Salinomycin in cancer: A new mission for an old agent

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Received February 26, 2010; Accepted May 10, 2010

DOI: 10.3892/mmr_00000296

Abstract. Salinomycin is a monocarboxylic polyether ionophore isolated from *Streptomyces albus* that has been used for more than 30 years as an agricultural antibiotic to prevent coccidiosis in poultry and to improve nutrient absorption and feed efficiency in ruminants and swine. As a inonophore with strict selectivety for alkali ions and a strong preference for potassium, salinomycin interferes with transmembrane potassium potential and promotes the efflux of K^+ ions from mitochondria and cytoplasm. Salinomycin has recently been shown to kill human cancer stem cells and to inhibit breast cancer growth and metastasis in mice. Salinomycin is also able to induce massive apoptosis in human cancer cells of different origins that display multiple mechanisms of drug and apoptosis resistance. Salinomycin activates an unconventional pathway of apoptosis in human cancer cells that may contribute to the breakdown of apoptosis resistance. The ability of salinomycin to effectively kill both cancer stem cells and apoptosis-resistant cancer cells may define the compound as a novel and effective anticancer agent.

Contents

1. Introduction

During the course of a screening program for new antibiotics in 1974, Miyazaki *et al* (1) isolated a new biologically active substance from the culture broth of *Streptomyces albus* (strain No. 80614) that was termed salinomycin. Salinomycin is a 751 Da monocarboxylic polyether antibiotic that constitutes a large pentacyclic molecule with a unique tricyclic spiroketal ring system and an unsaturated six-membered ring (Fig. 1). It is a lipophilic, anionic and weakly acidic compound with the molecular formula $C_{42}H_{70}O_{11}$ (1,2). Salinomycin acts in different biological membranes, including cytoplasmic and mitochondrial membranes, as a ionophore with strict selectivity for alkali ions and a strong preference for potassium, thereby promoting mitochondrial and cellular potassium efflux and inhibiting mitochondrial oxidative phosphorylation (3-5).

Salinomycin has been shown to exhibit antimicrobial activity against gram-positive bacteria including mycobacteria and *Staphylococcus aureus*, some filamentous fungi, *Plasmodium falciparum*, and *Eimeria spp.*, protozoan parasites responsible for the poultry disease coccidiosis (1,6,7). Therefore, salinomycin has been used for more than 30 years as an effective anticoccidial drug in poultry (8) and is also fed to ruminants and pigs to improve nutrient absorption and feed efficiency (9-11).

In addition to its versatile antimicrobial activitiy, salinomycin is a positive ionotropic and chronotropic agent that increases cardiac output, left ventricular systolic pressure, heart rate, mean arterial pressure, coronary artery vasodilatation and blood flow, and plasma catecholamine concentrations as demonstrated in dogs receiving an intravenous injection of 150 $\mu g \cdot kg^{-1}$ salinomycin (12). However, salinomycin has never been used as a drug in humans, probably due to the considerable toxicity observed in mammals (13-16).

2. Effects of salinomycin on human cancer stem cells

Cancer stem cells comprise a unique subpopulation of tumor cells that possess tumor initiation and self-renewal capacity and the ability to give rise to the heterogeneous lineages of cancer cells that make up the bulk of the tumor (17-19). Cancer stem cells have been identified in a variety of human neoplasias, including cancers of the blood, breast, brain, bone, skin, liver, bladder, ovary, prostate, colon and pancreas (19,20). Cancer stem cells display numerous mechanisms of resistance to chemotherapeutic drugs and irradiation therapy, allowing them to survive current cancer therapies and to initiate long-term tumor recurrence and metastasis (21,22).

Of note, Gupta *et al* (23) demonstrated that salinomycin selectively kills human breast cancer stem cells *in vitro*. In

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Key words: salinomycin, cancer stem cells, cancer cells, apoptosis, apoptosis resistance, anticancer agent

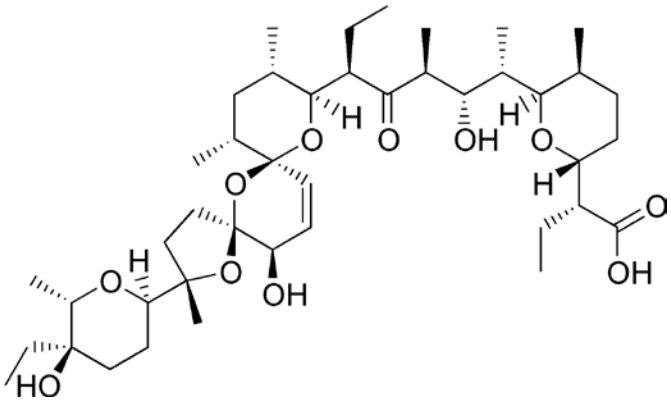

Figure 1. Structural formula of salinomycin. The pentacyclic molecule with a unique tricyclic spiroketal ring system has a mass of 751 Da, a molecular formula of $C_{42}H_{70}O_{11}$, a melting point of 113˚C and a UV absortion at 285 nm (1).

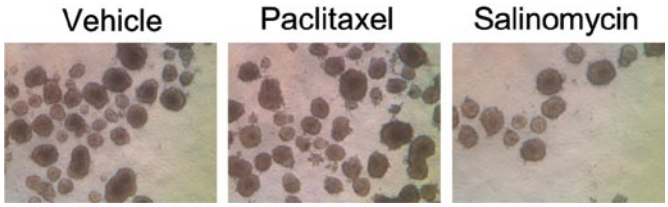

Figure 2. Salinomycin, but not paclitaxel, reduces the number of cancer stem cells in breast cancer tumors as demonstrated in a tumorsphere formation assay with tumor cells from explanted breast cancer tumors of mice treated daily with 5 mg•kg-1 salinomycin for five weeks. Adapted with permission from Elsevier B.V. (23).

a complex experimental system, the authors used oncogenic transformed immortalized human mammary epithelial cells (HMLER), in which knockdown of E-cadherin by RNA interference resulted in the generation of cells undergoing epithelial-mesenchymal transition (EMT) and displaying characteristic properties of cancer stem cells (24-26). These human breast cancer stem-like cells, termed HMLER-shEcad, are capable of forming tumorspheres in suspension cultures, show high and low expression of CD44 and CD24, respectively, and exhibit resistance to chemotherapeutic drugs and cytotoxic agents such as paclitaxel, doxorubicin, actinomycin D, campthotecin and staurosporine (23).

In a robotic high-throughput screening approach, about 16,000 compounds from chemical libraries, including biological molecules and natural extracts, were tested for activity against HMLER-shEcad cells and control cells that had not undergone EMT (23). Only one compound markedly and selectively reduced the viabililty of stem-like HMLER-shEcad cells: salinomycin. In subsequent experiments, it was demonstrated that salinomycin, in contrast to the chemotherapeutic drug paclitaxel, selectively reduces the proportion of $CD44^{high}/CD24^{low}$ stem-like cells in cultures of mixed populations of HMLER-shEcad cells and control cells that had not undergone EMT. Moreover, pre-treatment of HMLER-shEcad cells with salinomycin resulted in inhibition of HMLER-shEcad-induced tumorsphere formation, which was not observed after pre-treatment of the cells with paclitaxel (23).

Global gene expression profiling was employed to show that, in $CD44^{high}/CD24^{low}$ HMLER cells, salinomycin, but not paclitaxel, was capable of changing a gene expression signature characteristic of breast cancer stem cells and mammary epithelial progenitor cells isolated from human tumors. For example, expression of genes that inversely correlates with metastasis-free survival and overall survival of breast cancer patients (27,28) was down-regulated by salinomycin (23). Expression of a set of genes that promote the expansion of mammary epithelial stem cells and the formation of mammospheres (29) was also markedly down-regulated by salinomycin (23). By contrast, genes probably involved in mammary epithelial differentiation that encode membrane-associated or secreted proteins as components of the extracellular matrix were up-regulated by salinomycin (23).

As a proof of principle, it was demonstrated that salinomycin inhibits the ability of breast cancer stem-like cells to form tumors in mice. Pre-treatment of HMLER cells for seven days with salinomycin and subsequent injection of the cells into NOD/SCID mice resulted in a >100-fold decrease in tumor-seeding ability, relative to pre-treatment of the cells with paclitaxel. Finally, salinomycin treatment of NOD/SCID mice with breast cancer tumors established by injection of human breast cancer cells resulted in a reduction of the tumor mass and metastasis, and explanted tumors showed a reduced number of breast cancer stem cells (Fig. 2) as well as an increased epithelial differentiation (23).

In addition, a recent study demonstrated that salinomycin was capable of overcoming ATP-binding cassette (ABC) transporter-mediated multidrug and apoptosis resistance in human leukemia stem cell-like cells (30). One of the most important mechanisms of drug resistance in leukemia stem cells and other cancer stem cells is the expression of ABC transporters belonging to a highly conserved superfamily of transmembrane proteins capable of exporting a wide variety of molecules and structurally unrelated chemotherapeutic drugs from the cytosol, thereby conferring multidrug resistance, which is a major obstacle to the success of cancer chemotherapy (31-33). As shown in the study, expression of functional ABC transporters such as P-glycoprtein, BCRP and MRP8 confers resistance of human KG-1a leukemia stem cell-like cells to a broad spectrum of chemotherapeutic drugs including the proteasome inhibitor bortezomib, but not to salinomycin (Fig. 3). Moreover, salinomycin does not permit long-term adaptation of KG-1a cells to apoptosis-inducing concentrations, whereas the cells can be adapted to proliferate in the presence of apoptosis-inducing concentrations of bortezomib and doxorubicin (30).

All these findings strongly suggest that salinomycin is a selective killer of human cancer stem cells and a new promising agent for the elimination of cancer stem cells.

3. Effects of salinomycin on human cancer cells

A recent study revealed that salinomycin induces apoptosis and overcomes apoptosis resistance in human cancer cells of different origins (34). First, it was demonstrated that salinomycin at doses lower than those used by Gupta *et al* induced massive apoptosis in $CD4^+$ T-cell leukemia cells isolated from patients with acute T-cell leukemia (Fig. 4). Notably, salinomycin failed to induce apoptosis in normal $CD4^+$ T

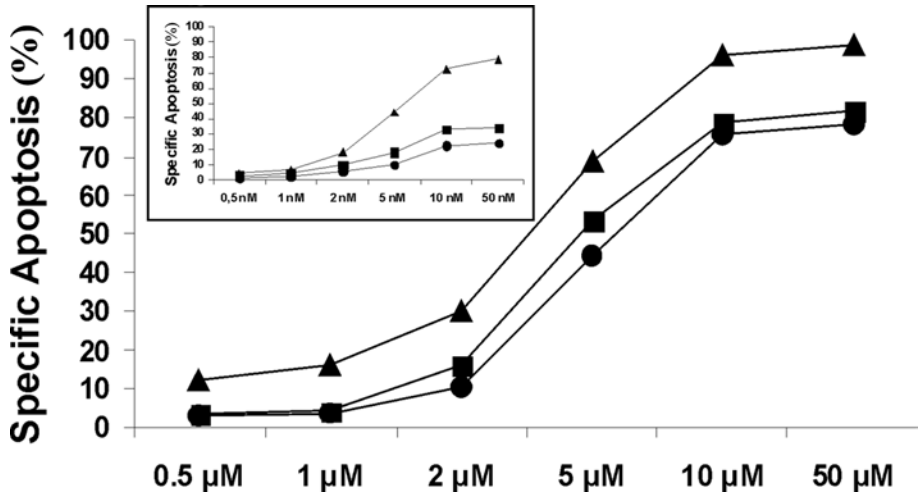

Figure 3. Salinomycin induces apoptosis in a dose-dependent manner in human leukemia stem cell-like KG-1a cells expressing high (●) and low (■) levels of the ABC transporters P-glycoprotein, MCRP and MRP8. More differentiated myeloblastic KG-1 cells (▲) which lack expression of ABC transporters are also sensitive to apoptosis induction by salinomycin. Insert: proteasome inhibitor bortezomib induces dose-dependent apoptosis in KG-1 cells (▲), but not in leukemia stem cell-like KG-1a cells (● and ■). Data adapted from ref. 30.

cells isolated from healthy humans (Fig. 4), suggesting that salinomycin selectively kills malignant cells. Secondly, various human leukemia and lymphoma cells were shown to undergo apoptosis in response to treatment with salinomycin. Since the induction of p53-mediated apoptosis is a central mechanism of the cytotoxicity of many anticancer drugs (35,36), lymphoblastic leukemia cell types expressing a functional (wild-type) tumor suppressor protein p53 or lacking p53 expression due to a homozygous nonsense mutation in the p53 gene were investigated. It was shown that salinomycin is capable of inducing apoptosis in both wild-type p53 cells and p53-lacking cells, indicating that the induction of apoptosis by salinomycin is independent of the p53 status

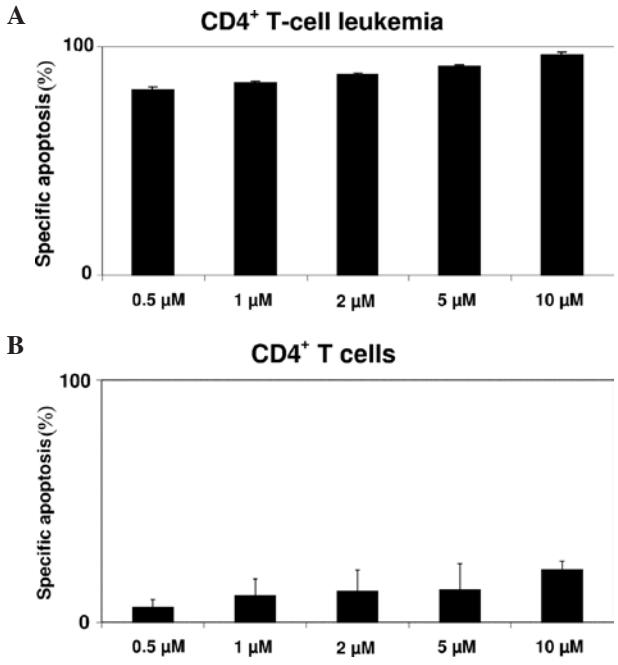

Figure 4. (A) Salinomycin induces massive apoptosis in CD4+ T-cell leukemia cells isolated from the peripheral blood of patients with acute CD4+ T-cell leukemia. (B) Salinomycin fails to induce marked apoptosis in normal CD4+ T-cells isolated from the peripheral blood of healthy humans. Adapted with permission from Elsevier B.V. (34).

of the cell (34). Next, p53-lacking lymphoblastic leukemia cells were transfected with a plasmid encoding the human anti-apoptotic protein Bcl-2, leading to stable overexpression of Bcl-2 and resistance of the cells to apoptosis induced by chemotherapeutic drugs (37). In these cells, salinomycin was able to markedly induce apoptosis even at the low concentrations used for the induction of apoptosis in non-resistant cells (34). Other types of human cancer cells displaying multidrug resistance and general resistance to apoptosis induced by chemotherapeutic drugs, cytotoxic agents and γ-irradiation were investigated for their ability to undergo apoptosis in response to salinomycin treatment. For example, human Burkitt lymphoma cells, which exhibit apoptosis resistance and hyperproliferation due to the increased expression and proteolytic activity of 26S proteasomes in response to adaptation to lethal concentrations of the proteasome inhibitor bortezomib (38), undergo massive apoptosis in response to treatment with salinomycin at low doses effective in non-resistant cells (34). Moreover, human uterine sarcoma cells, which display resistance to a large panel of chemotherapeutic drugs by virtue of the expression of P-glycoprotein, a transmembrane efflux pump that eliminates various drugs and small molecules from the cytosol (39-41), undergo apoptosis in response to salinomycin treatment (34).

Salinomycin activates a distinct and unconventional pathway of apoptosis in cancer cells that is not accompanied by cell cycle arrest, and that is independent of tumor suppressor protein p53, caspase activation, the CD95/DC95 ligand system and the 26S proteasome (34). This might be one reason why salinomycin can overcome multiple mechanisms of drug and apoptosis resistance in human cancer cells. Many cancer cells harbor or acquire multiple mechanisms of apoptosis resistance mediated by the loss of p53 and overexpression of Bcl-2, P-glycoprotein or 26S proteasomes with enhanced proteolytic activity (42-44). Salinomycin, however, appears to be capable of overcoming these mechanisms of drug and apoptosis resistance, suggesting a possible future use of salinomycin in the treatment of drug-resistant and aggressive cancers.

4. Conclusion and perspective

Salinomycin is a well defined agricultural antibiotic that has been used for more than 30 years in the prevention of coccidiosis in poultry and for improving nutrient absorption and feed efficiency in ruminants and swine. A notable recent discovery was that salinomycin selectively kills human cancer stem cells, inhibits breast cancer growth and metastasis in mice and induces massive apoptosis in various apoptosis-resistant human cancer cells. Cancer stem cells are known to exhibit resistance to a broad spectrum of chemotherapeutic drugs, thereby surviving current cancer therapies and initiating long-term tumor recurrence, relapse and metastasis (21,22). Development of multiple mechanisms of drug and apoptosis resistance is a hallmark of aggressive, advanced and recurrent cancer (45,46). It is intriguing that both cancer stem cells and apoptosis-resistant cancer cells are effectively killed by salinomycin, although at present only *in vitro*. The exact mechanism of salinomycin-induced apoptosis remains unclear, but it appears that salinomycin activates an unconventional pathway of apoptosis that may contribute to the breakdown of apoptosis resistance in cancer cells. Salinomycin is a potassium ionophore that interferes with transmembrane potassium potential and promotes the efflux of K^+ ions from mitochondria and cytoplasm. A decrease in intracellular potassium concentration has previously been shown to be essential for the induction of apoptosis in human lymphoma cells (47), suggesting that salinomycin-induced apoptosis is mediated, at least in part, by the ability of salinomycin to deplete cytoplasmic and mitochondrial potassium and/or to interfere with potassium membrane potential. Potassium channels of the mitochondrial and cytoplasmic membrane are overexpressed in many human cancer cells, play pivotal roles in the regulation of tumorigenesis, tumor cell proliferation, cell cycle progression and apoptosis (48-50), and may constitute novel and promising molecular targets for cancer therapy (51). Now that the potassium ionophore antibiotic salinomycin has been shown to kill human breast cancer stem cells and apoptosis-resistant cancer cells *in vitro*, the investigation of its safety, toxicity, pharmacology and anticancer activity in humans is a challenge for the coming years.

References

1. Miyazaki Y, Shibuya M, Sugawara H, Kawaguchi O and Hirsoe C: Salinomycin, a new polyether antibiotic. J Antibiot 27: 814-821, 1974.
2. Kinashi H, Otake N, Yonehara H, Saito S and Saito Y: The structure of salinomycin, a new member of the polyether antibiotics. Tetrahedron Lett 14: 4955-4958, 1973.
3. Mitani M, Yamanishi T and Miyazaki Y: Salinomycin: a new monovalent cation ionophore. Biochem Biophys Res Commun 27: 1231-1236, 1975.
4. Mitani M, Yamanishi T, Miyazaki Y and Otake N: Salinomycin effects on mitochondrial ion translocation and respiration. Antimicrob Agents Chemother 9: 655-660, 1976.
5. Pressman BC and Lattanzio FA: Cardiovascular effects of ionophores. In: Frontiers of Biological Energetics Vol 2. Dutton PL, Leigh JS and Scarpa A (eds). Academic Press, New York, pp245-1252, 1978.
6. Mahmoudi N, De Julian-Ortiz JV, Ciceron L, *et al*: Identification of new antimalarial drugs by linear discriminant analysis and topological virtual screening. J Antimicrob Chemother 57: 489-497, 2006.
7. Danforth HD, Ruff MD, Reid WM and Miller RL: Anticoccidial activity of salinomycin in battery raised broiler chickens. Poult Sci 56: 926-932, 1977.
8. Daugschies A, Gässlein U and Rommel M: Comparative efficacy of anticoccidials under the conditions of commercial broiler production and in battery trials. Vet Parasitol 76: 163-171, 1998.
9. Callaway TR, Edrington TS, Rychlik JL, *et al*: Ionophores: their use as ruminant growth promotants and impact on food safety. Curr Issues Intest Microbiol 4: 43-51, 2003.
10. Lindemann MD, Kornegey ET, Stahly TS, Cromwell GL, Easter RA, Kerr BJ and Lucas DM: The efficacy of salinomycin as a growth promotant for swine from 9-97 kg. J Anim Sci 61: 782-788, 1985.
11. Butaye P, Devriese LA and Haesebrouck F: Antimicrobial growth promoters used in animal feed: effects of less well known antibiotics on gram-positive bacteria. Clin Microbiol Rev 16: 175-188, 2003.
12. Fahim M, Del Valle G and Pressman BC: Comparison of the effects of the ionophore salinomycin and adrenaline on the haemodynamics and work efficiency of the dog heart. Cardiovasc Res 20: 145-152, 1986.
13. Plumlee KH, Johnson B and Galey FD: Acute salinomycin toxicosis in pigs. J Vet Diagn Invest 7: 419-420, 1995.
14. Van der Linde-Sipman JS, van der Ingh TS, van Nes JJ, Verhagen H, Kersten JG, Beynen AC and Plekkringa R: Salinomycin-induced polyneuropathy in cats: morphologic and epidemiologic data. Vet Pathol 36: 152-156, 1999.
15. Aleman M, Magdesian KG, Peterson TS and Galey FD: Salinomycin toxicosis in horses. J Am Vet Med Assoc 230: 1822-1826, 2007.
16. Story P and Doube A: A case of human poisoning by salinomycin, an agricultural antibiotic. N Z Med J 117: 799, 2004.
17. Clarke MF, Dick JE, Dirks PB, *et al*: Cancer stem cells – perspectives on current status and future directions: AACR workshop on cancer stem cells. Cancer Res 66: 9339-9344, 2006.
18. Ward RJ and Dirks PB: Cancer stem cells: at the headwater of tumor development. Annu Rev Pathol 2: 175-189, 2007.
19. Frank NY, Schatton T and Frank MH: The therapeutic promise of the cancer stem cell concept. J Clin Invest 120: 41-50, 2010.
20. Ailles LE and Weissman IL: Cancer stem cells in solid tumors. Curr Opin Biotechnol 18: 460-466, 2007.
21. Dean M, Fojo T and Bates S: Tumor stem cells and drug resistance. Nat Rev Cancer 5: 275-284, 2005.
22. Eyler CE and Rich JN: Survival of the fittest: cancer stem cells in therapeutic resistance and angionesis. J Clin Oncol 26: 2839-2845, 2008.
23. Gupta PB, Onder TT, Jiang G, Tao K, Kuperwasser C, Weinberg RA and Lander ES: Identification of selective inhibitors of cancer stem cells by high-throughput screening. Cell 138: 645-659, 2009.
24. Elenbaas B, Spirio L, Koerner F, *et al*: Human breast cancer cells generated by oncogenic transformation of primary mammary epithelial cells. Genes Dev 15: 50-65, 2001.
25. Onder TT, Gupta PB, Mani SA, Yang J, Lander ES and Weinberg RA: Loss of E-cadherin promotes metastasis via multiple downstream transcriptional pathways. Cancer Res 68: 3645-3654, 2008.
26. Mani SA, Guo W, Liao MJ, *et al*: The epithelial-mesenchymal transition generates cells with properties of stem cells. Cell 133: 704-715, 2008.
27. Liu R, Wang X, Chen GY, *et al*: The prognostic role of a gene signature from tumorigenic breast-cancer cells. N Engl J Med 356: 217-226, 2007.
28. Shipitsin M, Campbell LL, Argani P, *et al*: Molecular definition of breast tumor heterogeneity. Cancer Cell 11: 259-273, 2007.
29. Dontu G, Abdallah WM, Foley JM, Jackson KW, Clarke MF, Kawamura MJ and Wicha MS: In vitro propagation and transcriptional profiling of human mammary stem/progenitor cells. Genes Dev 17: 1253-1270, 2003.
30. Fuchs D, Daniel V, Sadeghi M, Opelz G and Naujokat C: Salinomycin overcomes ABC transporter-mediated multidrug and apoptosis resistance in human leukemia stem cell-like KG-1a cells. Biochem Biophys Res Commun 394: 1098-1104, 2010.
31. Wulf GG, Wang RY, Kuehnle I, *et al*: A leukemic stem cell with intrinsic drug efflux capacity in acute myeloid leukemia. Blood 98: 1166-1173, 2001.
32. Eckford PD and Sharom FJ: ABC efflux pump-based resistance to chemotherapy drugs. Chem Rev 109: 2989-3011, 2009.
33. Dean M: ABC transporters, drug resistance, and cancer stem cells. J Mammary Gland Biol Neoplasia 14: 3-9, 2009.

34. Fuchs D, Heinold A, Opelz G, Daniel V and Naujokat C: Salinomycin induces apoptosis and overcomes apoptosis resistance in human cancer cells. Biochem Biophys Res Commun 390: 743-749, 2009.
35. Lowe SW, Ruley HE, Jacks T and Housman DE: p53-dependent apoptosis modulates the cytotoxicity of anticancer agents. Cell 74: 957-967, 1993.
36. Lowe SW, Bodis S, McClatchey A, *et al*: p53 status and the efficacy of cancer therapy in vivo. Science 266: 807-810, 1994.
37. Nencioni A, Wille L, Dal Bello G, *et al*: Cooperative cytotoxicity of proteasome inhibitors and tumor necrosis factor-related apoptosis-inducing ligand in chemoresistant Bcl-2 overexpressing cells. Clin Cancer Res 11: 4259-4265, 2005.
38. Fuchs D, Berges C, Opelz G, Daniel V and Naujokat C: Increased expression and altered subunit composition of proteasomes induced by continuous proteasome inhibition establish apoptosis resistance and hyperproliferation of Burkitt lymphoma cells. J Cell Biochem 103: 270-283, 2008.
39. Chen G, Duran GE, Steger KA, Lacayo NJ, Jaffrezou JP, Dumontet C and Sikic BI: Multidrug-resistant human sarcoma cells with a mutant P-glycoprotein, altered phenotype and resistance to cyclosporins. J Biol Chem 272: 5974-5982, 1997.
40. Leoni LM, Hamel E, Genini D, Shih H, Carrera CJ, Cottam HB and Carson DA: Indanocine, a microtubule-binding indanone and a selective inducer of apoptosis in multidrug-resistant cancer cells. J Natl Cancer Inst 92: 217-224, 2000.
41. Kuznetsov G, Xu Q, Rudolph-Owen L, *et al*: Potent in vitro and in vivo anticancer activities of des-methyl, des-amino pateamine A, a synthetic analogue of marine natural product pateamine A. Mol Cancer Ther 8: 1250-1260, 2009.
42. Lage H: An overview of cancer multidrug resistance: a still unresolved problem. Cell Mol Life Sci 65: 3145-3167, 2008.
43. Wolter KG, Verhaegen M, Fernandez Y, *et al*: Therapeutic window for melanoma treatment provided by selective effects of the proteasome on Bcl-2 proteins. Cell Death Differ 14: 1605-1616, 2007.
44. Smith L, Lind MJ, Drew PJ and Cawkwell L: The putative roles of the ubiquitin/proteasome pathway in resistance to anticancer drugs. Eur J Cancer 43: 2330-2338, 2007.
45. Blagosklonny MV: Why therapeutic response may not prolong the life of a cancer patient: selection for oncogenic resistance. Cell Cycle 4: 1693-1698, 2005.
46. Wilson TR, Johnston PG and Longley DB: Anti-apoptotic mechanisms of drug resistance in cancer. Curr Cancer Drug Targets 9: 307-319, 2009.
47. Bortner CD, Hughes FM Jr and Cidlowski JA: A primary role for K^+ and Na^+ efflux in the activation of apoptosis. J Biol Chem 272: 32436-32442, 1997.
48. Burg ED, Remillard CV and Yuan JX: K^+ channels in apoptosis. J Membrane Biol 209: 3-20, 2006.
49. Wang Z: Roles of K^+ channels in regulating tumour cell proliferation and apoptosis. Pflugers Arch 448: 274-286, 2004.
50. Ouadid-Ahidouch H and Ahidouch A: K^+ channel expression in human breast cancer cells: involvement in cell cycle regulation and apoptosis. J Membrane Biol 221: 1-6, 2008.
51. Villalonga N, Ferreres JC, Argiles JM, Condom E and Felipe A: Potassium channels are a new target field in anticancer drug design. Recent Pat Anticancer Drug Discov 2: 121-123, 2007.