**Table 1. Sites of action of agents targeting mitochondrial complexes and conclusions**

|  |  |  |  |
| --- | --- | --- | --- |
| Drugs | Effect target | Application | Reference |
| Mitomycin metformin | CI | PANC-1、TNBC | (Cheng et al., 2019b) |
| Mito-DFO | CI | MCF-7、MDA-MB-231 | (Sandoval-Acuna et al., 2021) |
| BAY87-2243 | CI | - | (Sica et al., 2019) |
| IAC-S010759 (OPi) | CI | Multiple MAPKi-resistant BRAF-mutant melanoma models, acute myeloid leukemia (AML) models | (Molina et al., 2018; Vashisht Gopal et al., 2019) |
| EVT-701 | CI | In vitro and in vivo efficacy of OXPHOS-Eµ-Myc lymphoma in mouse, NSCLC, and NH-B-cell lymphoma models | (Luna Yolba et al., 2021) |
| ME-143/ME-344 | CI and mildly inhibit CIII | HEK293T human embryonic kidney | (Lim et al., 2015) |
| Mito-MGN | CI | B16-F10、B16-F0 | (Cheng et al., 2020; AbuEid et al., 2021) |
| Lippia organoids extract | CI | MDA-MB-231 | (Raman et al., 2017; Raman et al., 2018) |
| Mitochondria-targeted hydroxyurea（Mito-Hu） | CI | Miapaca2 | (Boddapati et al., 2008; Cheng et al., 2021) |
| Mito-lonidamine（Mito-LND） | CI | A549、H2030BrM3 | (Cheng et al., 2019a) |
| Mito-Tamoxifen | Inhibit CI and CII | HCT116、DU 145、MCF-7 | (Rohlenova et al., 2017; Ezrova et al., 2021) |
| α-TOS | CII | MCF-7、MDA-MB-453、NSC、B9rec、B10、B1 | (Dong et al., 2008) |
| γ-Tocotrienol（γ-T3） | CII | SGC-7901、MGC-803 | (Wang et al., 2019) |
| Mito-VES | CII | human T lymphoma Jurkat, Bax-Jurkat, and Bax-/Bak-Jurkat cells; human mesothelioma  cells Meso2, Ist-Mes-1, Ist-Mes-2, and MM-BI; human breast cancer  cells MCF7 (erbB2-low) and MDA-MB-453 (erbB2-high) and MCF7DD9 cells with transcriptionally inactive p53; human colorectal cells HCT116; human neuroblastoma TetN21 cells; human non-small-cell lung carcinoma cells H1299; human cervical cancer cells HeLa; mouse mesothelioma cells AE17; human nonmalignant mesothelial cells Met-5A; human fibroblasts A014578; rat ventricular myocyte-like cells HL1; and mouse atrial myocyte-like cells H9c2. | (Dong et al., 2011; Liang et al., 2021) |
| GinsenosideRh2 | CI, III and V | Hela、C33A、End1/e6e7 Cells | (Liu et al., 2021) |
| Mito-Atovaquone | CI, CIII | LKR13、unscc680、LKR13-luc | (Mudassar et al., 2020; Huang et al., 2022) |
| Capsaicin | CI, CIII | BxPC-3、AsPC-1 | (Pramanik et al., 2011) |
| Mitochondria-targeted carboxy-proxyl (Mito-CP) | COX IV、Mcl-1 were dramatically down-regulated | TT、MZ-CRC-1 | (Starenki and Park, 2013; Cheng et al., 2015; Hong et al., 2017) |
| Mito-CP-Ac | CIII | MiaPaCa-2、 PANC-1、 MCF-7、 MDA-MB-231、 MCF-10A and A431 Cells | (Zhou et al., 2022) |

Table 2. Other mechanisms of mitochondrial targeting agents and applications

|  |  |  |  |
| --- | --- | --- | --- |
| Drugs | Mechanism | Application | Reference |
| Mito-Q | Induction of mitochondrial uncoupling | MCF-7, MCF-10A, and MDA-MB-231 cells | (Cheng et al., 2012) |
| Lupane Triterpenoid Derivatives | The dose-dependent induction of ROS production reduced the cell membrane potential | K562、A549、ECA-109、HepG2、HL-7702、HL-60 | (Xu et al., 2022) |
| 3-O-(3'-acetylphenylacetate)-betulin with triphenyl phosphonium | Arrest of the tumor cell at the G2/M phase, caused ROS overproduction, decreased ψM, and induced apoptosis via the  mitochondria pathway. | A549、U87、Hela、MDA-MB231、HCT116 | (Kariyil et al., 2021) |
| Chloroform Fraction of Methanolic Extract of Seeds of Annona muricata (CMAM) | To induct S Phase arrest and ROS dependent caspase activated mitochondria-mediated  apoptosis | MDA-MB-231 | (Lin et al., 2011) |
| 18b-Glycyrrhetinic acid derivatives | The dose-dependent induction of cell apoptosis | A549、U87、Hela、MDA-MB231、HCT116、NCM460 | (Jin et al., 2019) |
| Triphenyl phosphonium conjugated glycyrrhetinic  acid derivatives | Apoptosis cells through the mitochondrial  pathway via the collapse of mitochondrial membrane potential, reactive oxygen species production and the  activation of caspase-9 and caspase-3 | HepG-2、A549、MCF-7、HT-29、A2780、HL-7702 | (Zheng et al., 2014) |
| Curcumin Derivative B63（B63） | ROS elevation caused by ER stress and mitochondrial dysfunction | SW620、SW480、HCT116、HIEC | (Kim et al., 2020) |
| CADD522 | Regulation of ROS levels induces apoptosis | Hs578t、RUNX2 KD、MCF7-RUNX2 | (Liu et al., 2018) |
| HA-ionic-TPP-DOX | Increased ROS production and slightly decreased mitochondrial membrane potential | MCF-7/ADR | (Wang et al., 2014) |
| Bardoxolone methyl (CDDO-Me) | Apoptosis was induced by increasing ROS and decreasing intracellular glutathione levels | EC109、KYse70 | (Wang et al., 2015; Ju et al., 2021) |
| Triphenyl phosphonium derivatives of CDDO | Mitochondrial membrane potential decreased and cell apoptosis was induced | MCF-7 | (Szabo et al., 2021) |
| Mito-chondriotropic PAP-1 Derivatives | Blockade of IMM Kv1.3 resulted in an initial hyperpolarization and apoptosis caused by cytochrome C release after ROS release | Jurkat T Cells、Primary pathology CD19+/ CD5+ B Cells, B16F10 Melanoma Cells, Pathological B-CLL Cells, | (He et al., 2022) |
| DNA methyltransferase (DNMT) inhibitor RG108 | RG108 treatment could reduce ROS accumulation and inhibit apoptosis, which is mediated, at least partially, through LRP1ePI3K/AKT signaling pathway | HEI-OC1 | (Xu et al., 2018) |
| Pyruvate Dehydrogenase Kinase (PDK1) Inhibitors | The extracellular acidification rate and lactate formation were decreased, and ROS production was increased | NCI-H1650 | (Sharma et al., 2019) |
| Mitochondrial targeted Doxorubicin (Dox) delivery System based on N-(2-hydroxypropyl) methyl acrylamide copolymer and Mitochondrial Distributed Bcl-2 Function switching peptide NuBCP-9 Delivery System (PN9) | Imbalance of mitochondrial homeostasis | 4T1 | (O'Neill et al., 2016) |
| Azelastine | Inducing ROS levels to increase is helpful to increase oxidative stress and stress in rough endoplasmic reticulum and induce apoptosis | Hela | (Bazhin et al., 2016) |
| SkQ1 | Scavenging excess free radicals in mitochondria | Mia-Paca、Dan-G | (Yang et al., 2016) |

**Table 3. Research progress and effect of mitochondrial targeting agents in combination with other drugs**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Drugs | Effect target | Application | Drug combination | Reference |
| Mitomycin metformin | CI | PANC-1、TNBC | Iron chelators, DFX, and deferoxamine synergistically inhibited proliferation | (Cheng et al., 2019b) |
| BAY87-2243 | CI | - | Combined with DMKG affects metabolic activity | (Sica et al., 2019) |
| Mito-Tamoxifen | CI, CII | HCT116、DU 145、MCF-7 | Doxorubicin-induced apoptosis was attenuated | (Rohlenova et al., 2017; Ezrova et al., 2021) |
| Mito-VES | CII | human T lymphoma Jurkat, Bax-Jurkat, and Bax-/Bak-Jurkat cells; human mesothelioma  cells Meso2, Ist-Mes-1, Ist-Mes-2, and MM-BI; human breast cancer  cells MCF7 (erbB2-low) and MDA-MB-453 (erbB2-high) and MCF7DD9 cells with transcriptionally inactive p53; human colorectal cells HCT116; human neuroblastoma TetN21 cells; human non-small-cell lung carcinoma cells H1299; human cervical cancer cells HeLa; mouse mesothelioma cells AE17; human nonmalignant mesothelial cells Met-5A; human fibroblasts A014578; rat ventricular myocyte-like cells HL1; and mouse atrial myocyte-like cells H9c2. | The combination of Mito-VES and doxorubicin hydrochloride significantly enhanced the anti-tumor effect of dual-loaded nanocapsules in nude mice bearing xenotransplantation drug resistant human chronic myeloid leukemia K562/ADR tumor, and the tumor inhibition rate was up to 82.38% | (Dong et al., 2011; Liang et al., 2021) |
| Mito-CP-Ac | CIII and  inhibit mitochondrial oxygen consumption | MiaPaCa-2, PANC-1, MCF-7, MDA-MB-231, MCF-10A and A431 Cells | Combined use of 2-DG would synergistically enhance cytotoxic selectivity in cancer cells | (Zhou et al., 2022) |
| Mito-Q | Induction of mitochondrial uncoupling | MCF-7, MCF-10A, and MDA-MB-231 cells | Combined use of 2-DG would synergistically enhance cytotoxic selectivity in cancer cells | (Cheng et al., 2012) |

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