNT/β-catenin signaling pathway in glioma stem cells [76, 77]. Furthermore, RES was found to induce apoptosis in MOLT-4 cells by suppressing the NOTCH signaling pathway [78, 79]. Thus, in light of available experimental data, RES represents an impressive candidate with many benefits hoping to be used either alone or in combination with chemotherapy in the management of HCC.

5. CONCLUSIONS

Herein, we presented an overview of the possible targets contributed to HCC prevention. We also highlighted the potential of RES against HCC through blocking of the Akt/GSK3β/Snail signaling and suppression of EMT. Future studies are mandatory to uncover the diversity of signaling pathways enforcing EMT programs during HCC and to evaluate the possibility of applying RES to patients at high risk of developing the disease [80, 81].

REFERENCES

[1]Njei B, Rotman Y, Ditah I, Lim JK. Emerging trends in hepatocellular carcinoma incidence and mortality. Hepatology [Baltimore, Md]. 2015;61[1]:191-9.
[2] Yu SJ. A concise review of updated guidelines regarding the management of hepatocellular carcinoma around the world: 2010-2016. Clinical and molecular hepatology. 2016;22[1]:7-17.
[3] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA: a cancer journal for clinicians. 2015;65[2]:87-108.

[4] Maucort-Boulch D, de Martel C, Franceschi S, Plummer M. Fraction and incidence of liver cancer attributable to hepatitis B and C viruses worldwide. Int J Cancer. 2018;142[12]:2471-7.
[5] Lok ASF. Does antiviral therapy for hepatitis B and C prevent hepatocellular carcinoma? Journal of gastroenterology and hepatology. 2011;26[2]:221-7.
[6] Bhosale P, Motiwale L, Ingle A, Gadre RV, Kurapati K. Protective effect of Rhodotorula glutinis NCIM 3353 on the development of hepatic preneoplastic lesions. Curr Sci. 2002;83.
[7] Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. The World Allergy Organization journal. 2012;5[1]:9-19.
[8] Al-Attar AM, Al-Rethea HA. Chemoprotective effect of omega-3 fatty acids on thioacetamide induced hepatic fibrosis in male rats. Saudi journal of biological sciences. 2017;24[4]:956-65.
[9] Pitot HC, Sirica AE. The stages of initiation and promotion in hepatocarcinogenesis. Biochimica et biophysica acta. 1980;605[2]:191-215.
[10] Tatematsu M, Mera Y, Inoue T, Satoh K, Sato K, Ito N. Stable phenotypic expression of glutathione S-transferase placental type and unstable phenotypic expression of gamma-glutamyltransferase in rat liver preneoplastic and neoplastic lesions. Carcinogenesis. 1988;9[2]:215-20.
[11] Oyagbemi AA, Azeez OI, Saba AB. Hepatocellular carcinoma and the underlying mechanisms. African health sciences. 2010;10[1]:93-8.
[12] El–Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. Gastroenterology. 2007;132[7]:2557-76.
[13] Thiery JP. Epithelial-mesenchymal transitions in tumour progression. Nature reviews Cancer. 2002;2[6]:442-54.
[14] Abdel-Hamid NM, Abdel-Ghany MI, Nazmy MH, Amgad SW. Can methanolic extract of Nigella sativa seed affect glyco-regulatory enzymes in experimental hepatocellular carcinoma? Environmental health and preventive medicine. 2013;18[1]:49-56.
[15] Sharma S, Tanwar A, Gupta D. Curcumin: an adjuvant therapeutic remedy for liver cancer. Hepatoma Research. 2016;2:62.
[16] Mansour M, Bekheet S, Al-Rejaie S, Shabanah O, Alhowiriny T, Cherkess Alrikabi A, et al. Ginger ingredients inhibit the development of diethylnitrosoamine induced premalignant phenotype in rat chemical hepatocarcinogenesis model. BioFactors [Oxford, England]. 2010;36:483-90.
[17] Al-Rejaie SS, Aleisa AM, Al-Yahya AA, Bakheet SA, Alsheikh A, Fatani AG, et al. Progression of diethylnitrosamine-induced hepatic carcinogenesis in carnitine-depleted rats. World J Gastroenterol. 2009;15[11]:1373-80.
[18] Thiery JP, Sleeman JP. Complex networks orchestrate epithelial-mesenchymal transitions. Nat Rev Mol Cell Biol. 2006;7[2]:131-42.
[19] Ribatti D, Tamma R, Annese T. Epithelial-Mesenchymal Transition in Cancer: A Historical Overview. Translational oncology. 2020;13[6]:100773.
[20] Micalizzi DS, Farabaugh SM, Ford HL. Epithelial-mesenchymal transition in cancer: parallels between normal development and tumor progression. Journal of mammary gland biology and neoplasia. 2010;15:117-34.
[21] Yan L, Xu F, Dai C-l. Relationship between epithelial-to-mesenchymal transition and the inflammatory microenvironment of hepatocellular carcinoma. Journal of Experimental & Clinical Cancer Research. 2018;37[1]:203.
[22] Yao D, Dai C, Peng S. Mechanism of the mesenchymal–epithelial transition and its relationship with metastatic tumor formation. Molecular cancer research. 2011;9[12]:1608-20.
[23] Georgakopoulos-Soares I, Chartoumpekis DV, Kyriazopoulou V, Zaravinos A. EMT Factors and Metabolic Pathways in Cancer. Frontiers in oncology. 2020;10.
[24] Kalluri R. EMT: when epithelial cells decide to become mesenchymal-like cells. The Journal of clinical investigation. 2009;119[6]:1417-9.
[25] Acloque H, Adams MS, Fishwick K, Bronner-Fraser M, Nieto MA. Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease. The Journal of clinical investigation. 2009;119[6]:1438-49.
[26] Hugo H, Ackland ML, Blick T, Lawrence MG, Clements JA, Williams ED, et al. Epithelial—mesenchymal and mesenchymal—epithelial transitions in carcinoma progression. Journal of cellular physiology. 2007;213[2]:374-83.
[27] Brabletz S, Schuhwerk H, Brabletz T, Stemmler MP. Dynamic EMT: a multi-tool for tumor progression. The EMBO Journal. 2021;40[18]:e108647.
[28] Wells A, Yates C, Shepard CR. E-cadherin as an indicator of mesenchymal to epithelial reverting transitions during the metastatic seeding of disseminated carcinomas. Clinical & experimental metastasis. 2008;25:621-8.
[29] Chuang K-T, Chiou S-S, Hsu S-H. Recent Advances in Transcription Factors Biomarkers and Targeted Therapies Focusing on Epithelial–Mesenchymal Transition. Cancers. 2023;15[13]:3338.
[30] Gonzalez DM, Medici D. Signaling mechanisms of the epithelial-mesenchymal transition. Science signaling. 2014;7[344]:re8-re.
[31] Zavadil J, Böttinger EP. TGF-β and epithelial-to-mesenchymal transitions. Oncogene. 2005;24[37]:5764-74.
[32] Fabregat I, Moreno-Càceres J, Sánchez A, Dooley S, Dewidar B, Giannelli G, et al. TGF-β signalling and liver disease. The FEBS journal. 2016;283[12]:2219-32.
[33] Araki K, Shimura T, Suzuki H, Tsutsumi S, Wada W, Yajima T, et al. E/N-cadherin switch mediates cancer progression via TGF-β-induced epithelial-to-mesenchymal transition in extrahepatic cholangiocarcinoma. Br J Cancer. 2011;105[12]:1885-93.
[34] Puisieux A, Brabletz T, Caramel J. Oncogenic roles of EMT-inducing transcription factors. Nature cell biology. 2014;16[6]:488-94.
[35] Thuault S, Valcourt U, Petersen M, Manfioletti G, Heldin C-H, Moustakas A. Transforming growth factor-β employs HMGA2 to elicit epithelial–mesenchymal transition. Journal of Cell Biology. 2006;174[2]:175-83.
[36] Ozdamar B, Bose R, Barrios-Rodiles M, Wang H-R, Zhang Y, Wrana JL. Regulation of the Polarity Protein Par6 by TGFß Receptors Controls Epithelial Cell Plasticity. Science. 2005;307[5715]:1603-9.
[37] Luo K. Signaling Cross Talk between TGF-β/Smad and Other Signaling Pathways. Cold Spring Harbor perspectives in biology. 2017;9[1].
[38] Chapnick DA, Warner L, Bernet J, Rao T, Liu X. Partners in crime: the TGFβ and MAPK pathways in cancer progression. Cell & Bioscience. 2011;1[1]:42.
[39] Vallée A, Lecarpentier Y, Guillevin R, Vallée JN. Interactions between TGF-β1, canonical WNT/β-catenin pathway and PPAR γ in radiation-induced fibrosis. Oncotarget. 2017;8[52]:90579-604.
[40] Sun J, Chen W, Wen B, Zhang M, Sun H, Yang X, et al. Biejiajian Pill Inhibits Carcinogenesis and Metastasis via the Akt/GSK-3β/Snail Signaling Pathway in Hepatocellular Carcinoma. Front Pharmacol. 2021;12:610158.
[41] Liu L, Dai Y, Chen J, Zeng T, Li Y, Chen L, et al. Maelstrom promotes hepatocellular carcinoma metastasis by inducing epithelial-mesenchymal transition by way of Akt/GSK-3β/Snail signaling. Hepatology [Baltimore, Md]. 2014;59[2]:531-43.
[42] Lan Y, Han J, Wang Y, Wang J, Yang G, Li K, et al. STK17B promotes carcinogenesis and metastasis via AKT/GSK-3β/Snail signaling in hepatocellular carcinoma. Cell Death & Disease. 2018;9[2]:236.
[43] Duda P, Akula SM, Abrams SL, Steelman LS, Martelli AM, Cocco L, et al. Targeting GSK3 and Associated Signaling Pathways Involved in Cancer. Cells. 2020;9[5].
[44] Franke TF, Kaplan DR, Cantley LC, Toker A. Direct Regulation of the Akt Proto-Oncogene Product by Phosphatidylinositol-3,4-bisphosphate. Science. 1997;275:665 - 8.
[45] Franke TF, Kaplan DR, Cantley LC. PI3K: Downstream AKTion Blocks Apoptosis. Cell. 1997;88:435-7.
[46] Thomas-Tikhonenko A. Cancer genome and tumor microenvironment: Springer; 2010.
[47] Alessi DR, Andjelkovic M, Caudwell B, Cron P, Morrice N, Cohen P, et al. Mechanism of activation of protein kinase B by insulin and IGF-1. Embo j. 1996;15[23]:6541-51.
[48] Chen JC, Chen Y, Lin JH, Wu JM, Tseng SH. Resveratrol suppresses angiogenesis in gliomas: Evaluation by color Doppler ultrasound. 2006;26[null]:1237.
[49] Cross DAE, Alessi DR, Cohen P, Andjelkovich M, Hemmings BA. Inhibition of glycogen synthase kinase-3 by insulin mediated by protein kinase B. Nature. 1995;378[6559]:785-9.
[50] Sutherland C, Leighton IA, Cohen P. Inactivation of glycogen synthase kinase-3 β by phosphorylation: new kinase connections in insulin and growth-factor signalling. Biochemical Journal. 1993;296[1]:15-9.
[51] McCubrey JA, Fitzgerald TL, Yang LV, Lertpiriyapong K, Steelman LS, Abrams SL, et al. Roles of GSK-3 and microRNAs on epithelial mesenchymal transition and cancer stem cells. Oncotarget. 2017;8[8]:14221-50.
[52] Bachelder RE, Yoon SO, Franci C, de Herreros AG, Mercurio AM. Glycogen synthase kinase-3 is an endogenous inhibitor of Snail transcription: implications for the epithelial-mesenchymal transition. The Journal of cell biology. 2005;168[1]:29-33.
[53] Yook JI, Li X-Y, Ota I, Fearon ER, Weiss SJ. Wnt-dependent Regulation of the E-cadherin Repressor Snail *. Journal of Biological Chemistry. 2005;280[12]:11740-8.
[54] Wang Y, Shi J, Chai K, Ying X, P Zhou B. The role of snail in EMT and tumorigenesis. Current cancer drug targets. 2013;13[9]:963-72.
[55] Yang X, Han M, Han H, Wang B, Li S, Zhang Z, et al. Silencing Snail suppresses tumor cell proliferation and invasion by reversing epithelial-to-mesenchymal transition and arresting G2/M phase in non-small cell lung cancer. Int J Oncol. 2017;50[4]:1251-60.
[56] Prokop JW, Liu Y, Milsted A, Peng H, Rauscher FJ. A method for in silico identification of SNAIL/SLUG DNA binding potentials to the E-box sequence using molecular dynamics and evolutionary conserved amino acids. Journal of Molecular Modeling. 2013;19[9]:3463-9.
[57] Batlle E, Sancho E, Francí C, Domínguez D, Monfar M, Baulida J, et al. The transcription factor Snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nature Cell Biology. 2000;2[2]:84-9.
[58] Cano A, Pérez-Moreno MA, Rodrigo I, Locascio A, Blanco MJ, del Barrio MG, et al. The transcription factor Snail controls epithelial–mesenchymal transitions by repressing E-cadherin expression. Nature Cell Biology. 2000;2[2]:76-83.
[59] Dong C, Wu Y, Yao J, Wang Y, Yu Y, Rychahou PG, et al. G9a interacts with Snail and is critical for Snail-mediated E-cadherin repression in human breast cancer. The Journal of clinical investigation. 2012;122[4]:1469-86.
[60] Wang Y, Shi J, Chai K, Ying X, Zhou BP. The Role of Snail in EMT and Tumorigenesis. Current cancer drug targets. 2013;13[9]:963-72.

[61] Rajasekaran D, Elavarasan J, Sivalingam M, Ganapathy E, Kumar A, Kalpana K, et al. Resveratrol interferes with N-nitrosodiethylamine-induced hepatocellular carcinoma at early and advanced stages in male Wistar rats. Mol Med Rep. 2011;4[6]:1211-7.
[62] Bishayee A, Dhir N. Resveratrol-mediated chemoprevention of diethylnitrosamine-initiated hepatocarcinogenesis: inhibition of cell proliferation and induction of apoptosis. Chemico-biological interactions. 2009;179[2-3]:131-44.
[63] Ji Q, Liu X, Han Z, Zhou L, Sui H, Yan L, et al. Resveratrol suppresses epithelial-to-mesenchymal transition in colorectal cancer through TGF-β1/Smads signaling pathway mediated Snail/E-cadherin expression. BMC Cancer. 2015;15[1]:97.
[64] Floreani M, Napoli E, Quintieri L, Palatini P. Oral administration of trans-resveratrol to guinea pigs increases cardiac DT-diaphorase and catalase activities, and protects isolated atria from menadione toxicity. Life Sciences. 2003;72[24]:2741-50.
[65] Soleas GJ, Diamandis EP, Goldberg DM. Resveratrol: a molecule whose time has come? And gone? Clinical biochemistry. 1997;30[2]:91-113.
[66] Jang M, Cai L, Udeani GO, Slowing KV, Thomas CF, Beecher CW, et al. Cancer chemopreventive activity of resveratrol, a natural product derived from grapes. Science. 1997;275[5297]:218-20.
[67] Jang JY, Im E, Kim ND. Mechanism of Resveratrol-Induced Programmed Cell Death and New Drug Discovery against Cancer: A Review. International journal of molecular sciences. 2022;23[22].
[68] Li W, Ma J, Ma Q, Li B, Han L, Liu J, et al. Resveratrol inhibits the epithelial-mesenchymal transition of pancreatic cancer cells via suppression of the PI-3K/Akt/NF-κB pathway. Current medicinal chemistry. 2013;20[33]:4185-94.
[69] Yuan, Zhou, Huang, Wasan, Zhang, Sun, et al. Resveratrol inhibits the invasion and metastasis of colon cancer through reversal of epithelial mesenchymal transition via the AKT/GSK3β/Snail signaling pathway. Molecular Medicine Reports. 2019;20[3]:2783-95.
[70] Amin A, Wang D, Nannapaneni S, Lamichhane R, Chen ZG, Shin DM. Combination of resveratrol and green tea epigallocatechin gallate induces synergistic apoptosis and inhibits tumor growth in vivo in head and neck cancer models. Oncology Reports. 2021;45[5]:1-10.
[71] Bhat KP, Pezzuto JM. Cancer chemopreventive activity of resveratrol. Annals of the New York Academy of Sciences. 2002;957[1]:210-29.
[72] Xu J, Liu D, Niu H, Zhu G, Xu Y, Ye D, et al. Resveratrol reverses Doxorubicin resistance by inhibiting epithelial-mesenchymal transition [EMT] through modulating PTEN/Akt signaling pathway in gastric cancer. Journal of Experimental & Clinical Cancer Research. 2017;36:1-14.
[73] Quarta A, Gaballo A, Pradhan B, Patra S, Jena M, Ragusa A. Beneficial Oxidative Stress-Related trans-Resveratrol Effects in the Treatment and Prevention of Breast Cancer. Applied Sciences. 2021;11[22]:11041.
[74] Buhrmann C, Shayan P, Popper B, Goel A, Shakibaei M. Sirt1 is required for resveratrol-mediated chemopreventive effects in colorectal cancer cells. Nutrients. 2016;8[3]:145.
[75] González-González R, Ortiz-Sarabia G, Molina-Frechero N, Salas-Pacheco JM, Salas-Pacheco SM, Lavalle-Carrasco J, et al. Epithelial-Mesenchymal Transition Associated with Head and Neck Squamous Cell Carcinomas: A Review. Cancers. 2021;13[12].
[76] Cilibrasi C, Riva G, Romano G, Cadamuro M, Bazzoni R, Butta V, et al. Resveratrol Impairs Glioma Stem Cells Proliferation and Motility by Modulating the Wnt Signaling Pathway. PloS one. 2017;12[1]:e0169854.
[77] Karkon-Shayan S, Aliashrafzadeh H, Dianat-Moghadam H, Rastegar-Pouyani N, Majidi MM, Zarei M, et al. Resveratrol as an antitumor agent for glioblastoma multiforme: Targeting resistance and promoting apoptotic cell deaths. Acta histochemica. 2023;125 6:152058.
[78] Cecchinato V, Chiaramonte R, Nizzardo M, Cristofaro B, Basile A, Sherbet G, et al. Resveratrol-induced apoptosis in human T-cell acute lymphoblastic leukaemia MOLT-4 cells. Biochemical pharmacology. 2008;74:1568-74.
[79] Espinosa L, Inglés-Esteve J, Aguilera C, Bigas A. Phosphorylation by glycogen synthase kinase-3 beta down-regulates Notch activity, a link for Notch and Wnt pathways. The Journal of biological chemistry. 2003;278[34]:32227-35.
[80] Beshay ON, Ewees MG, Abdel-Bakky MS, Hafez S, Abdelrehim AB, Bayoumi AMA. Resveratrol reduces gentamicin-induced EMT in the kidney via inhibition of reactive oxygen species and involving TGF-β/Smad pathway. Life Sci. 2020;258:118178.
[81] Chen C-L, Chen Y-H, Tai M-C, Liang C-M, Lu D-W, Chen J-T. Resveratrol inhibits transforming growth factor-β2-induced epithelial-to-mesenchymal transition in human retinal pigment epithelial cells by suppressing the Smad pathway. Drug Design, Development and Therapy. 2017;11[null]:163-73.