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MINI-REVIEW ARTICLE

Anticancer Mechanisms of Bioactive Peptides

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Abstract: Despite technological advancement, there is no 100% effective treatment against metastatic cancer. Increasing resistance of cancer cells towards chemotherapeutic drugs along with detrimental side effects remained a concern. Thus, the urgency in developing new anticancer agents has been raised. Anticancer peptides have been proven to display potent activity against a wide variety of cancer cells. Several mode of actions describing their cytostatic and cytotoxic effect on cancer cells have been proposed which involves cell surface binding leading to membranolysis or internalization to reach their intracellular target. Understanding the mechanism of action of these anticancer peptides is important in achieving full therapeutic success. In the present article, we discuss the anticancer action of peptides accompanied by the mechanisms underpinning their toxicity to cancer cells.

Keywords: Anticancer peptides, anticancer, antitumor, mechanism of action, cytotoxicity, drug resistance, membranolysis.

1. INTRODUCTION

Increasing resistance of cancer cells towards chemotherapeutic drugs along with detrimental side effects for the past decades have raised the urgency in developing new anticancer agents. Recently, due to greater understanding of tumor biology, development of new generation of optimized therapeutic agents targeting genuine features of cancer cells have been developed and being evaluated [1]. Anticancer peptides (ACPs) are one of the untapped resource with low toxicity towards normal cells apart from anticancer activity against cancer cells [2]. Thus far, 60 peptide-based drugs have been approved by Food and Drug Administration (FDA) and much more are in the process of seeking approval [3]. Despite extensive research, information on how these ACPs act on the cellular level to prevent cancer cell proliferation and migration is limited. Many different laboratories have revealed novel anticancer mechanisms of ACPs beyond membrane pore formation, including interaction with tumor-relevant ion channels [4], tumor suppressor [5], mitochondrial porins [6], and anti-apoptotic proteins [7] to alter target molecules expression, act as inhibitors, activators, or direct inducers of cell death [8, 9] (Table **1**, Figure **1**). Understanding their mechanism of action is important in drug development optimization. In the present article, we discuss the anticancer action of peptides accompanied by the mechanisms underpinning their toxicity to cancer cells.

2. MITOCHONDRIA-MEDIATED APOPTOSIS

ACPs inducing cancer cell death *via* activation of apoptotic pathway is one of the standard approaches for cancer treatment [2]. Dysregulation of this programmed cellular self-destruction often results in development of cancer. Apoptotic cell death is characterized by chromatin condensation, cellular shrinkage, cell membrane blebbing as well as nuclear fragmentation [10]. Intrinsic pathway takes place *via* cytochrome c release triggered by stress or damage to the cells, subsequently inducing apoptotic cell death by downstream activation of caspase cascade, resulting in cleavage of multiple proteins [11]. The members of B-cell lymphoma cell 2 (Bcl-2) family are also responsible for the release of cytochrome c from the mitochondria at the early stage of apoptosis and can be divided into two groups of anti-apoptotic (Mcl-1, Bcl-2, Bcl-X and Bcl-XL) and pro-apoptotic (Bax and Bak) including BH3-only proteins (Bad, Bim, and Bid) [12, 13]. Cytochrome c allows the assembly of apoptosome complex by interacting with Apaf-1, which in turn activates pro-caspase 9. Once activated, caspase-9 cleaves caspase-3 and triggers proteolytic cleavage of intracellular proteins such as kinases, cytoskeletal proteins, DNA control proteins and endonucleases inhibitor, ultimately leading to nucleus fragmentation and disintegration of nuclear membrane [14-16].

Overexpression of anti-apoptotic proteins has been observed in various human cancers such as breast [17], prostate [39], pancreatic [40] cancer, and neuroblastoma [41] which contributed to cancer development, progression and chemoresistance [42]. In fact, anti-apoptotic proteins sequestered the well-conserved region of BH3-only proteins to prevent activation of Bax and Bak [43]. Molecules mimicking BH3-only protein were designed to disrupt the interaction of anti-apoptotic proteins with BH3-only proteins by binding to the hydrophobic groove of anti-apoptotic proteins, subsequently displacing BH3-only proteins to induce apoptosis [7]. A peptide derived from Bim BH3 domain, named 072RB was reported to possess anticancer activity

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Table 1. Various types of ACPs with their mechanisms.

ACPs	Cells and Tumor Xeno-grafts*	Mode of Action	References
072RB	B-CLL, AML*	Induction of apoptosis by downregulating Bcl-XL and Mcl-1.	[18]
NuBCP-9	ZR-75-1	Dislodge BH4 domain of Bcl-2 which blocked the antiapoptotic activity of Bcl-XL.	[19]
Antp-LP4	PBMCs	Induction of apoptosis by displacing hexokinase and Bcl-2 from VDAC1 and VDAC1 oligomerization.	[6]
Hexokinase II-Derived peptide	Hela	Induction of apoptosis by competitive disruption of hexokinase II-VDAC interaction.	[20]
Poropeptide Bax[106-134]	SK-MEL-28	Mitochondrial depolarization *via* direct mitochondrial outer membrane permeabilization .	[9]
DIM-LF11-318	A375	Membrane lysis *via* hydrophobic and electrostatic interaction with phosphatidylserine.	[21]
Pardaxin	HT1080	Pore formation *via* barrel-stave model in phosphatidylcholine membrane; Bilayer disruption *via* carpet-like model in phosphatidylglycerol membrane.	[22-26]
Kalata B1 and Kalata B2	HeLa, MM96L	Toroidal pore formation in phosphatidylethanolamine membrane.	[27-29]
P28	Mel-29, MEL-23, MEL-6, MCF-7, MDA-MB-231*	Induction of G2/M phase cell cycle arrest *via* inhibition of COP1 binding to p53.	[5, 30, 31]
BmKKx2	K562	Enhanced apoptosis by blocking hERG channels.	[32]
Ergtoxin	SKOV-3	Cell proliferation inhibition and cell cycle arrest by blocking hERG channels.	[33]
SOR-13, SOR-C27	SKOV-3*	Reduction of tumor growth *via* inhibition of TRPV6.	[34, 35]
Tv1	HCC	Inhibition of cell proliferation and induction of calcium-dependent apoptosis *via* inhibition of TRPV6 and TRPC6.	[36]
Chlorotoxin	STTG1,U251-MG	Reduction of cell migration by blocking CLC-3 channel.	[4, 37, 38]

in vitro and *in vivo*. Although the exact mechanism of action is not clear, the anticancer activity was exerted through the activation of apoptosis *via* downregulation of Bcl-XL and Mcl-1 in leukemia cells [18]. Furthermore, a Bcl-2-converting short peptide derived from nuclear receptor Nur77, NuBCP-9 was found to dislodge BH-4 domain of Bcl-2 to expose its BH-3 domain, eventually blocking anti-apoptotic effect of Bcl-XL and Bax/Bak activation in cancer cells [19]. Encapsulation of NuBCP-9 into nanoparticles (NPs) comprising diblock poly(lactic acid)-poly(ethylene glycol) (PLA-PEG) copolymers or tetrablock PLA-PEG-poly(propylene)-PEG (PLA-PEG-PPG-PEG) copolymers were designed by Kumar *et al.* [44]. *In vitro* administration of NuBCP-9/NPs induced apoptosis in human breast cancer (MCF-7) and liver cancer (HepG2) cells. *In vivo,* complete regression of Erlich mammary adenocarcinoma and prolonged survival of NuBCP-9/NPs-treated mice were demonstrated. Other than overexpressing anti-apoptotic proteins, cancer cells can circumvent apoptosis by overexpressing hexokinase, a key mitochondria-bound glycolytic enzyme involved in aerobic glycolysis to promote tumorigenesis *via* interaction with the most abundant isoform of voltage-dependent anion channel (VDAC), called VDAC1 [6, 45]. VDAC1-based cell-penetrating peptide (Antp-LP4), designed by Prezma *et al.* [6] was found to =induce displacement of hexokinase and Bcl-2 from VDAC1 of B-cell chronic lymphocytic leukaemia cells (CLL) subsequently resulting in the loss of mitochondrial membrane potential, depletion of ATP, VDAC1 oligomerization, and release of cytochrome c, followed by cell death. Similar results was shown in a study by Woldetsadik *et al.* [20], whereby competitive disruption of hexokinase II-VDAC interaction indeed resulted in apoptotic cell death following treatment with penetration-accelerating sequence-coupled hexokinase-II derived peptide in HeLa cells. Collectively, manipulation of the interaction between hexokinase and VDAC may be an avenue to potentiate the anticancer effects of ACPs.

3. MEMBRANE DISRUPTION

In some cases, apoptosis signalling pathways of cancer cells are compromised, resulting in resistance due to mutation and deficiency of pro-apoptotic proteins as tumor metastasize, thus rendering them ineffective as an inducer of apoptosis [46]. In order to reverse drug resistance and restore apoptosis, mechanisms of anticancer drugs mainly perturbing the membrane integrity are attracting attention as resistance is less likely to occur [47]. In a landmark study conducted by Valero *et al.* [9], found that the membrane insertion and pore-forming domain of Bax, called poropeptide Bax[106-134] specifically targeted and permeabilized mitochondrial outer membrane (MOM) without complex structural reorganization, triggering mitochondrial depolarization, release of cytochrome c and caspase-dependent apoptosis in cancer cells.

Furthermore, extensive studies have indicated that cationic bioactive peptides kill cancer cells by disrupting the integrity of the plasma membrane, mainly targeting the externalized negatively charged phosphatidylserine (PS) in most cancer cells including breast, skin, pancreatic, and skin [48]. A peptide derived from human cationic host defence peptide lactoferricin, DIM-LF11-318 recently showed fast killing properties by disrupting the membrane of melanoma cells exposing higher PS-level on the outer membrane leaflet in comparison with those exposing lesser PS [21]. Results from earlier study conducted by Wang *et al.* [49], confirmed that PS

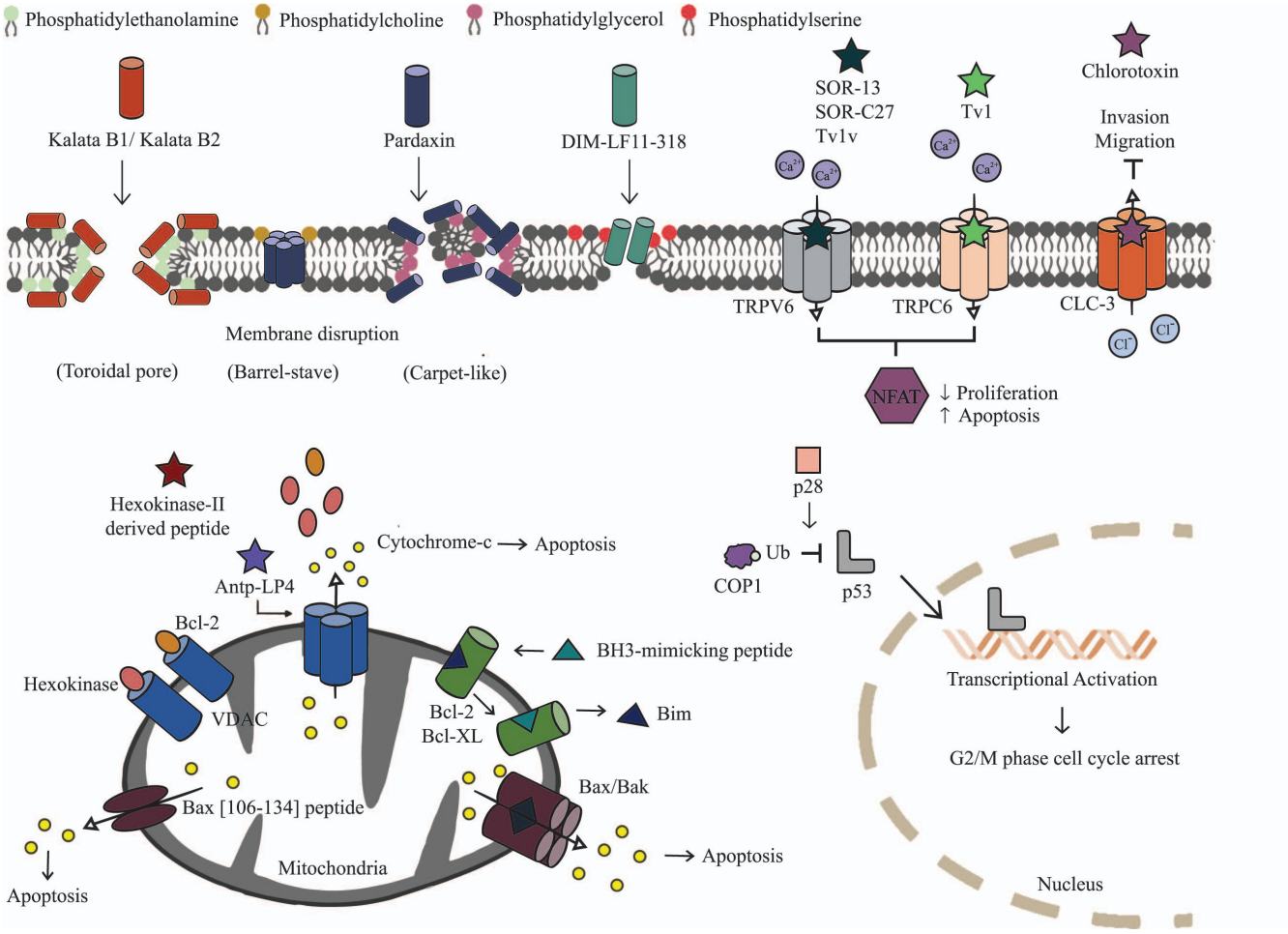

Figure (1). Schematic of anticancer mechanisms of various ACPs. *A higher resolution / colour version of this figure is available in the electronic copy of the article*.

not only provided sites for electrostatic interaction for cationic peptide with a binding ratio of 1:5 (peptide:PS) but also promoted that formation of α-helical conformation, which enhanced their membranolytic activity.

Membrane disruption induced by ACPs mainly occur in three modes: carpet-like, barrel-stave and toroidal pore model [50]. It is assumed that the peptides diffused laterally through the lipid bilayers upon interaction with the lipid head groups mediated by electrostatic properties, followed by self-assembly of peptides on the membrane surface and pore formation upon insertion [51]. In the barrel-stave model, peptides attach parallel to the plane of lipid bilayer at low peptide-lipid (P/L) molar ratio and insert perpendicularly to the cell membrane at high P/L ratio, thus lining the pore lumen parallel to the phospholipid chains with the polar face of peptides arranged towards the pore interior while the nonpolar face arranged towards hydrophobic core of the bilayer [52, 53]. In toroidal-pore model, instead of parallel orientation with phospholipid chains, peptides form pore by inducing local membrane curvature where the phospholipids bend inwards, forming toroidal-shaped pore where the phospholipid head groups line the pore lumen together with the peptides [54]. In carpet-like model, peptide oriented parallel to the plane of lipid bilayer to cover the membrane surface in a carpet-like format, resulting in unfavourable side chain interactions [53]. Upon exceeding a particular threshold, the membrane collapses in a surfactant-like manner into micelles [50]. Various studies revealed differences in the orientation behaviour of ACPs in different membrane disruption mechanisms which are dependent on the hydrophobic tail and headgroup types of the bilayer. Pardaxin, a fish antimicrobial peptide was reported to induce membrane injury to human fibrosarcoma (HT1080) cells [22]. Mechanistic study suggested that in the presence of phosphatidylglycerol (PG), pardaxin adopted a parallel orientation, indicating a carpet--like bilayer disruption model [24, 25]. Alternatively, pardaxin disrupted the membrane composing phosphatidylcholine (PC) *via* barrel stave mechanism, as evidenced by its

transmembrane orientation [23, 25, 26]. Furthermore, membrane-active and pore-forming cyclotides Kalata B1 and Kalata B2 were shown to bind specifically with phosphatidylethanolamine (PE)-containing membranes rather than those without PE [27-29, 55]. The interaction then resulted in the alteration of membrane packing constraints, subsequently opened or increased the existing membrane defects size, leading to the formation of pores [27].

4. P53-MEDIATED GROWTH INHIBITION PATHWAY

In healthy cells, the level of p53 is kept low due to rapid proteasomal degradation by ubiquitin E3 ligases such as constitutively photomorphogenic 1 (COP1) [56]. In response to various cellular stress, p53 is activated to induce protective reactions such as DNA repair, cell cycle arrest or apoptosis [57]. However, the oncosuppressive function of p53 is inactivated in most human cancer cells due to aberrations of ubiquitin-proteasome pathway or mutations [58]. A fragment of AMP/ACP azurin, p28 inheriting the tumor suppressor activity of Azurin was reported and a number of patents (WO2010080506, WO2010078042, US2010087377 have been granted for its anticancer activity [59]. This peptide demonstrated efficacy against human melanoma (MEL-23 and -29) and breast cancer (MCF-7, MDD2 and MDA-MB-231) cells *in vitro* and in MDA-MB-231 xenograph *in vivo* [5]. With efficient cellular penetration ability, binding of p28 with the L1 loop of DNA-binding domain of p53 inhibited p53 degradation signalling pathway by blocking interaction between p53 and COP1, which in turn resulted in the post--translational increase of p53 levels that induces G2/M phase cell cycle arrest [30, 31, 60]. Nonetheless, the contributing factors for this favourable trait is still unspecified. The phase I clinical study indicated that p28 was well tolerated in 15 patients with advanced, refractory and recurrent solid tumors without significant side effects and immunogenicity reported, which is in consistent with animal models [61]. Three patients are alive 25, 32 and 36 months from the start of treatment. Encouraged by the results, Pediatric Brain Tumor Consortium enrolled in the phase I clinical trial involving 18 children with recurrent or progressive central nervous system (CNS) tumors [62]. The results highlighted that p28 was safe for children with progressive CNS tumors. However, p28 lacked efficacy against paediatric CNS tumors as a single cytostatic agent, thus encouraged further combinatorial strategies.

5. ION CHANNELS

Ion channels are generally membrane-bound signalling proteins residing in plasma membrane or membranes of organelles, including mitochondria, endoplasmic reticulum and nucleus that mediate the transmembrane transport of metabolites and ions. In normal cells, ion channels regulate cellular homeostasis in response to changing physiological demands by controlling the transmembrane transport of ions and metabolites, membrane potentials and cell volume (osmoregulation) to modulate cell proliferation [63, 64]. Certain ion channels are aberrantly expressed in human cancers which participate in the neoplastic progression, invasion and metastasis of tumors [65] such as potassium (Kv) channels [66], chloride ion (Cl^-) channels [67], calcium ion (Ca^{2+}) channels [64] including transient receptor potential (TRP) channels [68].

5.1. K^+ Channel

Voltage-gated K^+ (Kv) channels are the most complex class of voltage-gated ion channels encoded by 40 genes belonging to 12 subfamilies (Kv1-Kv12), where their activities are tightly regulated by the changes in the cell's membrane potential [64]. Overexpression of Kv channels have been shown to be implicated in the transition of metastasis by inducing integrin-dependent intracellular signalling pathways [69] and upregulating vascular endothelial growth factor (VEGF) [70]. Human ether à-gogo-related gene (hERG) potassium channel, also known as Kv11.1 is upregulated in a number of cancer cells such as breast [71] and pancreatic [72], whereas no remarkable hERG protein expression is observed in non-cancerous cells [32]. In these, hERG controlled the pro-migratory phenotype in leukemic cells through the formation of macromolecular complex by recruiting growth factor receptors [73], integrin subunits [69], or chemokines [74]. It was found that blocking the hERG channels was able to inhibit the proliferation of leukemic cells [75-77]. A 36-residue peptide isolated from scorpion *Buthus martensii* Karsch, BmKKx2 is a potent hERG channel blocker, where *in vitro* investigation performed in human myelogenous leukemia (K562) cells demonstrated promising results. Specifically, blocking the hERG channels not only reduced cell proliferation, but also reduced the intracellular Ca^{2+} influx, thereby enhanced K562 cells apoptosis upon Ara-C induction [32]. Earlier experimental evidence confirmed that scorpion venom peptide, Ergtoxin inhibited the proliferation of SKOV-3 and facilitated cell cycle arrest by blocking hERG channels [33]. However, prolonged hERG channel activation impaired the proliferative activity of mammary gland adenocarcinoma-derived cells by inducing a cell senescence program [78]. Taken together, whether the activation or inhibition of over-expressed potassium channel in cancer cells is tumorigenic or tumor suppressive is highly dependent on the context.

5.2. Ca^{2+} Channel

Calcium ions (Ca^{2+}) are cellular messengers that regulates majority of cellular reactions, whereby malfunction of calcium homeostasis initiates calcium-sensitive pathways promoting tumor cell migration and metastasis [68]. Ca^{2+} homeostasis is tightly regulated by TRP channels, particularly TRP vanilloid 5 (TRPV5) and 6 (TRPV6), where upregulation of these channels augments development and progression of colon, thyroid, breast, and prostate cancer [35]. Derivatives of novel paralytic peptide Soricidin derived from *Blarina brevicauda*, SOR-13 and SOR-C27 (US patent, US20160206694A1) were proven to be a specific inhibitor of TRPV6 which inhibited Ca^{2+} uptake, thereby inhibited the activation of nuclear factor of activated T-cell (NFAT) tran-

scription factor [79] and reduced viability of various cancer cells overexpressing TRPV6 effectively [35]. *In vivo* fluorescence imaging and MRI images demonstrated that both SOR peptides had great bioaccumulation and tumor homing ability in mouse-bearing human ovarian carcinoma (SKOV-3) xenograft [35]. Moreover, clinical trial for the use of SOR-C13 in the treatment of late-stage solid tumor cancer highlighted that majority of the patients did not encounter significant toxicities, with two stage-IV pancreatic cancer patients showing tumor size reduction [34]. Similar results were obtained in hepatocellular carcinoma (HCC) cells overexpressing TRPV6 and TRPC6 treated with Tv1, a venom peptide isolated from predatory marine snail *Terebra variegata*. The proliferation of HCC cells were significantly inhibited upon inhibition of TRPV6 and TRP canonical 6 (TRPC6) channels by Tv1 peptide, thus leading to proliferation inhibition and calcium-dependent apoptosis [36]. Potent inhibition of tumor growth without systemic toxicity was also reported, justifying *in vitro* efficacy.

5.3. Cl^- Channel

Chloride ion (Cl^-) channels play a pivotal role in facilitating the transmembrane transport of Cl^- and regulating the pH, membrane potential, and cell volume, where the latter is responsible for the migration and infiltration of cancer cells [64]. The voltage-dependent Cl^- channel CLC family, particularly CLC-3 have been implicated in a glioma tumors [67]. This channel is not abundantly expressed in normal cells nor tumors of nonglial origin. In malignant glioma cells, Cl^- movement across the plasma membrane upon activation of CLC channels to facilitate the changes in cell volume and shape which are required for them to invade and migrate through the extremely narrow extracellular spaces of the brain, thereby forming distant satellite tumors [80]. Hence, inhibition of CLC channels preventing Cl^- flux may limit the extend of glioma cell shape alteration, and thus impedes glioma cell invasion and migration. This model is confirmed by various experimental evidences reporting anti-invasive effects of chlorotoxin, a peptide derived from venom of scorpion *Leiurus quinquestriatus,* which effectively reduced glioma cell migration by blocking highly expressed CLC-3 channel [4, 37, 38]. Radioactive iodine ^{131}I-labelled chlorotoxin (^{131}I-TM-601) has completed phase I and II clinical trials to treat glioblastomas and anaplastic astrocytomas [81, 82], and allowed by FDA to proceed to phase III as no toxicity and death were reported upon local administration [83]. Due to its specific binding, chlorotoxin has been used to brain gliomas delineation to measure tumor progression and improve resection of malignancies [84]. Peptides designed to block the ion channels specifically over-expressed by glioma might be a worthy therapeutic strategy in the treatment of highly aggressive glioblastoma.

CONCLUSION

Although the discovery of thousands of natural peptides leading to the millions of synthetic peptides have been found so far, only a few of them are being tested in clinical trials or show fairly good clinical efficacy. Hence, the current understanding of the cancer cells' abnormal metabolic pathway and the mode of action of ACPs are vital to increase the probability of peptide-based drugs advancing to clinical use. ACPs not only could act as a direct or indirect inducer of apoptosis but can also inhibit the proliferation and migration of cancer cells by targeting the tumor specific ion channels and membrane phospholipids. Additionally, inhibition of p53 ubiquitination and proteasomal degradation mediated by COP1 could also be a powerful strategy in the fight against cancer.

LIST OF ABBREVIATION

B-CLL	=	B-cell chronic lymphocytic leukemia cell;
AML	=	acute myeloid leukemia cells;
ZR-75-1	=	MCF-7, MDA-MB-231, human breast cancer cell lines;
PBMC	=	peripheral blood lymphocytes;
Hela	=	human cervical cancer cell line;
SK-MEL-28	=	A375, MM96L, MEL29, MEL-23, MEL-6, human melanoma cell lines;
HT1080	=	human fibrosarcoma cells;
K562	=	human myelogenic leukemia cell line;
SKOV-3	=	human ovarian cancer cell line;
HCC	=	hepatocellular carcinoma;
STTG1,U251-MG	=	human glioma cell lines.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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