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Review

Regulation of signaling pathways by Ampelopsin (Dihydromyricetin) in different cancers: exploring the highways and byways less travelled

Sundas Fayyaz[1*], Muhammad Zahid Qureshi[2], Saleh S Alhewairini[2], Seda Avnioglu[3], Rukset Attar[4], Uteuliyev Yerzhan Sabitaliyevich[5], Aleksandra Buha[6], Hina Salahuddin[7], Aima Adylova[5], Fatima Tahir[1], Edyta Pawlak-Adamska[8]

[1] Department of Biochemistry, Rashid Latif Medical College (RLMC), Lahore, Pakistan
[2] Department of Plant Production and Protection, College of Agriculture and Veterinary Medicine, Qassim University, Al-Qassim, Saudi Arabia
[3] Department of Anatomy, Faculty of Medicine, Alanya Alaaddin Keykubat University, Antalya, Turkey
[4] Department of Obstetrics and Gynecology, Yeditepe University, Ataşehir/İstanbul 34755, Turkey
[5] Department of Postgraduate Education and Research, Kazakhstan Medical University KSPH, Almaty, Kazakhstan
[6] Department of Toxicology "Akademik Danilo Soldatovic", University of Belgrade-Faculty of Pharmacy, Serbia
[7] Department of Zoology, University of Okara, Pakistan
[8] Department of Experimental Therapy, Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, Wroclaw, Poland

[*]**Correspondence to:** Sundas.khan23@yahoo.com

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Abstract: Ampelopsin or Dihydromyricetin is gradually emerging as a high-quality natural product because of its ability to modulate wide-ranging signaling pathways. Ampelopsin (Dihydromyricetin) has been reported to effectively modulate growth factor receptor (VEGFR2 and PDGFRβ) mediated signaling, TRAIL/TRAIL-R pathway, JAK/STAT and mTOR-driven signaling in different cancers. Ampelopsin (Dihydromyricetin) has also been shown to exert inhibitory effects on the versatile regulators which trigger EMT (Epithelial-to-Mesenchymal Transition). Findings obtained from in-vitro studies are encouraging and there is a need to comprehensively analyze how Ampelopsin (Dihydromyricetin) inhibits tumor growth in different cancer models. Better knowledge of efficacy of Ampelopsin (Dihydromyricetin) in tumor bearing mice will be helpful in maximizing its translational potential.

Key words: Ampelopsin; Dihydromyricetin; Cancer; Apoptosis; Therapy; Signaling.

Introduction

Drug development in the modern era of genomics and proteomics has become a highly integrated pipeline in which complementary multi-omics and high-throughput computational methodologies have gained the position of criss-cross fibres.

Natural product research has gained momentum in the past three decades because of high-quality pharmacological properties and excellent potential to modulate myriad of signaling cascades (1,2). Integration of genomic, proteomic and transcriptomic characterization of different cancers has helped in improving our understanding about underlying mechanisms of cancer development, drug resistance and metastasis. Solutions to these challenges rely heavily on our rapidly evolving knowledge of cancer biology, in parallel with a deeper and conceptual comprehension of the molecular basis of different cancers (3,4,5). Therapeutic targeting of deregulated signaling pathways by bioactive molecules from natural sources has captivated extra-ordinary attention (6-18).

There are some good reviews which have analyzed general pharmacological properties of Ampelopsin in different diseases and how it exerts multiple effects at molecular level (19,20). However, there is scarcity of specialized reviews that specifically address the advancements related to this ability of Ampelopsin to modulate multiple signal transduction cascades in different cancers.

Regulation of growth factor receptor mediated signaling by Ampelopsin

VEGF/VEGFR signaling pathway has emerged as an ideal therapeutic target for inhibition of tumor growth and angiogenesis. Blockade of the ligand binding to the extracellularly located domains of the kinase receptors using monoclonal antibodies is an effective strategy. Bevacizumab is a humanized monoclonal antibody that inhibits the association of VEGF-ligands to VEGFR2 (21,22). Another classical strategy to block VEGF/VEGFR pathway is by interfering with the activation of VEGFR2 using receptor-tyrosine kinase inhibitors. Sunitinib and Sorafenib are the most advanced inhibitors (21,22).

Ampelopsin effectively reduced the phosphorylated levels of VEGFR2, AKT and ERK1/2 in HUVECs

(Human umbilical vein endothelial cells) (23). Ampelopsin exerted repressive effects on HIF-1α expression and its transcriptional target VEGF in HepG2 cells (23).

Another important and comprehensively investigated signaling pathway is PDGF/PDGFR signaling axis (24,25).

Expression levels of the PDGFRβ were found to be overexpressed in the lysates from fibroblasts obtained from carcinoma tissues. Treatment of the fibroblasts with dihydromyricetin inhibited the expression of PDGFRβ (26). Furthermore, Ampelopsin (Dihydromyricetin) inactivated ERK1/2 and AKT in the fibroblasts. Proliferation rate of the A549 lung cancer cells co-cultured with fibroblasts was markedly increased. However, there was a significant decline in the proliferation rate of Ampelopsin-treated cells (26). Overall the findings are interesting but there is an immense need to explore how deregulated PDGF/PDGFR signaling axis can be therapeutically exploited in different cancers.

Keeping in view the fact that there are practical challenges associated with the development of multi-drug cocktails and multi-targeted single agents, it will be exciting to evaluate which approach stands out as "clinically effective" with minimum off-target effects.

In the upcoming section we will summarize the developments associated with restoration of apoptotic pathway by Ampelopsin.

Restoration of TRAIL mediated signaling by Ampelopsin

Selective targeting of cancer cells has always been a pinnacle objective for basic and clinical researchers (27,28). Molecular machinery of apoptosis can be categorized into two main signaling pathways: mitochondrial-dependent intrinsic pathway that is mostly engaged by entry of truncated bid into mitochondria and release of mitochondrially localized proteins into cytoplasm to trigger activation of caspase-9. Extrinsic pathway can be triggered by TNF, TNF-related apoptosis-inducing ligand (TRAIL) and FasL. TRAIL/TRAIL-R pathway has gained appreciation because of its excellent ability to induce apoptosis specifically in cancer cells. TRAIL pro-apoptotic signaling pathway is regulated by different checkpoints that play instrumental role in inactivation of apoptotic machinery (29-32). The first checkpoint works at the membrane. This checkpoint mainly deals with interaction of TRAIL with its specific receptors. Loss of interaction will severely impair TRAIL-induced apoptosis. Ligand/receptor interaction is highly specific and tightly controlled by expression levels of cell surface receptors, whether by overexpression of the decoy receptors, loss of DR4 or DR5 expression or by post-translational modifications through glycosylation. Second checkpoint is interference with the formation of DISC (Death inducible signaling complex) in cancer cells. Ineffective formation of DISC severely impaired activation of caspase-8. Therefore scientists are focusing on the use of different strategies to induce apoptosis in TRAIL-resistant cancers. Stimulation of expression of death receptors, re-balancing of pro- and anti-apoptotic proteins are some of the highly investigated dimensions in the studies associated with TRAIL-based therapeutics (33,34).

Ampelopsin effectively induced an increase in the levels of DR4, DR5 and simultaneously reduced the expression of Bcl-2 protein. Ampelopsin also potentiated the release of cytochrome c from mitochondria in HepG2 cells (35).

Ampelopsin has also recently been tested against Epstein-Barr virus (EBV)-expressing cancer cells (36). Detailed mechanistic insights revealed that Ampelopsin potentiated caspase-8 dependent apoptosis via upregulation of TRAIL and DR5. Knockdown of DR5 drastically impaired Ampelopsin-mediated apoptotic cell death. Ampelopsin induced apoptosis in EBV-positive cells through upregulation of TRAIL/DR5 pathway (36). Ampelopsin dose-dependently promoted DR4 and DR5 expression in U251 and A172 glioma cells (37).

Efficacy of agonistic TRAIL receptor antibodies and recombinant soluble TRAIL was found to be remarkably enhanced when combined with small-molecule inhibitors of IAP proteins such as SMAC mimetics. Currently, available evidence related to regulation of TRAIL/TRAIL-R pathway by Ampelopsin is insufficient and needs detailed investigation.

JAK-STAT signaling

JAK (Janus kinase)-STAT (signal transducer and activator of transcription) signaling has captivated recognition because of its ability to transcriptionally regulate an array of oncogenic and tumor suppressor genes. In this section, we will be focusing on the potential of Dihydromyricetin to induce phosphorylation of STAT proteins.

Dihydromyricetin (Ampelopsin) sensitized acute myeloid leukemia cells to all-trans retinoic acid (ATRA)-induced myeloid differentiation by activation of STAT1 (38). Phosphorylated levels of STAT1 were found to be considerably enhanced in the cells combinatorially treated with Dihydromyricetin and ATRA (38). It has previously been revealed that Dihydromyricetin promoted activation of STAT3 that consequently resulted in induction of autophagy (39). However, use of autophagy inhibitors induced apoptosis in HNSCC (head and neck squamous cell carcinoma) cells (39).

However, these findings portray one side of regulation of STAT proteins. Available data is insufficient and cutting-edge research is required to unveil how Dihydromyricetin (Ampelopsin) effectively inhibited different STAT proteins to inhibit/prevent cancer.

mTOR-driven Signaling

mTOR (mechanistic Target of Rapamycin) is a ubiquitous serine/threonine kinase that tactfully modulates growth, proliferation and survival of cells. It is an essential kinase constituent of both mTORC2 and mTORC1 complexes. mTOR inhibitors have been shown to effectively interfere with signaling networks in different cancers.

Ampelopsin dose- and time-dependently suppressed AKT-mTOR pathway as evidenced by reduction in the levels of p-AKT, p-mTOR and p-p70S6K (ribosomal protein S6 kinase) in MCF-7 and MDA-MB-231 cancer cells (40). IGF-1 (insulin-like growth factor-1) is used as an AKT activator in different cellular studies.

It was observed that pretreatment with IGF-1 partially restored AKT-mTOR pathway inhibited by Ampelopsin. Overall, these findings highlighted that Ampelopsin induced protective autophagy in breast cancer cells through inhibition of AKT-mTOR pathway. However, use of autophagy inhibitors substantially enhanced Ampelopsin-mediated apoptosis in breast cancer cells (40). Dihydromyricetin inhibited mTOR-driven pathway and induced autophagy in HepG2 cells (41).

It is relevant to mention that autophagy behaves as a "double-edged sword" in different cancers. Although it robustly potentiates killing of cancer cells but there are various contexts in which protective autophagy is "switched on". Therefore it is necessary to use autophagy inhibitors to maximize the killing effects of different drugs.

ER stress

Increasingly it is being realized that whenever ER stress is induced, cells strategically trigger a string of highly co-ordinated complementary mechanisms which are known as unfolded protein response (UPR) to deal with misfolded proteins. Essentially, Protein kinase RNA-like endoplasmic reticulum (ER) kinase (PERK) has a critical significance in signaling module. Upon activation, PERK phosphorylated eIF2α (eukaryotic translation initiator factor-2α) and exerted inhibitory effects on protein synthesis.

Ampelopsin-treated colon cancer cells exhibited high levels of p-PERK, p-eIF2α, GRP78, and CHOP. Ampelopsin induced an increase in phosphorylated levels of p38-MAPK and JNK. Salubrinal pretreatment effectively attenuated Ampelopsin-induced phosphorylation of p38-MAPK and JNK (42). Additionally, ER stress inhibition markedly reduced the Ampelopsin-dependent phosphorylation of AMPK and expression of XAF1 (XIAP-Associated Factor-1) in colon cancer cells (42). Overall these findings clearly showcased that Ampelopsin induced apoptotic death in colon cancer cells through ER stress-driven AMPK/MAPK/XAF1 signaling axis.

Regulation of HDACs by Ampelopsin

Histone deacetylases (HDACs) have emerged as multitalented regulators of human genome. HDACs deacetylated Histone and controlled transcriptional regulation of various genes. HDAC inhibitors have been approved for the treatment of hematological malignancies and are being clinically evaluated individually and in combination with other agents for efficacy against different cancers.

HDAC2 was transcriptionally and translationally repressed by Ampelopsin. HDAC2 downregulation induced an increase in Histone acetylation and also enhanced the expression levels of tumor suppressive genes (43).

Ubiquitin ligases

There is a pressing need to dissect these complex and interconnected protein regulatory circuits.

F-BOX and WD40 domain protein-7 (FBXW7) encoded an E3 ubiquitin ligase whose WD40 domain interacted with target proteins and promoted their degradation (43). Ampelopsin reduced FBXW7α, FBXW7γ and GSK3β and increased phosphorylated levels of c-Myc at Thr58. Ampelopsin induced apoptosis independently of FBXW7α/γ and c-Myc was phosphorylated at Thr58 by another kinase other than GSK3β (43).

Our recent knowledge of these molecular mechanisms is far from complete and a number of important questions remain unanswered including the identification of ubiquitin ligases that regulate the stability of signaling proteins, the spatial and temporal nature of ubiquitylation during apoptotic signaling, interdependence and relationship with other post-translational modifications.

AMPK– GSK3β–Sox2 signaling axis

GSK3β played a key oncogenic role in osteosarcoma growth by regulation of NF-κB signaling. Dihydromyricetin suppressed the activity of GSK3β. Dihydromyricetin inactivated GSK3β through the activation of AMPKα (44). Dihydromyricetin triggered downregulation of SOX2 and reduced the formation of osteospheres. SOX2 is a transcriptional factor which belongs to high-mobility group (HMG) domain family and has an important role in embryonic development, maintenance of pluripotency and self-renewal of osteosarcoma stem cells. SOX2 mRNA and protein were found to be considerably reduced in Dihydromyricetin-treated cells (44). Collectively, these findings strongly suggested that Dihydromyricetin worked effectively against osteosarcoma cells mainly through regulation of p38MAPK and AMPK– GSK3β–SOX2 signaling pathways.

Interplay between TFEB and MALAT1: regulation of non-coding RNA by Ampelopsin (Dihydromyricetin)

Dihydromyricetin increased autophagic flux in the A431 cells as evidenced by downregulation of P62/SQSTM1 and upregulation of LC3-II (45). Furthermore, pharmacological or genetic blockade of autophagy drastically reduced Dihydromyricetin-induced cell death. Dihydromyricetin induced TFEB de-phosphorylation and promoted nuclear accumulation of TFEB. Dihydromyricetin robustly enhanced TFEB luciferase activity and the mRNA levels of ATG5, UVRAG, MAP1LC3B, ATP6V0D1, CTSB and LAMP1. Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), a long non-coding RNA was found to be overexpressed in various cancers (45). Overexpression of MALAT1 significantly prevented the activation of TFEB and increased TFEB phosphorylation in Dihydromyricetin-treated cells. Findings obtained from RNA immunoprecipitation assay revealed that use of TFEB antibody increased enrichment of MALAT1 in A431 cells which indicated binding between TFEB and MALAT1 (45).

Dihydromyricetin improved efficacy of chemotherapeutic drugs

Development of resistance against chemotherapeutic drugs is extremely challenging. Researchers are

identifying new options to overcome drug resistance and simultaneously minimize drug-associated off-target effects. Contextually, landscape of drug resistance portrayed after three decades of multidrug-resistance research has provided us with a broader overview of a myriad of strategies in which cancer cells elude chemotherapeutic drugs to survive under hostile environment.

P-glycoprotein (P-gp) and SORCIN (soluble resistance-related calcium-binding protein) have been shown to play central role in drug resistance (46). Dihydromyricetin efficiently downregulated P-gp by interfering with ERK and AKT. Combination of Dihydromyricetin and ondansetron significantly increased intracellular accumulation of Adriamycin. More importantly, Dihydromyricetin demonstrated stronger binding affinity for SORCIN as compared to Adriamycin (46). Dihydromyricetin dose-dependently downregulated mRNA and protein levels of SORCIN. Dihydromyricetin potentiated anti-cancer effects of Adriamycin in female BALB/cJNju-Foxn1nu/Nju mice xenografted with MCF-7/ADR cells (47). Overall these results demonstrated that Dihydromyricetin markedly reduced P-gp and SORCIN and concordantly enhanced efficacy of Adriamycin.

Molecular pathogenesis of colitis-associated cancer (CAC) is complicated and azoxymethane (AOM)/Dextran sodium sulfate (DSS) are used to induce cancer models (48). Dihydromyricetin -driven CPT-11 induced enhanced Immunoglobulin G levels and reduced abundance of Fusobacterium in the gut. Low dose of Dihydromyricetin enhanced effects of CPT-11 (irinotecan) inhibited tumor formation in ApcMin/+ mouse model of colon cancer (48).

Dihydromyricetin transcriptionally and translationally downregulated MRP2 (multidrug resistance protein-2) (49). NRF2 (Nuclear Factor Erythroid 2, Related Factor 2) has been shown to regulate MRP2 expression. Dihydromyricetin interfered with NRF2-driven signaling and exerted repressive effects on expression of MRP2 in oxaliplatin-resistant HCT116 cells (49). Dihydromyricetin markedly sensitized doxorubicin- and paclitaxel-resistant ovarian cancer cells by exerting inhibitory effects on survivin (50).

Conclusion

Ampelopsin is gradually gaining interest because of its remarkable properties to pleiotropically modulate wide ranging signaling pathways in different diseases. More importantly, Ampelopsin has also been noted to be effective against different cancers. We have discussed these aspects in previous sections about how Ampelopsin regulated different cascades and inhibited/prevented cancer growth. Realistically, different pathways although have been explored but these findings can merely be considered as ″Tip of an Iceberg″ and we have to go a long way to search for convincing answers for many outstanding questions.

Dihydromyricetin downregulated Notch1 and Hes1 in HepG2 and QGY7701 cells (51). However, these aspects have to be deeply studied in cancer models.

There is a need to further explore the effects of Ampelopsin by combining it with different clinically approved drugs. Comprehensive analysis of combinatorial treatments in xenografted mice models will be helpful in realistic and evidence-based evaluation of true potential of Ampelopsin. Additionally, nanotechnological approaches will improve the bioavailability of Ampelopsin and we can efficiently deliver the payload to the target sites.

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