European Journal of Medicinal Chemistry 164 (2019) 366–377

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Review article

A medicinal chemistry perspective on salinomycin as a potent anticancer and anti-CSCs agent

Michał Antoszczak

Department of Bioorganic Chemistry, Faculty of Chemistry, Adam Mickiewicz University, Umultowska 89b, 61–614 Poznań, Poland

ARTICLE INFO

Article history:
Received 29 November 2018
Received in revised form
20 December 2018
Accepted 24 December 2018
Available online 24 December 2018

Keywords:
Salinomycin
Polyether ionophores
Cancer stem cells
Targeted therapy
Multi-drug resistance
Sensitizing effects
Synergy
Mechanism of action
Toxicity

ABSTRACT

Tumors are phenotypically heterogeneous and include a small sub-population of cancer cells (2–5% of the tumor mass) with stem-cell like properties. The cancer stem cell hypothesis postulates that the cancer stem cells (CSCs) show the ability to seed the tumor to distant tissues/organs, and their presence results in cancer progression and relapses. Extensive efforts have therefore been directed at new therapy strategies to eliminate not only non-CSCs, but also cancer cells with stem-cell like properties. Importantly, in 2009, the natural ionophore – salinomycin (**SAL**) was shown to be promising in this respect; **SAL** selectively and efficiently reduced the proportion of breast CSCs *in vitro* and *in vivo*. Since this original report, **SAL** has been shown to be active against numerous cancer cells and CSCs of different origin, including those that display multi-drug resistance. This concise review article is focused on the possible role of **SAL** in future cancer therapy.

Contents

1. Introduction 366
2. Salinomycin – promising anticancer agent 367
3. *In vitro* and *in vivo* anticancer activity of salinomycin 368
4. Synergistic effects of salinomycin 370
5. Mechanism of anticancer activity of salinomycin 372
6. Salinomycin toxicity 373
7. Conclusions 373
Acknowledgment 373
References 374

1. Introduction

Cancers are globally the second cause of death in developed countries after cardiovascular diseases. The characteristic feature of this extensive and diverse group of more than 100 diseases is intensive proliferation and invasive growth of cancer cells, which additionally have the ability to spread (metastasize) from the primary tumors to distant tissues and organs. According to the report published by the World Health Organization, over eight million people die because of cancer each year, which constitutes about 13% of the total number of deaths. It is also estimated that the number of oncological patients will rise systematically in the next few decades; in 2020 there are predicted to be about 20 million of new cancer patients worldwide [1].

Phenotypic heterogeneity within tumors (Fig. 1A and B) is a

E-mail address: michant@amu.edu.pl.

https://doi.org/10.1016/j.ejmech.2018.12.057
0223-5234/

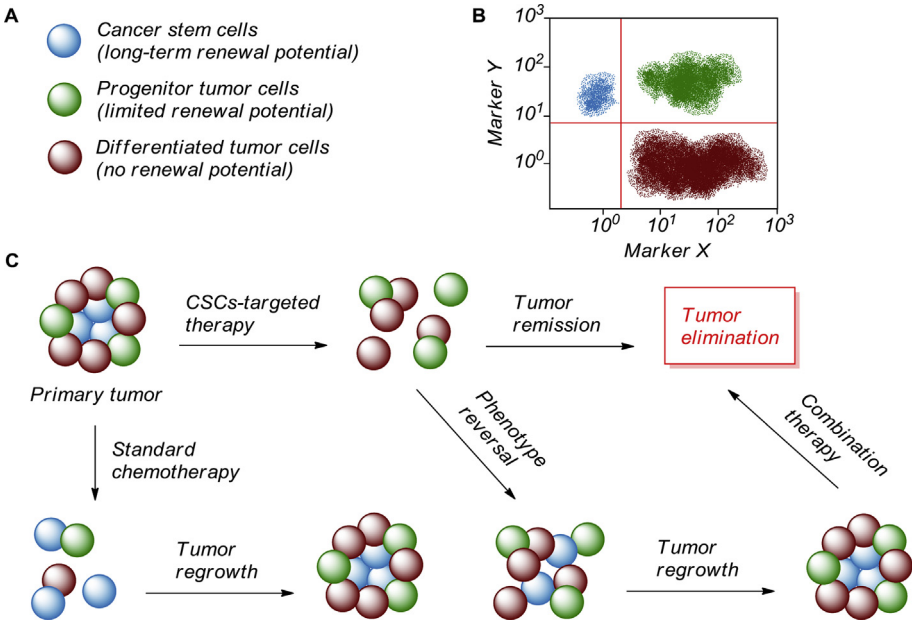

Fig. 1. Phenotypic heterogeneity within tumors and future implications for cancer stem cell-targeted therapies. **(A)** Tumors are phenotypically heterogeneous and include various sub-populations of cancer cells that are characterized by different renewal potential. **(B)** Markers found to be expressed non-uniformly within the tumor may be used to isolate such different intratumoral sub-populations of cancer cells. **(C)** Evidence from preclinical and clinical studies demonstrates that most of the currently used chemotherapeutic agents effectively eliminate the highly proliferating and relatively differentiated cells that form the bulk of the tumor rather than the more quiescent cancer stem cells (CSCs). Standard chemotherapy destroys the majority of stromal cells within the main tumor cell population and paradoxically, the elimination of non-CSCs by such treatment may allow more space for CSCs to expand and evolve into more aggressive and therapeutically resistant heterogenic tumors with higher self-renewal potential. According to the dynamic CSCs model, differentiated cancer cells can also reverse their phenotype and acquire CSCs properties that results in tumor regrowth. Combination therapy of hierarchical tumors using novel CSC-targeted drugs may eradicate CSC sub-population and inhibit therefore the root of chemoresistance and tumor remission, thereby improving clinical outcomes.

phenomenon that poses a significant obstacle towards effective cancer therapy [2]. The huge difficulty of treating tumors stems from the fact that it is not easy to administer a chemotherapeutic drug or a combination of such drugs that will target each of the different sub-populations of cancer cells [3]. Cancer stem cells (CSCs), also defined as cancer initiating cells, are particularly problematic as they exhibit up-regulated mechanisms of cellular defense and they are simultaneously more resistant to currently existing treatments [4]. CSCs, a small neoplastic cell sub-population (2–5% of the tumor mass) whose presence has been confirmed in many liquid and solid tumors [5–7], are endowed with self-renewal or multi-lineage differentiation capacity into any of the cancer cell type [8]. Furthermore, CSCs are capable of initiating the tumor in different location, and are also linked to angiogenesis, cancer survival, recurrence and progression [9,10].

Extensive efforts have therefore been directed at new therapeutic strategies to target and eliminate not only non-CSCs, but also cancer cells with stem-cell like properties (Fig. 1C). The naturally-occurring ionophore – salinomycin may open a more promising therapeutic approach to this aim, as it is found to effectively destroy both non-CSCs and CSCs, including cancer cells with the multi-drug resistance (MDR) phenotype, whose presence constitutes another significant clinical challenge in the effective cancer treatment. All these aspects are summarized and discussed in detail in the next sections of this review article.

2. Salinomycin – promising anticancer agent

The natural product – salinomycin (**SAL**, Fig. 2A), a polyether K^+-selective membrane ionophore from *Streptomyces albus* [11], exhibits a broad spectrum of antimicrobial activity against eukaryotic parasites, Gram-positive bacteria, viruses, protozoa and some fungi [12,13]. For a long time, **SAL** has been widely used in veterinary medicine as feed additive to control coccidiosis, the single-cell parasitic disease of the intestinal tract, and as non-hormonal growth promoter [14]. In 1981, a total synthesis of **SAL** was proposed by Kishi et al. [15] which was successfully developed in subsequent years by other chemists [16–21]. Intensive studies on **SAL** biosynthesis were recently carried out [22–27] and finally a biosynthetic model for the preparation of **SAL** was presented in 2012 [26].

SAL pentacyclic molecule contains in its structure 11 oxygen atoms as components of various functional groups (carboxyl group, three hydroxyl groups, ketone group and five ether oxygen atoms). Characteristic of the structure of **SAL** is the presence of unique tricyclic 6-6-5 bis-spiroketal ring system with *cis* isomerism that has been rarely found among other naturally-occurring compounds [28–30]. Although **SAL** exists as an open-chain structure, due to the presence of a carboxyl group at one end of the molecule and a hydroxyl group at the opposite site, it has the possibility to form 'head-to-tail' intramolecular hydrogen bonds, leading finally to the formation of a pseudocyclic 'crown ether-like' structure (Fig. 2A). In such a structure, the oxygen atoms are directed to the interior of the molecule, so that **SAL** can effectively bind cations. The outer part of the **SAL** molecule is hydrophobic which greatly facilitates its diffusion (and ion flux) through the lipid bilayers, according to the electroneutral transport mechanism (Fig. 2B) [31].

Interestingly, the accumulating evidence points to the ion transport properties as the origin of **SAL** phenotype effects [32–34]. Functionally, the polyether skeleton of **SAL** has the ability to form complexes with both mono- and divalent cations, showing particularly high affinity to potassium cations [35]. It has been found however, that **SAL** was more effective as a mobile carrier of monovalent cations than divalent ones [36]. In 2017, it was further proven that **SAL** was able to form complexes with organic amines [37].

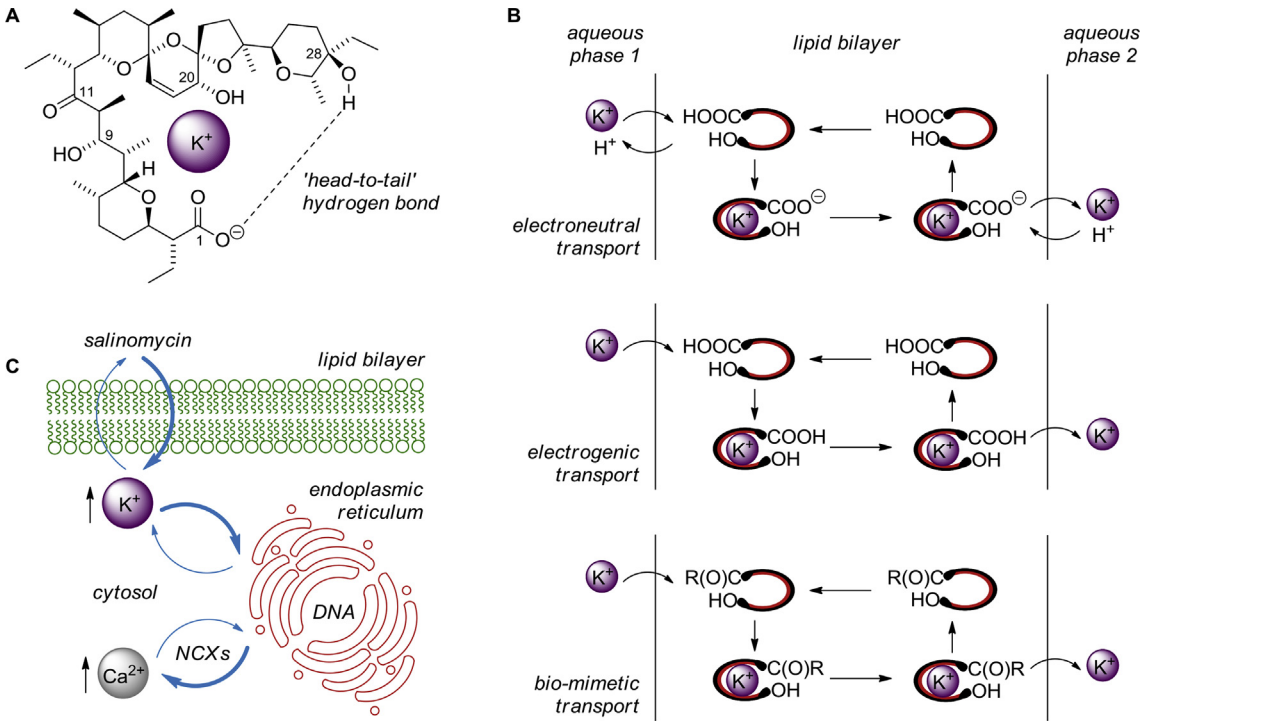

Fig. 2. **(A)** Structure and mode of K^+ complex formation by salinomycin; **(B)** the electroneutral, electrogenic and bio-mimetic mechanism of cation transport realized by ionophore antibiotics; and **(C)** schematic representation of the proposed mechanism of action of salinomycin that finally leads to the Wnt/β-catenin inhibition.

The knowledge of mechanism of cation transport realized by **SAL** is essential for understanding of the bio-action of this natural product (and other ionophore antibiotics) and for explanation of the broad spectrum of its biological properties. The electroneutral (non-electrogenic) transport mechanism (Fig. 2B), explaining at least partially the high bioactivity of **SAL**, is carried out in an inert or basic environment, because only under such conditions the carboxyl group may undergo deprotonation [38–40]. **SAL** interferes with transmembrane potassium potential. The K^+ cation complexed inside the polyether pocket of **SAL** is transferred in the form of electroneutral complex across the biological membranes from the extracellular environment into the targeted cells, where the cation is released. It disturbs the natural Na^+/K^+ concentration gradient and induces the Ca^{2+} release into cytosol by means of Na^+/Ca^{2+} exchangers (NCXs), changes the intracellular pH, leads to vacuolization and consequently to programmed cell death (apoptosis) (Fig. 2C) [41].

However, in the cancer cells and their immediate vicinity often acidification takes place, which is related to the process of anaerobic glucose metabolism and is known as the Warburg effect [42]. Due to the fact that under such conditions **SAL** and other ionophore antibiotics, including inostamycin, ionomycin, lasalocid acid, monensin, nanchangmycin and nigericin [13,31,43,44], are also active against cancer cells, an alternative mechanism of cation transport (electrogenic) has been recently proposed (Fig. 2B) [38,39]. It may be effectively carried out by ionophores with a protonated carboxyl group [38,39]. Moreover, the biomimetic transport mechanism, a type of electrogenic one, has been described in the scientific literature. It is realized by ionophore antibiotics with a modified carboxyl group, for example by their amides or esters (Fig. 2B) [38,39].

As highlighted above, **SAL** is a well-defined antibiotic that has been widely used in veterinary medicine as an anticoccidial agent as well as to improve nutrient absorption and feed efficiency in ruminants and swine because of its significant antimicrobial activity [12,13]. However, the attention of scientists and oncologists from around the world has been attracted mainly by very potent anticancer activity of **SAL** discovered less than ten years ago. Recently, many publications have appeared reporting the extremely high potential of **SAL** to induce massive apoptosis in human cancer cells of different origins, both *in vitro* and *in vivo*; the efficacy of this compound has been demonstrated for cancer cells characterized by MDR as well as for CSCs. Interestingly, it has also been proven that **SAL** in combination with other chemotherapeutics or together with radiation therapy may be used as a sensitizing agent in cancer therapy.

3. *In vitro* and *in vivo* anticancer activity of salinomycin

According to the concept of tumor cell plasticity, migrating breast non-CSCs are able to utilize the epithelial-mesenchymal transition (EMT) mechanism in order to switch between different cellular identities, to undergo de-differentiation to cancer cells exhibiting a cancer stem cell phenotype and to gain them the migratory and invasive capabilities. There is increasing evidence suggesting a link between EMT and CSCs [45–47]. Gupta et al. have used this attribute in 2009 to develop a high-throughput screening to identify structures that selectively inhibit the proliferation of breast CSCs *in vitro* and *in vivo* [48]. The authors screened a collection of ~16,000 molecules for their effects against EMT-induced breast CSCs. From among them, only 32 compounds selectively exhibited the toxicity towards tumorigenic cancer cells with stem-cell like properties; four agents (**SAL**, abamectin, etoposide and nigericin) were confirmed in follow-up studies, wherein **SAL** showed the highest CSC-specific toxicity. **SAL** selectively inhibited tumor growth and significantly reduced the relative proportion of breast CSCs both *in vitro* and *in vivo*. It should be noted that the clinical chemotherapeutic drug paclitaxel (taxol) that is frequently used in breast cancer therapy, displayed nearly 100-times lower activity relative to that of **SAL** [48]. Since this

original report, **SAL** has shown activity across numerous cancer cell lines of different origin, including colorectal, gastric, hepatocellular, leukemia, lung, osteosarcoma, ovarian, prostate and squamous ones (Table 1) [13,49].

One of the first studies in the field of anticancer activity of **SAL** has been performed by Naujokat et al.; in 2009, the authors demonstrated that **SAL** induced massive apoptosis in a dose-dependent manner of human leukemia, lymphoma and uterine sarcoma cells, including those that display multiple mechanisms of MDR. For instance, the leukemia cells isolated from the peripheral blood of cancer patients with acute T-cell leukemia underwent programmed cell death in response to exposure to **SAL**. The use of the highest dose of **SAL** resulted in the killing of almost all leukemic cells without damaging the normal T-cells, proving its high selectivity of action [50]. In further studies, the same authors have found that **SAL** may be regarded as a novel and effective agent for the elimination of human leukemia cells that exhibit characteristics of leukemia stem cells [51]. Lu et al. have clearly evidenced that **SAL** selectively induces apoptosis in chronic lymphocytic leukemia cells, the most frequent form of human leukemia in the Western world [52]. In addition, it has been also observed recently that low-dose **SAL** results in anti-leukemic responses in both acute myeloid leukemia and mixed-lineage leukemia [53], and induces apoptosis and differentiation in human acute promyelocytic leukemia cells [54].

The evidence that **SAL** induces dose- and time-dependently apoptosis of human prostate cancer cells, including both androgen-responsive as well as androgen-refractive cancer cells, was presented for the first time in 2011. **SAL** exposure reduced the viability of prostate cancer cells at a lower dose than non-malignant prostate epithelial cells. It is worth noting here that the chemo-resistance of the hormone-independent human prostate cancer cells to **SAL** was higher than that of the hormone-dependent cancer cells [55]. In 2012, Iljin et al. confirmed that **SAL** inhibits prostate cancer cell growth, reduces cell migration and impacts on prostate CSC functions, and, similarly to above mentioned results, does not affect non-malignant prostate epithelial cells. **SAL** was at least 10-fold more potent growth inhibitor of the studied prostate cancer cells when compared with non-malignant prostate epithelial cells. Of note, **SAL** showed similar effects as an antihelmintic drug niclosamide and as an antihistamine agent terfenadine [56]. All these observations have been confirmed once again very recently; the cytotoxicity of **SAL** to human prostate cancer cells was stronger than to non-malignant prostate cells, and exposure to **SAL** induced G2/M phage arrest and apoptosis of cancer cells. Furthermore, **SAL** reduced resistance and relapse of prostate tumor by killing cancer cells and CSCs [57].

Osteosarcoma is the most common primary bone tumor in children and adolescents, and is typically associated with poor prognosis, resulting from a failure to target the CSCs in osteosarcoma. **SAL** was able to target osteosarcoma cells with stem-cell like properties both *in vitro* and *in vivo*, and had simultaneously minimal severe side effects on mesenchymal stem cells. Wang et al. have observed significantly lower sphere and tumor formation as well as higher reduction in tumorigenic ability after **SAL** treatment [58]. In the same year, **SAL** was identified as a novel and potent gastric anti-CSCs agent towards which commonly used cytostatic drugs (5-fluorouracil and cisplatin) were ineffective [59]. Very recently, it has been also found that **SAL** is a promising agent for the systemic treatment of chondrosarcoma [60].

Lung cancer is the leading cause of cancer-related death worldwide and is classified into two main subtypes – non-small cell lung cancer which accounts for approximately 85% of all lung cancers, and small-cell lung cancer which is diagnosed in 15% of cases [61]. The main reason for the terrifyingly high rates of mortality in lung cancer patients is that the tumors are generally diagnosed in the latter stages of the disease and that effectiveness of the currently used treatments is either therapeutically insufficient or beneficial to a small population of patients only [62]. Importantly, the extremely promising effects of **SAL** on cell survival, colony growth, migration, and invasion of human non-small cell lung cancer cells and CSCs have been documented, although these cancer cells were resistant to standard chemotherapeutics, like 5-fluorouracil, cisplatin and gemcitabine [62–65]. **SAL** did not reduce the size of the primary tumor [63] but reduced the tumorsphere-forming potential of CSC sub-population, decreased the expression of the cancer cells with stem-cell like properties as well as metastatic tumor burden by hampering lung cancer migration, both *in vitro* and *in vivo* [62–66].

Moreover, three Chinese research groups have independently demonstrated the interesting properties of **SAL** against colorectal cancer cells [67–69]. **SAL** effectively induced apoptosis in cisplatin-resistant colorectal cancer cells [68], destroyed selectively the colorectal cancer cell sub-populations that were identified as CSCs,

Table 1
Anticancer activity of salinomycin against various cancer cells and cancer stem cells.

Type of cancer	Cancer cell line	Activity *in vitro*/*in vivo*	References
bladder cancer	5637, T24	*in vitro*	[94,95]
breast cancer	4T1-luc, Hs578T, MCF-7, MDA-MB-231, MDA-MB-436, T47D	*in vitro* and *in vivo*	[48,66,72,73,75,101]
cholangiocarcinoma	EGI-1, Mz-ChA-1, p246, p254, TFK-1	*in vitro* and *in vivo*	[89,90]
chondrosarcoma	SW1353	*in vitro*	[60]
colon cancer	COGA2, COGA10	*in vitro*	[66]
colorectal carcinoma	CT26, HCT-116, HT29, MC38, SW480, SW620	*in vitro* and *in vivo*	[67–70]
endometrial cancer	Hec-1, RENT4	*in vitro*	[97]
gastric cancer	AGS, BGC-823, KATO-III, MKN-28, MKN-45, NCI-N87, SGC-7901, SNU-1, SNU-16	*in vitro*	[59]
glioma	DBTRG-05MG, EFC-2, GL261, U87MG, U251MG	*in vitro* and *in vivo*	[98–100]
head and neck carcinoma	HN-1, HN-30, JLO-1, UMSCC-10B	*in vitro* and *in vivo*	[96,101]
hepatocellular carcinoma	BEL-7402, HepG2, HCCLM3, Huh7, MHCC-97H, SMMC-7721	*in vitro* and *in vivo*	[86–88]
leukemia	A9Mp, hAML1-3, KG-1a, MAF9p, Molt-4 and Jurkat $CD4^+$ T-cell	*in vitro* and *in vivo*	[50–54]
lung cancer	A549, LLC, LNM35	*in vitro*	[64–66]
lymphoma	Namalwa Burkitt	*in vitro*	[50]
nasopharyngeal carcinoma	CNE-1, CNE-2, CNE-2/DDP	*in vitro* and *in vivo*	[84,85]
osteosarcoma	MG63, SAOS2, SAOS2/MTX30, U2OS, U2OS/MTX300	*in vitro* and *in vivo*	[58]
ovarian cancer	A2780, A2780/ADR, A2780/DDP, C13, OV2008, OVCAR-3, SKOV3	*in vitro* and *in vivo*	[78–83,101]
pancreatic cancer	AsPC-1, Colo357, MiaPaCa-2, PANC-1, Panc02, SW1990	*in vitro* and *in vivo*	[91–93]
prostate cancer	DU-145, LNCaP, PC-3, VCaP	*in vitro* and *in vivo*	[55–57]
squamous cell carcinoma	OCTT2, SCC9	*in vivo*	[71]
uterine sarcoma	MES-SA/Dx5	*in vitro*	[50]

and decreased the malignant traits in these cells. The tested cancer cells were ~10-fold more sensitive to **SAL** than to oxaliplatin, a commonly used anti-colorectal cancer drug [69]. Very recently, a murine model to investigate the effectiveness of **SAL** against human colorectal cancer cells has been proposed. **SAL** markedly impaired tumor cell viability, proliferation and migration, and induced necrotic cell death both *in vitro* and *in vivo* [70].

In the original report of Basu et al., **SAL** was found to equally target both epithelial-like and mesenchymal-like sub-populations in squamous cell carcinoma cell lines of the breast cancer as well as to deplete the latter population in a mouse xenograft model, in contrast to cisplatin. What should be stressed here, the sub-population of mesenchymal-like cells displaying phenotypic plasticity and increased resistance to both cytotoxic and targeted agents was recognized as stem cell-like cancer cells [71]. **SAL** was also able to induce growth inhibition, permanent cell cycle arrest, apoptosis and senescence of different breast cancer cells, including triple-negative human breast cancer cells [72,73]. Moreover, higher resistance of non-tumor breast cancer cells to **SAL** was observed [72]. In a recent study, Marchal et al. have compared the effects of **SAL** on breast CSCs to that of a newly identified small anticancer compound bozepinib; both agents showed a similar range of half maximal inhibitory concentrations (IC_{50}) [74]. Additionally, **SAL** could be applied at a relatively low concentration for a longer time to overcome drug-resistance of breast cancer cells [75].

Although much progress in its treatment has been made, ovarian cancer is the most lethal gynecologic malignancy. Maximal surgical cytoreduction followed by platinum-based chemotherapy is the standard treatment for patients with ovarian cancer. However, the problem with this therapy is that ovarian cancer cells are resistant to the action of cisplatin [76]. Importantly, **SAL** elicited a dose-dependent inhibition of cell growth and a pronounced inhibitory effect on cell proliferation in ovarian cancer cells [77], including both cisplatin-sensitive and cisplatin-resistant ovarian cancer cells [78–83], such as the adriamycin-resistant ovarian cancer cells [83]. Testa et al. have observed, however, that MDR ovarian cancer cell lines are moderately less sensitive than their chemosensitive counterparts to the apoptotic effects induced by **SAL** [83].

In further studies, the scientists from other research groups have demonstrated that **SAL** can effectively inhibit proliferation and invasion, and/or induce apoptosis of human nasopharyngeal carcinoma cells and CSCs (activity *in vitro* and *in vivo*) [84,85], human hepatocellular carcinoma cells (activity *in vitro* and *in vivo*) [86–88], human cholangiocarcinoma cells – a primary liver cancer that is characterized by aggressive tumor growth, high recurrence rates, and resistance against common chemotherapeutical regimes (activity *in vitro* and *in vivo*) [89,90], human pancreatic cancer cells (activity *in vitro* and *in vivo*) [91–93], human bladder cancer cells (activity *in vitro* and *in vivo*) [94,95], human head and neck squamous cell carcinoma stem cells (activity *in vitro*) [96] as well as human endometrial CSCs (activity *in vitro* and *in vivo*) [97]. The effects of **SAL** on brain tumors have also been explored. It has been shown that glioblastoma multiforme cells and glioma tumor cells surviving to hydroxyurea or aphidicolin are slowly depleted by treatment with **SAL** [98,99]. **SAL** had the ability to inhibit the tumor growth of glioma stem cells by selectively suppressing glioma-initiating cells [100].

In 2012, only three years after the discovery of the anticancer properties of **SAL**, Naujokat and Steinhart successfully used **SAL** in the treatment of a small group of patients with invasive carcinoma of the head, neck, breast and ovary. Monotherapy with 200–250 $\mu g\,kg^{-1}$ of **SAL** administered intravenously every second day resulted in the inhibition of disease progression with the appearance of few side effects only. Importantly, long-term acute adverse effects, including nausea, vomiting, alopecia, and gastrointestinal disorders, were not observed [101].

4. Synergistic effects of salinomycin

An ideal anticancer strategy would be to look for agents that target both non-CSCs and CSCs within tumors. Alternatively, it may be preferable to develop novel synergistic combinations that combine agents with specific toxicity towards non-CSCs together with the ones that specifically target CSCs sub-populations within tumors. In this context, the sensitizing effects of anti-CSCs agent **SAL** on tumor cells of various origin have been noticed recently both in combination with other chemotherapeutic drugs and with radiotherapy (Table 2).

In 2010, Testa et al. proved that **SAL** treatment restores vinblastine sensitivity in vinblastine-resistant cells; similar results have been observed in human cisplatin-sensitive ovarian epithelial carcinoma cells exposed to doxorubicin alone or in combination with **SAL** [83]. Treatment with **SAL** alone reduced the stemness marker expression and spheroid-forming ability of ovarian CSCs, while the therapy with paclitaxel alone did not decrease the viability of cancer cells with stem cell-like properties. Interestingly, the treatment with a combination of both agents decreased the viability of ovarian CSCs and promoted cancer cell apoptosis [102]. In the original report published recently, a combination of **SAL** and homogenous, spherical in shape silver nanoparticles showed a stronger synergistic interaction in ovarian cancer cells than in breast cancer cells. A combined treatment increased the therapeutic potential and demonstrated the relevant targeted therapeutic effect in the treatment of ovarian cancer [103].

Since **SAL** inhibited the growth of CSCs, intensive studies have been conducted in pancreatic cancer cells using **SAL** combined with gemcitabine which suppresses the viability of non-CSC pancreatic cancer cells. It has been found that the combination of **SAL** with gemcitabine could eliminates the engraftment of human pancreatic cancer cells more effectively than either of the agents alone. It suggested that administration of **SAL**, a selective anti-CSCs agent, may be a potential therapeutic strategy for improving the efficacy of gemcitabine in the treatment of patients diagnosed with pancreatic cancer [104].

Although much success in developing novel anticancer drugs has been made, drug resistance remains a major obstacle in cancer treatment. It may be a pre-existing, inherent feature of cancer cells or a feature acquired during the course of treatment, leading to cancer relapse after months or years; MDR can also be found through the promotion of drug efflux [105,106]. In this context, chemotherapy in combination with **SAL** may improve MDR cancer therapy. **SAL** and 5-fluorouracil were used in combination therapy on MDR hepatocellular carcinoma cell lines and nude mice to study whether **SAL** could increase the sensitivity of hepatoma cells to the traditional chemotherapeutics. Interestingly, the combination of **SAL** and 5-fluorouracil resulted in synergistic enhancement of cytotoxicity and cell growth inhibition in liver tumors both *in vitro* and *in vivo* [107].

The recently performed studies have clearly proved that **SAL** and metformin are effective EMT-inhibiting agents in non-small cell lung cancer cell lines [108]. On the basis of this result, scientists from different research groups have shown that **SAL** in combination with metformin, but also with cisplatin and erlotinib, acted synergistically to inhibit the growth and alveosphere formation of non-small cell lung cancer cells [109–111]. In contrast, a combination of **SAL** and paclitaxel did not improve the effect of single therapies on lung primary tumors and their metastasis [63]. On the other hand, **SAL** interacted with HDAC inhibitors to kill parental and stem-like human glioblastoma cells [112] and was able to potentiate the

Table 2
Synergistic anticancer co-action of salinomycin with other agents or irradiation.

Type of cancer	Synergy	Cancer cell line	Activity *in vitro*/ *in vivo*	References
breast cancer	Akt inhibitors, antimitotic agents, doxorubicin, etoposide, frondoside A, panobinostat, radiation, resveratrol, 4-hydroxytamoxifen, tamoxifen, trastuzumab, silver nanoparticles	BT-474, HCC1937, Hs578T, MCF-7, MCF-7/LCC2, MCF-7/LCC9, MDA-MB-231, MDA-MB-436, MDA-MB-468, T47D	*in vitro* and *in vivo*	[73,103,117–121,123,124,129–134,136]
cholangiocarcinoma	doxorubicin	Huh-28, RBE	*in vitro*	[127]
chondrosarcoma	doxorubicin	SW1353	*in vitro*	[60]
colorectal carcinoma	gefitinib, nelfinavir	HCT-116, HT-29, LoVo, SW480, SW1116, SW1116-GEF	*in vitro* and *in vivo*	[115,118]
gastric cancer	17-AAG, cisplatin	SGC-7901	*in vitro*	[125,126]
glioma	HDAC inhibitors, TRAIL, radiation	A172, GBM6, GBM12, U251, T98G, TB10	*in vitro* and *in vivo*	[112,113,140]
head and neck squamous cell carcinoma	cisplatin, paclitaxel, radiation	HLaC-78, JLO-1, UMSCC-10B	*in vitro*	[96,139]
hepatocellular carcinoma	5-fluorouracil, doxorubicin, etoposide	HepG2, Huh7, LM3, SMMC-7721, SNU-387, SNU-449	*in vitro* and *in vivo*	[107,116,128]
leukemia	doxorubicin	CEM-VBL10, CEM-VBL100	*in vitro*	[83]
lung cancer	erlotinib, cisplatin, metformin, nelfinavir	A549, H1650, H1703, H1975, HCC95, HCC4006, NCI-H460, NCI-H1975, NCI-H2122, NCI-H3122	*in vitro*	[108–111,118]
nasopharyngeal carcinoma	radiation	CNE-2, SUNE1IR	*in vitro*	[136,137]
osteosarcoma	adriamycin, cisplatin, methotrexate	U2OS/MTX300, U2OS/OCT4	*in vitro*	[58]
ovarian cancer	antimitotic agents, paclitaxel, silver nanoparticles	A2780, ES2	*in vitro*	[102,103,117]
pancreatic cancer	gemcitabine	AsPC-1, SW1990	*in vitro* and *in vivo*	[104]
soft tissue sarcomas	doxorubicin	A204, HT-1080	*in vitro*	[114]
uterine sarcoma	doxorubicin, etoposide	MES-SA/Dx5	*in vitro*	[116]

cytotoxic effects of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on these cancer cells [113]. **SAL** increased chemosensitivity to the effects of doxorubicin in chondrosarcoma [60] and soft tissue sarcomas [114], and enhanced the cytotoxic effects of the commonly used chemotherapeutic drugs (adriamycin, cisplatin and methotrexate) to osteosarcoma CSCs compared to the effects of these agents alone [58]. Synergistic induction of apoptosis by **SAL** and gefitinib through lysosomal and mitochondrial dependent pathway overcame gefitinib resistance in colorectal cancer, with a relatively low toxicity to normal cells [115].

Furthermore, co-treatment with **SAL** reduced the viability and increased the apoptosis of the breast, liver and MDR uterine cancer cells treated with etoposide and doxorubicin, suggesting that **SAL** was capable of targeting cancers originating from various organs when combined with these drugs. The results also demonstrated that doxorubicin was more efficient in combination with **SAL** than etoposide in combination chemotherapy [116]. Low concentration of **SAL** could sensitize the breast and ovarian cancer cells to antimitotic (microtubule-targeting) drugs, such as colchicine, docetaxel, paclitaxel and vinblastine, irrespective of their specific targeting domains [117]. **SAL** worked synergistically with cisplatin or paclitaxel in inducing cell death and differentiation in head and neck squamous cell carcinoma stem cells [96] as well as with nelfinafir, a widely used anti-HIV agent, to selectively kill TSC2-deficient cancer cells [118].

Resveratrol is a natural polyphenol having antiproliferative activity against breast cancer cells. Recently, a novel combination of **SAL** and resveratrol for targeting breast cancer cells has been reported [119–121]. Such a combination significantly enhanced cellular toxicity of low dose resveratrol in ER-positive but not in triple-negative breast cancer cells. A combination of resveratrol with **SAL** was observed to be more potent that a combination with rapamycin, a widely used mTOR inhibitor [119]. In contrast, Shukla et al. have showed in the same year that resveratrol synergistically potentiated the anticancer activity of **SAL** also against triple-negative breast cancer cells [120].

In 2013, a novel **SAL**-sensitization mechanism in cancer cells was identified; Yoon et al. indicated that Akt deactivation may promote the sensitivity of cancer cells to **SAL** [122], and this observation was exploited in further studies [123,124]. **SAL** could be applied to increase treatment efficacy for cancer cells treated with AZD5363, an inhibitor of protein kinase B (Akt) that is currently in clinical trials [123]. Co-treatment using **SAL** and MK-2206 or LY294002, another anticancer drugs in clinical trials, could be used as a therapeutic method to sensitize cancer cells through targeting of the PI3K/Akt/mTOR pathway as well. Collectively, these results indicated that the sensitization mechanism observed when **SAL** was combined with MK-2206 or LY294002 could also take place when combined with other Akt inhibitors [124]. Furthermore, Zhang et al. have demonstrated that a combination of **SAL** and cisplatin or 17-AAG inhibited proliferation and induced apoptosis of human gastric cancer cells. The alterations in gastric cancer cells co-treated with these agents were more significant when compared with those in cancer cells treated with one drug only [125,126].

SAL was also identified to exert synergistic cytotoxicity with doxorubicin in cholangiocarcinoma and in hepatocellular carcinoma cells through reversing/inhibiting doxorubicin-induced EMT [127,128]. Similarly, **SAL** could enhance doxorubicin-induced cytotoxicity and reversed the resistance of doxorubicin in MDR human breast cancer cells *via* diminishing drug efflux pump expression and its activity [129,130]. As far as breast cancer is concerned, **SAL** co-treatment enhanced tamoxifen cytotoxicity in both tamoxifen-sensitive and tamoxifen-resistant breast tumor cells *i.a.* by facilitating lysosomal degradation of receptor tyrosine kinases [131,132]. The treatment of breast cancer mammospheres with **SAL** alone reduced the expression of defined stem cell markers, indicating its selectivity towards CSCs. Although trastuzumab did not reduce the expression of these cancer stem-like markers, a combinational

treatment of mammospheres with **SAL** and trastuzumab was superior to single treatment with each of the agent that efficiently targeted both HER2-positive cancer cells and CSCs [133]. It is of note that **SAL** was additionally able to potentiate the antiproliferative activity of 4-hydroxytamoxifen and frondoside A against breast cancer cells [73], and acted as a promising drug for the eradication of triple-negative breast cancer cells in combination with histone deacetylase inhibitor panobinostat (LBH589) [134].

It is well known that many cancers are resistant to radiotherapy and the existence of proliferatively quiescent CSCs is clearly one of the reasons, along with the fact that they may exist within hypoxic niches resulting in lower levels of reactive oxygen species (ROS) and enhanced free radical scavenging systems [135]. It is therefore worth noting that **SAL** sensitized radiation-treated breast cancer cells by causing their DNA damage [136]. Moreover, Zhang et al. have found that **SAL** can reverse radioresistance and promote radiation-induced apoptosis in resistant to irradiation human nasopharyngeal carcinoma cells [137,138]. It is postulated that **SAL** and radiation are an effective combination therapy against head and neck squamous cell carcinoma. A combined treatment with **SAL** and radiation revealed very recently a significantly higher reduction of tumor cell viability, proliferation, motility and secretory capacity compared to the cells receiving only one of the treatments alone [139]. Very recently, it has been also shown that combined treatment of ^{125}I seeds and **SAL** induces enhanced growth inhibition against human glioma cells through induction of cell apoptosis. Further investigation has revealed that such combination therapy triggers enhanced DNA damage through inducing ROS generation [140].

5. Mechanism of anticancer activity of salinomycin

Although results of intensive studies have brought significant progress in this issue, the precise anticancer mechanism of **SAL** is still not fully understood and needs further investigation. The effects on several signal transduction pathways were however invoked to explain the change in phenotype composition after **SAL** treatment. Notably, it was demonstrated that **SAL** treatment inhibits Wnt signaling pathway involved in tumorigenesis and embryogenesis through more than one mechanism [52]; the other pathways that were inhibited by **SAL** include KRas [141] and modulation of Hedgehog signaling [142–144]. Alterations in genes involved in stemness-related pathways, including Wnt, Notch and Hedgehog, have been proved to play a pivotal role in breast cancer progression [145].

Mechanistically, the demonstrated effects of **SAL** treatment in different types of human cancers include decreased mitochondrial membrane potential, decreased ATP levels, increased ROS production (oxidative stress) that caused DNA damage and cell death, and interfering with ABC drug transporters [56,146–152]. The ABC transporters, like P-glycoprotein, constitute a group of transmembrane macromolecules that extrude a variety of substrates, including structurally unrelated chemotherapeutic drugs, from the cytosol, thereby conferring MDR [153,154]. The intense research conducted recently, unveiled that **SAL** becomes a substrate of ABC transporter, induces conformational change and blocks the MDR of P-glycoprotein (MDR1/ABCB1) that finally reduces its activity [83]. Moreover, **SAL** was able to induce programmed cell death in human cancer cells that exhibit resistance to apoptosis not only by interacting with P-glycoprotein, but also by overexpression of Bcl-2 or 26S proteasomes with enhanced proteolytic activity [50]. In contrast, it has been shown in another publication that **SAL** is able to decrease the expression of Bcl-2 and simultaneously to increase the expression of Bax as well as to cleave both caspase-3 and caspase-9 [147].

SAL treatment has been also found to produce endoplasmic reticulum (ER) stress in different cancer cell lines leading to autophagy, which plays a role in various stages of tumorigenesis [62,155–159]. ER stress is a cellular defense mechanism that can force epithelial stem cells [160] and stem-like cancer cells to differentiate [161,162], and it is well known that this response can be induced by depletion of ER Ca^{2+} stores [162,163]. Importantly, increased level of cytosolic Ca^{2+} was observed as a result of **SAL**-mediated alkali-metal cation transport across the ER membrane (Fig. 2C) [88,150,164]. Caspase-independent apoptosis was postulated by Fuchs et al. who demonstrated that **SAL** activated a distinct apoptotic pathway, which was not accompanied by cell cycle arrest and that was independent of the tumor suppressor protein p53, caspase activation, FAS/FAS ligand and the CD95/CD95L system [50]. In contrast, Zhang et al. have suggested that **SAL** induces p53 translocation to mitochondria and forms a complex with cyclophilin-D, which is required for mitochondrial permeability transition pore opening and subsequent programmed necrosis [98]. There is also a report on cell death induction by **SAL** *via* inactivation of Stat3 [165,166], downregulation of Skp2 [166], abolished Stat1 interactions and reduced telomerase activity [167].

Functionally, **SAL** is one of the representatives of membrane ionophores which show significant affinity to alkali cations, especially to K^+, and the accumulating evidence points to the ion transport properties as the origin of its phenotype effects [31]. Earlier it has been postulated that a decrease in intracellular K^+ concentration was essential for the induction of apoptosis in human lymphoma cells [168,169]. Potassium channels of the mitochondrial and cytoplasmic membranes which are overexpressed in many human cancer cells, play the pivotal roles in the regulation of tumorigenesis, tumor cell proliferation, cell cycle progression and apoptosis, and may constitute novel and promising molecular targets for cancer therapy [170]. In this context, **SAL** may interfere with transmembrane potassium potential and promote the efflux of K^+ cations from mitochondria and/or cytoplasm, suggesting that apoptosis induced by **SAL** is mediated, at least in part, by its ability to deplete cytoplasmic and/or mitochondrial K^+, and to interfere with potassium membrane potential (Fig. 2C). Although the molecular basis of the changes in phenotype composition, *i.e.* which ion fluxes in the cell, are mediated by **SAL** to induce phenotype effects, is still unknown, the data provide a connection between the ionophoric activity of **SAL** in the ER, and between the previously described changes in phenotype composition *via* suppressing of proximal Wnt [52,58,164,171–173] and/or mTORC1 signaling [174,175].

On the other hand, Li et al. and Łos et al. have shown that **SAL** induces autophagic flux [150,158]. The authors have shown a massive autophagic response to **SAL** in prostate and breast cancer cells, and this response has been substantially stronger than that to the commonly used autophagic inducer – rapamycin; these findings suggest possible clinical application of **SAL** in combination with autophagy inhibitors, such as chloroquine [150]. In contrast, Yue et al. have presented **SAL** as an inhibitor of functional autophagy without altering the lysosomal acidity, but through an unknown mechanism of attenuating lysosomal proteases [176]; this comparison is complicated by the fact that the above-mentioned studies employed different cancer cellular models [150,158,176]. According to other authors, it was found that **SAL** mediated with regulation of autophagy that enhanced its anticancer activity by many different ways, including activating of AMP-activated protein kinase, ROS induction, mediation of PI3K/Akt/mTOR and ERK/p38 MAPK-dependent signaling [177–183]. On the other hand, it has been indicated very recently that **SAL**-induced autophagy blocks apoptosis *via* the ATG3/AKT/mTOR signaling axis in PC-3 prostate cancer cells [184].

It is of note that **SAL** suppressed cell viability concomitant with the downregulation of cyclin D1 and increased $p27^{kip1}$ nuclear accumulation; mammosphere formation assays revealed that **SAL** downregulates the transcription factors Nanog, Oct4 and Sox2 [185]. **SAL** blocked also cancer cell migration by disrupting stress fiber integrity [92] and through the dephosphorylated FAK and ERK1/2 pathways, reflecting the changes in cell stiffness resulting from the increased actin cytoskeleton [186]. Li et al. showed that **SAL** has the ability to reverse transforming growth factor-β1 (TGF-β1) accompanied with down-regulation of MMP-2; **SAL** was able to inhibit TGF-β1-induced EMT phenotypic transition and the activation of key signaling molecules involved in both Smad and non-Smad signals, which cooperatively regulate the induction of EMT [187].

New growth in the vascular network is important since the proliferation and metastatic spread of cancer cells depends on an adequate supply of oxygen and nutrients as well as the removal of waste products; new blood vessels form through the processes called angiogenesis [188]. In this context, it has been found very recently that **SAL** exerts antiangiogenic and antitumorigenic activities by inhibiting vascular endothelial growth factor receptor 2-mediated angiogenesis [189] as well as by suppressing the VEGF-VEGFR2-Akt/FAK signaling axis [190].

6. Salinomycin toxicity

Like any other bioactive substance, **SAL** used in the amount above a certain dose also induces toxic effects. It is postulated that the neuronal and muscular toxicity of **SAL** is mediated by the uncontrolled and abrupt elevation of cytosolic Na^+/K^+ concentration that consecutively enhances Ca^{2+} concentration inside the cells due to NCX exchangers in the plasma membrane and mitochondria [152,191]. A high level of intracellular Ca^{2+} induced the activation of calpain triggering a caspase-dependent apoptosis [152] and may result in normal cell necrosis [192]. P-gp can also be a major determinant of the pharmacokinetic behavior and toxicity of **SAL** [193].

Several reports describing the toxicity effects of **SAL** on animals and humans have been published whose authors distinguished many different symptoms, such as rhabdomyolysis, myocardial insufficiency, neuropathy and metabolic acidosis [191]. For example, **SAL** accidently fed to cats induced severe axonal and demyelinating neuropathy [194]; the toxic effects of **SAL** on rat neuronal cells at concentrations effective against CSCs were proved [152]. There was also a case report on human poisoning by **SAL**; accidently ingested unknown concentration of **SAL** resulted in life-threatening neuropathy, rhabdomyolysis and 6-week hospitalization. The concentration of **SAL** in the plasma was not determined, but it was estimated that 1 mg kg^{-1} of the body weight was ingested [195]. In China, a group of 14 people accidentally ingested high concentrations of **SAL** during a banquet due to the misuse substitution of **SAL** powder as starch. Clinical symptoms included diarrhea, dizziness, limb anesthesia, nausea, stomachache, vomiting, weakness and dark red to brown urine [196].

However, Boehmerle and Endres demonstrated an attenuation of **SAL** toxicity by inhibition of NCX and calpain [152]. Indeed, a significant reduction in **SAL** neuronal toxicity was observed by inhibiting the mitochondrial NCXs, using the benzodiazepine derivate CGP37157. Importantly, the tumor toxicity of **SAL** was simultaneously not inhibited by CGP37157, which may be a novel and very promising dual-drug strategy in future cancer therapy [197]. The interaction between **SAL** and hepatoprotective agent silybin resulted in considerable toxicity reduction [198] as well as it was found that **SAL** underwent rapid metabolism in liver microsomes and had a high intrinsic clearance [199].

Since **SAL** was found to selectively destroy CSCs, its effects on normal human bone marrow mesenchymal stem cells (hBMSCs) were also elucidated. Low-dose **SAL** showed no negative effects on the essential functional properties as well as immunophenotype and multi-differentiation capacity of hBMSCs. Cytotoxic effects were observed at concentrations of $\geq$30 μM only; neither the migration capability nor the ability to form spheroids was affected [200]. All these findings were confirmed recently by other scientists; hBMSCs were treated with low-dose **SAL** (100 nM) for four weeks and no differences were observed in cell morphology or cytoskeletal structures following **SAL** exposure. The differentiation into adipocytes and osteocytes was not counteracted, proliferation capability was not inhibited and no genotoxic effects were observed after four weeks of **SAL** exposure as well [201]. On the other hand, Kleinsasser et al. revealed significant cytotoxic effects in human nasal mucosa cells and peripheral blood lymphocytes at **SAL** concentrations of 10–20 μM without observation of any genotoxic effects [202].

7. Conclusions

Cancers are characterized by uncontrollable and unstoppable growth and cell division, and cancer cells also have the ability to metastasize to other tissues and organs. Although oncology has had several milestones in the fight against cancers, the patients are still waiting for development of effective ways to combat the disease. Chemotherapy, whose action is based on the inhibition of cell division, is effective towards many types of cancers but to many others it is completely unsuccessful. Therefore, the search for new biologically active substances is of top importance. Over the last few decades, natural compounds have been commonly used in cancer treatment, and there is much evidence indicating that salinomycin (**SAL**), a naturally-occurring polyether antibiotic, is a candidate for novel and very effective anticancer drug.

There is no doubt that **SAL** has remarkable and unusual anticancer properties. Within just a few years, the high activity of **SAL** was proved against cancer cells and cancer stem cells of different origin, including those that display multi-drug resistance. Every year, there are dozens of new articles describing the new discoveries in the field of **SAL** bioactivity. Particularly interesting are new reports on the synergistic effects of **SAL** treatment in combination with other chemotherapeutic drugs or radiotherapy that significantly increase the effectiveness of the dual therapy applied.

SAL, like any other bioactive substance, is toxic when applied above a certain concentration. However, the results have clearly shown that it is able to effectively suppress cancer progression with the appearance of a few minor side effects only, when used in the appropriate dose. It should be emphasized here that long-term acute adverse effects, including nausea, vomiting, alopecia, and gastrointestinal disorders, have not been observed, which proves its huge therapeutic potential.

For sure, in the coming years there will be further, numerous scientific reports regarding the anticancer activity of **SAL** as well as its synergistic co-actions both *in vitro* and *in vivo*. In the light of all data presented in this review article, **SAL** should be approved in future for cancer therapy as a powerful and very selective drug that will bring hope and real help to cancer patients worldwide.

Acknowledgment

M.A. wishes to acknowledge the Polish Science Centre (NCN) for financial support by grant SONATA (2016/23/D/ST5/00242) and the Foundation for Polish Science (FNP) for a scholarship START.

References

[1] World Health Organization – Cancer, [on-line access: 2018–11–27]. http://www.who.int/cancer/en/.
[2] J.E. Visvader, G.J. Lindeman, Cancer stem cells in solid tumours: accumulating evidence and unresolved questions, Nat. Rev. Canc. 8 (2008) 755–768.
[3] N.D. Marjanovic, R.A. Weinberg, C.L. Chaffer, Cell plasticity and heterogeneity in cancer, Clin. Chem. 59 (2013) 168–179.
[4] M. Dean, T. Fojo, S. Bates, Tumour stem cells and drug resistance, Nat. Rev. Canc. 5 (2005) 275–284.
[5] J.E. Visvader, G.J. Lindeman, Cancer stem cells: current status and evolving complexities, Cell Stem Cell 10 (2012) 717–728.
[6] M. Mimeault, S.K. Batra, New promising drug targets in cancer- and metastasis-initiating cells, Drug Discov. Today 15 (2010) 354–364.
[7] D. Bonnet, J.E. Dick, Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell, Nat. Med. 3 (1997) 730–737.
[8] S.O. Iseghohi, Cancer stem cells may contribute to the difficulty in treating cancer, Genes Dis 3 (2016) 7–10.
[9] A. Markowska, S. Sajdak, J. Markowska, A. Huczyński, Angiogenesis and cancer stem cells: new perspectives on therapy of ovarian cancer, Eur. J. Med. Chem. 142 (2017) 87–94.
[10] R. Lamb, B. Ozsvari, C.L. Lisanti, H.B. Tanowitz, A. Howell, U.E. Martinez-Outschoorn, F. Sotgia, M.P. Lisanti, Antibiotics that target mitochondria effectively eradicate cancer stem cells, across multiple tumor types: treating cancer like an infectious disease, Oncotarget 6 (2015) 4569–4584.
[11] Y. Miyazaki, M. Shibuya, H. Sugawara, O. Kawaguchi, C. Hirsoe, Salinomycin, a new polyether antibiotic, J. Antibiot. (Tokyo) 27 (1974) 814–821.
[12] M. Antoszczak, J. Rutkowski, A. Huczyński, Structure and biological activity of polyether ionophores and their semi-synthetic derivatives, in: G. Brahmachari (Ed.), Bioactive Natural Products. Chemistry and Biology, Weinheim, 2015.
[13] M. Antoszczak, A. Huczyński, Anticancer activity of polyether ionophore – salinomycin, Anti Cancer Agents Med. Chem. 15 (2015) 575–591.
[14] J. Dewangan, S. Srivastava, S.K. Rath, Salinomycin: a new paradigm in cancer therapy, Tumor Biol. 39 (2017), 1010428317695035.
[15] Y. Kishi, S. Hatakeyama, M.D. Lewis, Total synthesis of narasin and salinomycin, in: K.J. Laidler (Ed.), Frontiers of Chemistry, Oxford, 1982.
[16] J.S. Yadav, V.K. Singh, P. Srihari, Formation of substituted tetrahydropyrans through oxetane ring opening: application to the synthesis of C1-C17 fragment of salinomycin, Org. Lett. 16 (2014) 836–839.
[17] J. Esteve, C. Jiménez, J. Nebot, J. Velasco, P. Romea, F. Urpí, Highly stereoselective titanium-mediated aldol reactions from chiral α-silyloxy ketones. A reliable tool for the synthesis of natural products, Tetrahedron 67 (2011) 6045–6056.
[18] J. Sperry, Y.C. Liu, M.A. Brimble, Synthesis of natural products containing spiroketals via intramolecular hydrogen abstraction, Org. Biomol. Chem. 8 (2010) 29–38.
[19] M.A. Brimble, F.A. Farés, Synthesis of bis-spiroacetal ring systems, Tetrahedron 55 (1999) 7661–7706.
[20] P.J. Kocieński, R.C.D. Brown, A. Pommier, M. Procter, B. Schmidt, Synthesis of salinomycin, J. Chem. Soc., Perkin Trans. 1 (1998) 9–40.
[21] M.A. Brimble, H. Prabaharan, Approaches to the D–E ring of the polyether antibiotic salinomycin using Sharpless asymmetric dihydroxylation, Tetrahedron 54 (1998) 2113–2128.
[22] Z. Zhu, H. Li, P. Yu, Y. Guo, S. Luo, Z. Chen, X. Mao, W. Guan, Y. Li, SlnR is a positive pathway-specific regulator for salinomycin biosynthesis in Streptomyces albus, Appl. Microbiol. Biotechnol. 101 (2017) 1547–1557.
[23] C. Jiang, Z. Qi, Q. Kang, J. Liu, M. Jiang, L. Bai, Formation of the Δ18,19 double bond and bis(spiroacetal) in salinomycin is atypically catalyzed by SlnM, a methyltransferase-like enzyme, Angew. Chem., Int. Ed. Engl. 54 (2015) 9097–9100.
[24] H. Luhavaya, S.R. Williams, H. Hong, L. Gonzaga de Oliveira, P.F. Leadlay, Site-specific modification of the anticancer and antituberculosis polyether salinomycin by biosynthetic engineering, Chembiochem 15 (2014) 2081–2085.
[25] M. Izumikawa, M. Murata, K. Tachibana, Y. Ebizuka, I. Fujii, Cloning of modular type I polyketide synthase genes from salinomycin producing strain of Streptomyces albus, Bioorg. Med. Chem. 11 (2003) 3401–3405.
[26] M.E. Yurkovich, P.A. Tyrakis, H. Hong, Y. Sun, M. Samborskyy, K. Kamiya, P.F. Leadlay, A late-stage intermediate in salinomycin biosynthesis is revealed by specific mutation in the biosynthetic gene cluster, Chembiochem 13 (2012) 66–71.
[27] C. Jiang, H. Wang, Q. Kang, J. Liu, L. Bai, Cloning and characterization of the polyether salinomycin biosynthesis gene cluster of Streptomyces albus XM211, Appl. Environ. Microbiol. 78 (2012) 994–1003.
[28] M. Suzuki, R. Ueoka, K. Takada, S. Okada, S. Ohtsuka, Y. Ise, S. Matsunaga, Isolation of spirastrellolides A and B from a marine sponge Epipolasis sp. and their cytotoxic activities, J. Nat. Prod. 75 (2012) 1192–1195.
[29] D.H. Berg, R.L. Hamill, The isolation and characterization of narasin, a new polyether antibiotic, J. Antibiot. (Tokyo) 31 (1978) 1–6.
[30] J.W. Westley, J.F. Blount, R.H. Evans Jr., C.M. Liu, C-17 epimers of deoxy-(O-8)-salinomycin from Streptomyces albus (ATCC 21838), J. Antibiot. (Tokyo) 30 (1977) 610–612.
[31] A. Huczyński, Polyether ionophores – promising bioactive molecules for cancer therapy, Bioorg. Med. Chem. Lett 22 (2012) 7002–7010.
[32] B. Borgström, X. Huang, C. Hegardt, S. Oredsson, D. Strand, Structure-activity relationships in salinomycin: cytotoxicity and phenotype selectivity of semi-synthetic derivatives, Chem. Eur J. 23 (2017) 2077.
[33] X. Huang, B. Borgström, S. Kempengren, L. Persson, C. Hegardt, D. Strand, S. Oredsson, Breast cancer stem cell selectivity of synthetic nanomolar-active salinomycin analogs, BMC Canc. 16 (2016) 145.
[34] B. Borgström, X. Huang, M. Pošta, C. Hegardt, S. Oredsson, D. Strand, Synthetic modification of salinomycin: selective O-acylation and biological evaluation, Chem. Commun. 49 (2013) 9944–9946.
[35] A. Huczyński, Salinomycin: a new cancer drug candidate, Chem. Biol. Drug Des. 79 (2012) 235–238.
[36] M. Mitani, T. Yamanishi, Y. Miyazaki, Salinomycin: a new monovalent cation ionophore, Biochem. Biophys. Res. Commun. 66 (1975) 1231–1236.
[37] M. Antoszczak, J. Janczak, B. Brzezinski, A. Huczyński, Spectroscopic and structural studies of the first complex formed between salinomycin and organic amine, J. Mol. Struct. 1130 (2017) 719–726.
[38] Y.N. Antonenko, T.I. Rokitskaya, A. Huczyński, Electrogenic and non-electrogenic ion fluxes across lipid and mitochondrial membranes mediated by monensin and monensin ethyl ester, Biochim. Biophys. Acta Biomembr. 1848 (2015) 995–1004.
[39] A. Huczyński, J. Janczak, D. Łowicki, B. Brzezinski, Monensin A acid complexes as a model of electrogenic transport of sodium cation, Biochim. Biophys. Acta Biomembr. 1818 (2012) 2108–2119.
[40] N. Matsumori, A. Morooka, M. Murata, Conformation and location of membrane-bound salinomycin-sodium complex deduced from NMR in isotropic bicelles, J. Am. Chem. Soc. 129 (2007) 14989–14995.
[41] J. Jiang, H. Li, E. Qaed, J. Zhang, Y. Song, R. Wu, X. Bu, Q. Wang, Z. Tang, Salinomycin, as an autophagy modulator – a new avenue to anticancer: a review, J. Exp. Clin. Canc. Res. 37 (2018) 26.
[42] O. Warburg, On the origin of cancer cells, Science 123 (1956) 309–314.
[43] M. Huang, B. Liu, R. Liu, J. Li, J. Chen, F. Jiang, H. Ding, Z. Deng, T. Liu, Aglycone polyether nanchangmycin and its homologues exhibit apoptotic and anti-proliferative activities against cancer stem cells, ACS Pharmacol. Transl. Sci. 1 (2018) 84–95.
[44] S. Müller, T. Cañeque, V. Acevedo, R. Rodriguez, Targeting cancer stem cells with small molecules, Isr. J. Chem. 57 (2017) 239.
[45] R. Kalluri, R.A. Weinberg, The basics of epithelial-mesenchymal transition, J. Clin. Invest. 119 (2009) 1420–1428.
[46] H. Beug, Breast cancer stem cells: eradication by differentiation therapy? Cell 138 (2009) 623–625.
[47] K. Sampieri, R. Fodde, Cancer stem cells and metastasis, Semin. Canc. Biol. 22 (2012) 187–193.
[48] P.B. Gupta, T.T. Onder, G. Jiang, K. Tao, C. Kuperwasser, R.A. Weinberg, E.S. Lander, Identification of selective inhibitors of cancer cells by high-throughput screening, Cell 138 (2009) 645–659.
[49] C. Naujokat, D. Fuchs, G. Opelz, Salinomycin in cancer: a new mission for an old agent, Mol. Med. Rep. 3 (2010) 555–559.
[50] D. Fuchs, A. Heinold, G. Opelz, V. Daniel, C. Naujokat, Salinomycin induces apoptosis and overcomes apoptosis resistance in human cancer cells, Biochem. Biophys. Res. Commun. 390 (2009) 743–749.
[51] D. Fuchs, V. Daniel, M. Sadeghi, G. Opelz, C. Naujokat, Salinomycin overcomes ABC transporter-mediated multidrug and apoptosis resistance in human leukemia stem cell-like KG-1a cells, Biochem. Biophys. Res. Commun. 394 (2010) 1098–1104.
[52] D. Lu, M.Y. Choi, J. Yu, J.E. Castro, T.J. Kipps, D.A. Carson, Salinomycin inhibits Wnt signaling and selectively induces apoptosis in chronic lymphocytic leukemia cells, Proc. Natl. Acad. Sci. U.S.A. 108 (2011) 13253–13257.
[53] G.D. Roulston, C.L. Burt, L.M. Kettyle, K.B. Matchett, H.L. Keenan, N.M. Mulgrew, J.M. Ramsey, C. Dougan, J. McKiernan, I.V. Grishagin, K.I. Mills, A. Thompson, Low-dose salinomycin induces anti-leukemic responses in AML and MLL, Oncotarget 7 (2016) 73448–73461.
[54] Y. Zhao, L. Zhong, L. Liu, S.F. Yao, M. Chen, L.W. Li, Z.L. Shan, C.L. Xiao, L.G. Gan, T. Xu, B.Z. Liu, Salinomycin induces apoptosis and differentiation in human acute promyelocytic leukemia cells, Oncol. Rep. 40 (2018) 877–886.
[55] K.Y. Kim, S.N. Yu, S.Y. Lee, S.S. Chun, Y.L. Choi, Y.M. Park, C.S. Song, B. Chatterjee, S.C. Ahn, Salinomycin-induced apoptosis of human prostate cancer cells due to accumulated reactive oxygen species and mitochondrial membrane depolarization, Biochem. Biophys. Res. Commun. 413 (2011) 80–86.
[56] K. Ketola, M. Hilvo, T. Hyötyläinen, A. Vuoristo, A.L. Ruskeepää, M. Orešič, O. Kallioniemi, K. Iljin, Salinomycin inhibits prostate cancer growth and migration via induction of oxidative stress, Br. J. Canc. 106 (2012) 99–106.
[57] Y. Zhang, L. Liu, F. Li, T. Wu, H. Jiang, X. Jiang, X. Du, Y. Wang, Salinomycin exerts anticancer effects on PC-3 cells and PC-3-derived cancer stem cells in vitro and in vivo, BioMed Res. Int. 2017 (2017), 4101653.
[58] Q.L. Tang, Z.Q. Zhao, J.C. Li, Y. Liang, J.Q. Yin, C.Y. Zou, X.B. Xie, Y.X. Zeng, J.N. Shen, T. Kang, J. Wang, Salinomycin inhibits osteosarcoma by targeting its tumor stem cells, Cancer Lett. 311 (2011) 113–121.
[59] Q.M. Zhi, X.H. Chen, J. Ji, J.N. Zhang, J.F. Li, Q. Cai, B.Y. Liu, Q.L. Gu, Z.G. Zhu, Y.Y. Yu, Salinomycin can effectively kill ALDHhigh stem-like cells on gastric cancer, Biomed. Pharmacother. 65 (2011) 509–515.
[60] F. Perut, F.V. Sbrana, S. Avnet, A. De Milito, N. Baldini, Spheroid-based 3D cell cultures identify salinomycin as a promising drug for the treatment of chondrosarcoma, J. Orthop. Res. (2018), https://doi.org/10.1002/jor.23880.

[61] L. MacDonagh, S.G. Gray, E. Breen, S. Cuffe, S.P. Finn, K.J. O'Byrne, M.P. Barr, Lung cancer stem cells: the root of resistance, Cancer Lett. 372 (2016) 147–156.

[62] A.L. de Aberasturi, M. Redrado, M. Villalba, L. Larzabal, M.J. Pajares, J. Garcia, S.R. Evans, D. Garcia-Ros, M.E. Bodegas, L. Lopez, L. Montuenga, A. Calvo, TMPRSS4 induces cancer stem cell-like properties in lung cancer cells and correlates with ALDH expression in NSCLC patients, Cancer Lett. 370 (2016) 165–176.

[63] L. Larzabal, N. El-Nikhely, M. Redrado, W. Seeger, R. Savai, A. Calvo, Differential effects of drugs targeting cancer stem cell (CSC) and non-CSC populations on lung primary tumors and metastasis, PLoS One 8 (2013), e79798.

[64] K. Arafat, R. Iratni, T. Takahashi, K. Parekh, Y. Al Dhaheri, T.E. Adrian, S. Attoub, Inhibitory effects of salinomycin on cell survival, colony growth, migration, and invasion of human non-small cell lung cancer A549 and LNM35: involvement of NAG-1, PLoS One 8 (2013), e66931.

[65] Y. Wang, Effects of salinomycin on cancer stem cell in human lung adenocarcinoma A549 cells, Med. Chem. 7 (2011) 106–111.

[66] F. Kopp, A. Hermawan, P.S. Oak, A. Herrmann, E. Wagner, A. Roidl, Salinomycin treatment reduces metastatic tumor burden by hampering cancer cell migration, Mol. Canc. 13 (2014) 16.

[67] C. Zhang, Y. Tian, F. Song, C. Fu, B. Han, Y. Wang, Salinomycin inhibits the growth of colorectal carcinoma by targeting tumor stem cells, Oncol. Rep. 34 (2015) 2469–2476.

[68] J. Zhou, P. Li, X. Xue, S. He, Y. Kuang, H. Zhao, S. Chen, Q. Zhi, X. Guo, Salinomycin induces apoptosis in cisplatin-resistant colorectal cancer cells by accumulation of reactive oxygen species, Toxicol. Lett. 222 (2013) 139–145.

[69] T.T. Dong, H.M. Zhou, L.L. Wang, B. Feng, B. Lv, M.H. Zheng, Salinomycin selectively targets 'CD133+' cell subpopulations and decreases malignant traits in colorectal cancer lines, Ann. Surg. Oncol. 18 (2011) 1797–1804.

[70] J. Klose, J. Eissele, C. Volz, S. Schmitt, A. Ritter, S. Ying, T. Schmidt, U. Heger, M. Schneider, A. Ulrich, Salinomycin inhibits metastatic colorectal cancer growth and interferes with Wnt/β-catenin signaling in CD133+ human colorectal cancer cells, BMC Canc. 16 (2016) 896.

[71] D. Basu, K.T. Montone, L.P. Wang, P.A. Gimotty, R. Hammond, J.A. Diehl, A.K. Rustgi, J.T. Lee, K. Rasanen, G.S. Weinstein, M. Herlyn, Detecting and targeting mesenchymal-like subpopulations within squamous cell carcinomas, Cell Cycle 10 (2011) 2008–2016.

[72] A.M. Niwa, G.F. D'Epiro, L.A. Marques, S.C. Semprebon, D. Sartori, L.R. Ribeiro, M.S. Mantovani, Salinomycin efficiency assessment in non-tumor (HB4a) and tumor (MCF-7) human breast cells, Naunyn-Schmiedeberg's Arch. Pharmacol. 389 (2016) 557–571.

[73] Y. Al Dhaheri, S. Attoub, K. Arafat, S. AbuQamar, A. Eid, N. Al Faresi, R. Iratni, Salinomycin induces apoptosis and senescence in breast cancer: upregulation of p21, downregulation of survivin and histone H3 and H4 hyperacetylation, Biochim. Biophys. Acta 1830 (2013) 3121–3135.

[74] A. Ramirez, H. Boulaiz, C. Morata-Tarifa, M. Perán, G. Jiménez, M. Picon-Ruiz, A. Agil, O. Cruz-López, A. Conejo-Garcia, J.M. Campos, A. Sánchez, M.A. Garcia, J.A. Marchal, HER2-signaling pathway, JNK and ERKs kinases, and cancer stem-like cells are targets of bozepinib, Oncotarget 5 (2014) 3590–3606.

[75] J.H. Kim, T.Y. Kim, H.S. Kim, S. Hong, S. Yoon, Lower salinomycin concentration increases apoptotic detachment in high-density cancer cells, Int. J. Mol. Sci. 13 (2012) 13169–13182.

[76] A. Jemal, R. Siegel, E. Ward, T. Murray, J. Xu, C. Smigal, M.J. Thun, Cancer statistics, 2006, CA A Cancer J. Clin. 56 (2006) 106–130.

[77] A. Markowska, S. Sajdak, A. Huczyński, S. Rehlis, J. Markowska, Ovarian cancer stem cells: a target for oncological therapy, Adv. Clin. Exp. Med. 27 (2018) 1017–1020.

[78] F. Kaplan, F. Teksen, Apoptotic effects of salinomycin on human ovarian cancer cell line (OVCAR-3), Tumor Biol. 37 (2016) 3897–3903.

[79] B. Parajuli, H.G. Lee, S.H. Kwon, S.D. Cha, S.J. Shin, G.H. Lee, I. Bae, C.H. Cho, Salinomycin inhibits Akt/NF-κB and induces apoptosis in cisplatin resistant ovarian cancer cells, Cancer Epidemiol 37 (2013) 512–517.

[80] B. Parajuli, S.J. Shin, S.H. Kwon, S.D. Cha, R. Chung, W.J. Park, H.G. Lee, C.H. Cho, Salinomycin induces apoptosis via death receptor-5 up-regulation in cisplatin-resistant ovarian cancer cells, Anticancer Res. 33 (2013) 1457–1462.

[81] B. Zhang, X. Wang, F. Cai, W. Chen, U. Loesch, X.Y. Zhong, Antitumor properties of salinomycin on cisplatin-resistant human ovarian cancer cells in vitro and in vivo: involvement of p38 MAPK activation, Oncol. Rep. 29 (2013) 1371–1378.

[82] B. Zhang, X. Wang, F. Cai, W. Chen, U. Loesch, J. Bitzer, X.Y. Zhong, Effects of salinomycin on human ovarian cancer cell line OV2008 are associated with modulating p38 MAPK, Tumor Biol. 33 (2012) 1855–1862.

[83] R. Riccioni, M.L. Dupuis, M. Bernabei, E. Petrucci, L. Pasquini, G. Mariani, M. Cianfriglia, U. Testa, The cancer stem cell selective inhibitor salinomycin is a p-glycoprotein inhibitor, Blood Cells Mol. Dis. 45 (2010) 86–92.

[84] G. Zhang, S. Zhang, J. Ren, C. Yao, Z. Zhao, X. Qi, X. Zhang, S. Wang, L. Li, Salinomycin may inhibit the cancer stem-like populations with increased chemoradioresistance that nasopharyngeal cancer tumorspheres contain, Oncol. Lett. 16 (2018) 2495–2500.

[85] D. Wu, Y. Zhang, J. Huang, Z. Fan, F. Shi, S. Wang, Salinomycin inhibits proliferation and induces apoptosis of human nasopharyngeal carcinoma cell in vitro and suppresses tumor growth in vivo, Biochem. Biophys. Res. Commun. 443 (2014) 712–717.

[86] L. Xu, T. Wang, W.Y. Meng, J. Wei, J.L. Ma, M. Shi, Y.G. Wang, Salinomycin inhibits hepatocellular carcinoma cell invasion and migration through JNK/JunD pathway-mediated MMP9 expression, Oncol. Rep. 33 (2015) 1057–1063.

[87] J. Klose, M.V. Stankov, M. Kleine, W. Ramackers, D. Panayotova-Dimitrova, M.D. Jäger, J. Klempnauer, M. Winkler, H. Bektas, G.M. Behrens, F.W. Vondran, Inhibition of autophagic flux by salinomycin results in anticancer effect in hepatocellular carcinoma cells, PLoS One 9 (2014), e95970.

[88] F. Wang, L. He, W.Q. Dai, Y.P. Xu, D. Wu, C.L. Lin, S.M. Wu, P. Cheng, Y. Zhang, M. Shen, C.F. Wang, J. Lu, Y.Q. Zhou, X.F. Xu, L. Xu, C.Y. Guo, Salinomycin inhibits proliferation and induces apoptosis of human hepatocellular carcinoma cells in vitro and in vivo, PLoS One 7 (2012), e50638.

[89] J. Klose, E. Guerlevik, T. Trostel, F. Kühnel, T. Schmidt, M. Schneider, A. Ulrich, Salinomycin inhibits cholangiocarcinoma growth by inhibition of autophagic flux, Oncotarget 9 (2017) 3619–3630.

[90] T. Lieke, W. Ramackers, S. Bergmann, J. Klempnauer, M. Winkler, J. Klose, Impact of salinomycin on human cholangiocarcinoma: induction of apoptosis and impairment of tumor cell proliferation in vitro, BMC Canc. 12 (2012) 466.

[91] C. Xu, C. Xia, S.J. Zhang, H. Qin, D.M. Li, Q. Zhao, Effect of salinomycin on growth and migration of pancreatic cancer cells in vitro, World Chin. J. Dig. 23 (2015) 3831–3837.

[92] M. Schenk, B. Aykut, C. Teske, N.A. Giese, J. Weitz, T. Welsch, Salinomycin inhibits growth of pancreatic cancer and cancer cell migration by disruption of actin stress fiber integrity, Cancer Lett. 358 (2015) 161–169.

[93] L. He, F. Wang, W.Q. Dai, D. Wu, C.L. Lin, S.M. Wu, P. Cheng, Y. Zhang, M. Shen, C.F. Wang, J. Lu, Y.Q. Zhou, X.F. Xu, L. Xu, C.Y. Guo, Mechanism of action of salinomycin on growth and migration in pancreatic cancer cell lines, Pancreatology 13 (2013) 72–78.

[94] H. Qu, B. Ma, H.F. Yuan, Z.Y. Wang, S.J. Guo, J. Zhang, Effect of salinomycin on metastasis and invasion of bladder cancer cell line T24, Asian Pac. J. Trop. Med. 8 (2015) 578–582.

[95] R.J. Ou, A.P. Shi, H.M. Yang, H.M. Wang, N. Xu, Inhibitory effect of salinomycin on growth of human bladder cancer 5637 cells, J. Jilin Univ. (Med. Ed.) 40 (2014) 607–611.

[96] S.Z. Kuo, K.J. Blair, E. Rahimy, A. Kiang, E. Abhold, J.-B. Fan, J. Wang-Rodriguez, X. Altuna, W.M. Ongkeko, Salinomycin induces cell death and differentiation in head and neck squamous cell carcinoma stem cells despite activation of epithelial-mesenchymal transition and Akt, BMC Canc. 12 (2012) 556.

[97] S. Kusunoki, K. Kato, K. Tabu, T. Inagaki, H. Okabe, H. Kaneda, S. Suga, Y. Terao, T. Taga, S. Takeda, The inhibitory effect of salinomycin on the proliferation, migration and invasion of human endometrial cancer stem-like cells, Gynecol. Oncol. 129 (2013) 598–605.

[98] L.S. Qin, P.F. Jia, Z.G. Zhang, S.M. Zhang, ROS-p53-cyclophilin-D signaling mediates salinomycin-induced glioma cell necrosis, J. Exp. Clin. Canc. Res. 34 (2015) 57.

[99] Z.M. Delwar, D. Avramidis, A. Siden, M. Cruz, S. Yakisich, Depletion of drug-surviving glioma cells by a second phase treatment with low concentration of salinomycin, Drugs Ther. Stud. 10 (2011) 40–45.

[100] T. Chen, L. Yi, F. Li, R. Hu, S. Hu, Y. Yin, C. Lan, Z. Li, C. Fu, L. Cao, Z. Chen, J. Xian, H. Feng, Salinomycin inhibits the tumor growth of glioma stem cells by selectively suppressing glioma-initiating cells, Mol. Med. Rep. 11 (2015) 2407–2412.

[101] C. Naujokat, R. Steinhart, Salinomycin as a drug for targeting human cancer stem cells, J. Biomed. Biotechnol. 2012 (2012), 950658.

[102] H.G. Lee, S.J. Shin, H.W. Chung, S.H. Kwon, S.D. Cha, J.E. Lee, C.H. Cho, Salinomycin reduces stemness and induces apoptosis on human ovarian cancer stem cell, J. Gynecol. Oncol. 28 (2017) e14.

[103] X.F. Zhang, S. Gurunathan, Combination of salinomycin and silver nanoparticles enhances apoptosis and autophagy in human ovarian cancer cells: an effective anticancer therapy, Int. J. Nanomed. 11 (2016) 3655–3675.

[104] G.N. Zhang, Y. Liang, L.J. Zhou, S.P. Chen, G. Chen, T.P. Zhang, T. Kang, Y.P. Zhao, Combination of salinomycin and gemcitabine eliminates pancreatic cancer cells, Cancer Lett. 313 (2011) 137–144.

[105] J. Dittmer, B. Leyh, The impact of tumor stroma on drug response in breast cancer, Semin. Canc. Biol. 31 (2015) 3–15.

[106] G. Housman, S. Byler, S. Heerboth, K. Lapinska, M. Longacre, N. Snyder, S. Sarkar, Drug resistance in cancer: an overview, Cancers 6 (2014) 1769–1792.

[107] F. Wang, W. Dai, Y. Wang, M. Shen, K. Chen, P. Cheng, Y. Zhang, C. Wang, J. Li, Y. Zheng, J. Lu, J. Yang, R. Zhu, H. Zhang, Y. Zhou, L. Xu, C. Guo, The synergistic in vitro and in vivo antitumor effect of combination therapy with salinomycin and 5-fluorouracil against hepatocellular carcinoma, PLoS One 9 (2014), e97414.

[108] S. Koeck, A. Amann, J.M. Huber, G. Gamerith, W. Hilbe, H. Zwierzina, The impact of metformin and salinomycin on transforming growth factor β-induced epithelial-to-mesenchymal transition in non-small cell lung cancer cell lines, Oncol. Lett. 11 (2016) 2946–2952.

[109] C.L. Tung, J.C. Chen, C.H. Wu, Y.S. Peng, W.C. Chen, H.Y. Zheng, Y.J. Jian, C.L. Wei, Y.T. Cheng, Y.W. Lin, Salinomycin acts through reducing AKT-dependent thymidylate synthase expression to enhance erlotinib-induced cytotoxicity in human lung cancer cells, Exp. Cell Res. 357 (2017) 59–66.

[110] J.C. Ko, H.Y. Zheng, W.C. Chen, Y.S. Peng, C.H. Wu, C.L. Wei, J.C. Chen, Y.W. Lin, Salinomycin enhances cisplatin-induced cytotoxicity in human lung cancer cells via down-regulation of AKT-dependent thymidylate synthase

expression, Biochem. Pharmacol. 122 (2016) 90–98.
[111] Z. Xiao, B. Sperl, A. Ullrich, P. Knyazev, Metformin and salinomycin as the best combination for the eradication of NSCLC monolayer cells and their alveospheres (cancer stem cells) irrespective of EGFR, KRAS, EML4/ALK and LKB1 status, Oncotarget 5 (2014) 12877–12890.
[112] L. Booth, J.L. Roberts, A. Conley, N. Cruickshanks, T. Ridder, S. Grant, A. Poklepovic, P. Dent, HDAC inhibitors enhance the lethality of low dose salinomycin in parental and stem-like GBM cells, Cancer Biol. Ther. 15 (2014) 305–316.
[113] A. Calzolari, E. Saulle, M.L. De Angelis, L. Pasquini, A. Boe, F. Pelacchi, L. Ricci-Vitiani, M. Baiocchi, U. Testa, Salinomycin potentiates the cytotoxic effects of TRAIL on glioblastoma cell lines, PLoS One 9 (2014), e94438.
[114] S.T. Liffers, D.J. Tilkorn, I. Stricker, C.G. Junge, S. Al-Benna, M. Vogt, B. Verdoodt, H.U. Steinau, A. Tannapfel, I. Tischoff, A. Mirmohammadsadegh, Salinomycin increases chemosensitivity to the effects of doxorubicin in soft tissue sarcomas, BMC Canc. 13 (2013) 490.
[115] Z.Z. Zou, P.P. Nie, Y.W. Li, B.X. Hou, Rui-Li, X.P. Shi, Z.K. Ma, B.W. Han, X.Y. Luo, Synergistic induction of apoptosis by salinomycin and gefitinib through lysosomal and mitochondrial dependent pathway overcomes gefitinib resistance in colorectal cancer, Oncotarget 8 (2017) 22414–22432.
[116] J.H. Kim, M. Chae, W.K. Kim, Y.J. Kim, H.S. Kang, H.S. Kim, S. Yoon, Salinomycin sensitizes cancer cells to the effects of doxorubicin and etoposide treatment by increasing DNA damage and reducing p21 protein, Br. J. Pharmacol. 162 (2011) 773–784.
[117] J.H. Kim, H.I. Yoo, H.S. Kang, J. Ro, S. Yoon, Salinomycin sensitizes antimitotic drugs-treated cancer cells by increasing apoptosis via the prevention of G2 arrest, Biochem. Biophys. Res. Commun. 418 (2012) 98–103.
[118] E.A. Dunlop, C.E. Johnson, M. Wiltshire, R.J. Errington, A.R. Tee, Targeting protein homeostasis with nelfinavir/salinomycin dual therapy effectively induces death of mTORC1 hyperactive cells, Oncotarget 8 (2017) 48711–48724.
[119] R. Venkatadri, A.K.V. Iyer, V. Kaushik, N. Azad, A novel resveratrol–salinomycin combination sensitizes ER-positive breast cancer cells to apoptosis, Pharmacol. Rep. 69 (2017) 788–797.
[120] G. Rai, S. Suman, S. Mishra, Y. Shukla, Evaluation of growth inhibitory response of resveratrol and salinomycin combinations against triple negative breast cancer cells, Biomed. Pharmacother. 89 (2017) 1142–1151.
[121] J. Dewangan, D. Tandon, S. Srivastava, A.K. Verma, A. Yapuri, S.K. Rath, Novel combination of salinomycin and resveratrol synergistically enhances the anti-proliferative and pro-apoptotic effects on human breast cancer cells, Apoptosis 22 (2017) 1246–1259.
[122] J.H. Kim, A.R. Choi, Y.K. Kim, H.S. Kim, S. Yoon, Low amount of salinomycin greatly increases Akt activation, but reduces activated p70S6K levels, Int. J. Mol. Sci. 14 (2013) 17304–17318.
[123] A.R. Choi, M.J. Jung, J.H. Kim, S. Yoon, Co-treatment of salinomycin sensitizes AZD5363-treated cancer cells through increased apoptosis, Anticancer Res. 35 (2015) 4741–4747.
[124] A.R. Choi, J.H. Kim, S. Yoon, Sensitization of cancer cells through reduction of total Akt and downregulation of salinomycin-induced pAkt, pGSk3β, pTSC2, and p4EBP1 by cotreatment with MK-2206, BioMed Res. Int. 2014 (2014), 295760.
[125] Z. Zhang, J. Zhao, Q. Pang, A. Wang, M. Chen, X. Wei, An in vitro study on the effects of the combination of salinomycin with cisplatin on human gastric cancer cells, Mol. Med. Rep. 16 (2017) 1031–1038.
[126] Z. Zhang, J. Zhao, Z. Mi, Q. Pang, A. Wang, M. Chen, X. Liu, X. Wei, T. Liu, Effects of salinomycin and 17-AAG on proliferation of human gastric cancer cells in vitro, Mol. Med. Rep. 16 (2017) 1063–1070.
[127] Z. Yu, H. Cheng, H. Zhu, M. Cao, C. Lu, S. Bao, Y. Pan, Y. Li, Salinomycin enhances doxorubicin sensitivity through reversing the epithelial-mesenchymal transition of cholangiocarcinoma cells by regulating ARK5, Braz. J. Med. Biol. Res. 50 (2017) e6147.
[128] Y. Zhou, C. Liang, F. Xue, W. Chen, X. Zhi, X. Feng, X. Bai, T. Liang, Salinomycin decreases doxorubicin resistance in hepatocellular carcinoma cells by inhibiting the β-catenin/TCF complex association via FOXO3a activation, Oncotarget 6 (2015) 10350–10365.
[129] A. Hermawan, E. Wagner, A. Roidl, Consecutive salinomycin treatment reduces doxorubicin resistance of breast tumor cells by diminishing drug efflux pump expression and activity, Oncol. Rep. 35 (2016) 1732–1740.
[130] K.Y. Kim, S.H. Kim, S.N. Yu, S.K. Park, H.D. Choi, H.S. Yu, J.H. Ji, Y.K. Seo, S.C. Ahn, Salinomycin enhances doxorubicin-induced cytotoxicity in multidrug resistant MCF-7/MDR human breast cancer cells via decreased efflux of doxorubicin, Mol. Med. Rep. 12 (2015) 1898–1904.
[131] S. Manmuan, N. Sakunrangsit, W. Ketchart, Salinomycin overcomes acquired tamoxifen resistance through AIB1 and inhibits cancer cell invasion in endocrine resistant breast cancer, Clin. Exp. Pharmacol. Physiol. 44 (2017) 1042–1052.
[132] A.K. Sommer, A. Hermawan, F.M. Mickler, B. Ljepoja, P. Knyazev, C. Bräuchle, A. Ullrich, E. Wagner, A. Roidl, Salinomycin co-treatment enhances tamoxifen cytotoxicity in luminal A breast tumor cells by facilitating lysosomal degradation of receptor tyrosine kinases, Oncotarget 7 (2016) 50461–50476.
[133] P.S. Oak, F. Kopp, C. Thakur, J.W. Ellwart, U.R. Rapp, A. Ullrich, E. Wagner, P. Knyazev, A. Roidl, Combinatorial treatment of mammospheres with trastuzumab and salinomycin efficiently targets HER2-positive cancer cells and cancer stem cells, Int. J. Canc. 131 (2012) 2808–2819.
[134] M. Kai, N. Kanaya, S.V. Wu, C. Mendez, D. Nguyen, T. Luu, S. Chen, Targeting breast cancer stem cells in triple-negative breast cancer using a combination of LBH589 and salinomycin, Breast Canc. Res. Treat. 151 (2015) 281–294.
[135] M. Diehn, R.W. Cho, N.A. Lobo, T. Kalisky, M.J. Dorie, A.N. Kulp, D. Qian, J.S. Lam, L.E. Ailles, M. Wong, B. Joshua, M.J. Kaplan, I. Wapnir, F.M. Dirbas, G. Somlo, C. Garberoglio, B. Paz, J. Shen, S.K. Lau, S.R. Quake, J.M. Brown, I.L. Weissman, M.F. Clarke, Association of reactive oxygen species levels and radioresistance in cancer stem cells, Nature 458 (2009) 780–783.
[136] W.K. Kim, J.H. Kim, K. Yoon, S. Kim, J. Ro, H.S. Kang, S. Yoon, Salinomycin, a p-glycoprotein inhibitor, sensitizes radiation-treated cancer cells by increasing DNA damage and inducing G2 arrest, Invest. N. Drugs 30 (2012) 1311–1318.
[137] G. Zhang, W. Wang, C. Yao, J. Ren, S. Zhang, M. Han, Salinomycin overcomes radioresistance in nasopharyngeal carcinoma cells by inhibiting Nrf2 level and promoting ROS generation, Biomed. Pharmacother. 91 (2017) 147–154.
[138] Y. Zhang, Y. Zuo, Z. Guan, W. Lu, Z. Xu, H. Zhang, Y. Yang, M. Yang, H. Zhu, X. Chen, Salinomycin radiosensitizes human nasopharyngeal carcinoma cell line CNE-2 to radiation, Tumor Biol. 37 (2016) 305–311.
[139] T. Gehrke, S. Hackenberg, B. Polat, G. Wohlleben, R. Hagen, N. Kleinsasser, A. Scherzad, Combination of salinomycin and radiation effectively eliminates head and neck squamous cell carcinoma cells in vitro, Oncol. Rep. 39 (2018) 1991–1998.
[140] C. Liu, L. Wang, H. Qiu, Q. Dong, Y. Feng, D. Li, C. Li, C. Fan, Combined strategy of radioactive 125I seeds and salinomycin for enhanced glioma chemo-radiotherapy: evidences for ROS-mediated apoptosis and signaling cross-talk, Neurochem. Res. 43 (2018) 1317–1327.
[141] A.K. Najumudeen, A. Jaiswal, B. Lectez, C. Oetken-Lindholm, C. Guzmán, E. Siljamäki, I.M. Posada, E. Lacey, T. Aittokallio, D. Abankwa, Cancer stem cell drugs target K-ras signaling in a stemness context, Oncogene 35 (2016) 5248–5262.
[142] Y. Lu, C. Zhang, Q. Li, J. Mao, W. Ma, X. Yu, Z. Hou, L. Li, Inhibitory effect of salinomycin on human breast cancer cells MDA-MB-231 proliferation through Hedgehog signaling pathway, Chin. J. Pathol. 44 (2015) 395–398.
[143] Y.Z. Fu, Y.Y. Yan, M. He, Q.H. Xiao, W.F. Yao, L. Zhao, H.Z. Wu, Z.J. Yu, M.Y. Zhou, M.T. Lv, S.S. Zhang, J.J. Chen, M.J. Wei, Salinomycin induces selective cytotoxicity to MCF-7 mammosphere cells through targeting the Hedgehog signaling pathway, Oncol. Rep. 35 (2016) 912–922.
[144] Y. Lu, W. Ma, J. Mao, X. Yu, Z. Hou, S. Fan, B. Song, H. Wang, J. Li, L. Kang, P. Liu, Q. Liu, L. Li, Salinomycin exerts anticancer effects on human breast carcinoma MCF-7 cancer stem cells via modulation of Hedgehog signaling, Chem. Biol. Interact. 228 (2015) 100–107.
[145] V. Angeloni, P. Tiberio, V. Appierto, M.G. Daidone, Implications of stemness-related signaling pathways in breast cancer response to therapy, Semin. Canc. Biol. 31 (2015) 43–51.
[146] S.J. Zhao, X.J. Wang, Q.J. Wu, C. Liu, D.W. Li, X.T. Fu, H.F. Zhang, L.R. Shao, J.Y. Sun, B.L. Sun, J. Zhai, C.D. Fan, Induction of G1 cell cycle arrest in human glioma cells by salinomycin through triggering ROS-mediated DNA damage in vitro and in vivo, Neurochem. Res. 42 (2017) 997–1005.
[147] S.H. Kim, Y.J. Choi, K.Y. Kim, S.N. Yu, Y.K. Seo, S.S. Chun, K.T. Noh, J.T. Suh, S.C. Ahn, Salinomycin simultaneously induces apoptosis and autophagy through generation of reactive oxygen species in osteosarcoma U2OS cells, Biochem. Biophys. Res. Commun. 473 (2016) 607–613.
[148] H. Liu, M.Y. Lu, Z.M. He, Anti-proliferative effect of salinomycin on doxorubicin-resistant human breast cancer MCF-7/DOX cells, Chin. Pharmacol. Bull. 31 (2015) 549–554.
[149] A. Managò, L. Leanza, L. Carraretto, N. Sassi, S. Grancara, R. Quintana-Cabrera, V. Trimarco, A. Toninello, L. Scorrano, L. Trentin, G. Semenzato, E. Gulbins, M. Zoratti, I. Szabò, Early effects of the antineoplastic agent salinomycin on mitochondrial function, Cell Death Dis. 6 (2015) e1930.
[150] J.R. Jangamreddy, S. Ghavami, J. Grabarek, G. Kratz, E. Wiechec, B.A. Fredriksson, R.K. Rao Pariti, A. Cieślar-Pobuda, S. Panigrahi, M.J. Łos, Salinomycin induces activation of autophagy, mitophagy and affects mitochondrial polarity: differences between primary and cancer cells, Biochim. Biophys. Acta 1833 (2013) 2057–2069.
[151] B. Verdoodt, M. Vogt, I. Schmitz, S.-T. Liffers, A. Tannapfel, A. Mirmohammadsadegh, Salinomycin induces autophagy in colon and breast cancer cells with concomitant generation of reactive oxygen species, PLoS One 7 (2012), e44132.
[152] W. Boehmerle, M. Endres, Salinomycin induces calpain and cytochrome c-mediated neuronal cell death, Cell Death Dis. 2 (2011) e168.
[153] K. Moitra, H. Lou, M. Dean, Multidrug efflux pumps and cancer stem cells: insights into multidrug resistance and therapeutic development, Clin. Pharmacol. Ther. 89 (2011) 491–502.
[154] M. Dean, ABC transporters, drug resistance, and cancer stem cells, J. Mammary Gland Biol. Neoplasia 14 (2009) 3–9.
[155] S.N. Yu, S.H. Kim, K.Y. Kim, J.H. Ji, Y.K. Seo, H.S. Yu, S.C. Ahn, Salinomycin induces endoplasmic reticulum stress-mediated autophagy and apoptosis through generation of reactive oxygen species in human glioma U87MG cells, Oncol. Rep. 37 (2017) 3321–3328.
[156] J.R. Jangamreddy, S. Panigrahi, M.J. Łos, Monitoring of autophagy is complicated – salinomycin as an example, Biochim. Biophys. Acta Mol. Cell Res. 1853 (2015) 604–610.
[157] K.Y. Kim, Y.K. Seo, S.N. Yu, S.H. Kim, P.G. Suh, J.H. Ji, H.S. Yu, Y.M. Park, S.C. Ahn, Gene expression profiling from a prostate cancer PC-3 cell line treated with salinomycin predicts cell cycle arrest and endoplasmic reticulum stress, J. Canc. Sci. Ther. 5 (2013) 23–30.
[158] T. Li, L. Su, N. Zhong, X. Hao, D. Zhong, S. Singhal, X. Liu, Salinomycin induces

cell death with autophagy through activation of endoplasmic reticulum stress in human cancer cells, Autophagy 9 (2013) 1057–1068.
[159] E.J. White, V. Martin, J.L. Liu, S.R. Klein, S. Piya, C. Gomez-Manzano, J. Fueyo, H. Jiang, Autophagy regulation in cancer development and therapy, Am. J. Cancer Res. 1 (2011) 362–372.
[160] J. Heijmans, J.F. van Lidth de Jeude, B.K. Koo, S.L. Rosekrans, M.C. Wielenga, M. van de Wetering, M. Ferrante, A.S. Lee, J.J. Onderwater, J.C. Paton, A.W. Paton, A.M. Mommaas, L.L. Kodach, J.C. Hardwick, D.W. Hommes, H. Clevers, V. Muncan, G.R. van den Brink, ER stress causes rapid loss of intestinal epithelial stemness through activation of the unfolded protein response, Cell Rep. 3 (2013) 1128–1139.
[161] M.C.B. Wielenga, S. Colak, J. Heijmans, J.F. van Lidth de Jeude, H.M. Rodermond, J.C. Paton, A.W. Paton, L. Vermeulen, J.P. Medema, G.R. van den Brink, ER-stress-induced differentiation sensitizes colon cancer stem cells to chemotherapy, Cell Rep. 13 (2015) 489–494.
[162] Y.X. Feng, E.S. Sokol, C.A. Del Vecchio, S. Sanduja, J.H. Claessen, T.A. Proia, D.X. Jin, F. Reinhardt, H.L. Ploegh, Q. Wang, P.B. Gupta, Epithelial-to-mesenchymal transition activates PERK-eIF2α and sensitizes cells to endoplasmic reticulum stress, Cancer Discov. 4 (2014) 702–715.
[163] D. Mekahli, G. Bultynck, J.B. Parys, H. De Smedt, L. Missiaen, Endoplasmic-reticulum calcium depletion and disease, Cold Spring Harb. Perspect. Biol. 3 (2011) a004317.
[164] X. Huang, B. Borgström, J. Stegmayr, Y. Abassi, M. Kruszyk, H. Leffler, L. Persson, S. Albinsson, R. Massoumi, I.G. Scheblykin, C. Hegardt, S. Oredsson, D. Strand, The molecular basis for inhibition of stemlike cancer cells by salinomycin, ACS Cent. Sci. 4 (2018) 760–767.
[165] H. An, J.Y. Kim, E. Oh, N. Lee, Y. Cho, J.H. Seo, Salinomycin promotes anoikis and decreases the CD44+/CD24− stem-like population via inhibition of STAT3 activation in MDA-MB-231 cells, PLoS One 10 (2015), e0141919.
[166] K.H. Koo, H. Kim, Y.K. Bae, K. Kim, B.K. Park, C.H. Lee, Y.N. Kim, Salinomycin induces cell death via inactivation of Stat3 and downregulation of Skp2, Cell Death Dis. 4 (2013) e693.
[167] S.S. Chung, D. Adekoya, I. Enenmoh, O. Clarke, P. Wang, M. Sarkyssian, Y. Wu, J.V. Vadgama, Salinomycin abolished STAT3 and STAT1 interactions and reduced telomerase activity in colorectal cancer cells, Anticancer Res. 37 (2017) 445, 453.
[168] C.D. Bortner, F.M. Hughes Jr., J.A. Cidlowski, A primary role for K+ and Na+ efflux in the activation of apoptosis, J. Biol. Chem. 272 (1997) 32436–32442.
[169] F.M. Hughes Jr., C.D. Bortner, G.D. Purdy, J.A. Cidlowski, Intracellular K+ suppresses the activation of apoptosis in lymphocytes, J. Biol. Chem. 272 (1997) 30567–30576.
[170] H. Ouadid-Ahidouch, A. Ahidouch, K+ channels and cell cycle progression in tumor cells, Front. Physiol. 4 (2013) 220–227.
[171] R. Li, T. Dong, C. Hu, J. Lu, J. Dai, P. Liu, Salinomycin repressed the epithelial-mesenchymal transition of epithelial ovarian cancer cells via downregulating Wnt/β-catenin pathway, OncoTargets Ther. 10 (2017) 1317–1325.
[172] G.B. Jang, J.Y. Kim, S.D. Cho, K.S. Park, J.Y. Jung, H.Y. Lee, I.S. Hong, J.S. Nam, Blockade of Wnt/β-catenin signaling suppresses breast cancer metastasis by inhibiting CSC-like phenotype, Sci. Rep. 5 (2015) 12465.
[173] J. Mao, S. Fan, W. Ma, P. Fan, B. Wang, J. Zhang, H. Wang, B. Tang, Q. Zhang, X. Yu, L. Wang, B. Song, L. Li, Roles of Wnt/β-catenin signaling in the gastric cancer stem cells proliferation and salinomycin treatment, Cell Death Dis. 5 (2014) e1039.
[174] N. Mirkheshti, S. Park, S. Jiang, J. Cropper, S.L. Werner, C.S. Song, B. Chatterjee, Dual targeting of androgen receptor and mTORC1 by salinomycin in prostate cancer, Oncotarget 7 (2016) 62240–62254.
[175] W. Lu, Y. Li, Salinomycin suppresses LRP6 expression and inhibits both Wnt/β-catenin and mTORC1 signaling in breast and prostate cancer cells, J. Cell. Biochem. 115 (2014) 1799–1807.
[176] W. Yue, A. Hamaï, G. Tonelli, C. Bauvy, V. Nicolas, H. Tharinger, P. Codogno, M. Mehrpour, Inhibition of the autophagic flux by salinomycin in breast cancer stem-like/progenitor cells interferes with their maintenance, Autophagy 9 (2013) 714–729.
[177] K.Y. Kim, K.I. Park, S.H. Kim, S.N. Yu, S.G. Park, Y.W. Kim, Y.K. Seo, J.Y. Ma, S.C. Ahn, Inhibition of autophagy promotes salinomycin-induced apoptosis via reactive oxygen species-mediated PI3K/AKT/mTOR and ERK/p38 MAPK-dependent signaling in human prostate cancer cells, Int. J. Mol. Sci. 18 (2017) 1088.
[178] K.Y. Kim, K.I. Park, S.H. Kim, S.N. Yu, D. Lee, Y.W. Kim, K.T. Noh, J.Y. Ma, Y.K. Seo, S.C. Ahn, Salinomycin induces reactive oxygen species and apoptosis in aggressive breast cancer cells as mediated with regulation of autophagy, Anticancer Res. 37 (2017) 1747–1758.
[179] S. Endo, K. Nakata, A. Sagara, K. Koikawa, Y. Ando, S. Kibe, S. Takesue, H. Nakayama, T. Abe, T. Okumura, T. Moriyama, Y. Miyasaka, K. Ohuchida, T. Ohtsuka, K. Mizumoto, M. Nakamura, Autophagy inhibition enhances antiproliferative effect of salinomycin in pancreatic cancer cells, Pancreatology 17 (2017) 990–996.
[180] E. Xipell, M. Gonzalez-Huarriz, J.J. Martinez de Irujo, A. García-Garzón, F.F. Lang, H. Jiang, J. Fueyo, C. Gomez-Manzano, M.M. Alonso, Salinomycin induced ROS results in abortive autophagy and leads to regulated necrosis in glioblastoma, Oncotarget 7 (2016) 30626–30641.
[181] P. Pellegrini, M. Dyczynski, F.V. Sbrana, M. Karlgren, M. Buoncervello, M. Hägg-Olofsson, R. Ma, J. Hartman, S. Bajalica-Lagercrantz, D. Grander, P. Kharaziha, A. De Milito, Tumor acidosis enhances cytotoxic effects and autophagy inhibition by salinomycin on cancer cell lines and cancer stem cells, Oncotarget 7 (2016) 35703–35723.
[182] J.R. Jangamreddy, M.V. Jain, A.L. Hallbeck, K. Roberg, K. Lotfi, M.J. Łos, Glucose starvation-mediated inhibition of salinomycin induced autophagy amplifies cancer cell specific cell death, Oncotarget 6 (2015) 10134–10145.
[183] L.Q. Zhu, Y.F. Zhen, Y. Zhang, Z.X. Guo, J. Dai, X.D. Wang, Salinomycin activates AMP-activated protein kinase-dependent autophagy in cultured osteoblastoma cells: a negative regulator against cell apoptosis, PLoS One 8 (2013), e84175.
[184] Y. Zhang, F. Li, L. Liu, H. Jiang, X. Jiang, X. Ge, J. Cao, Z. Wang, L. Zhang, Y. Wang, Salinomycin-induced autophagy blocks apoptosis via the ATG3/AKT/mTOR signaling axis in PC-3 cells, Life Sci. 207 (2018) 451–460.
[185] H. An, J.Y. Kim, N. Lee, Y. Cho, E. Oh, J.H. Seo, Salinomycin possesses anti-tumor activity and inhibits breast cancer stem-like cells via an apoptosis-independent pathway, Biochem. Biophys. Res. Commun. 466 (2015) 696–703.
[186] J. Sun, Q. Luo, L. Liu, X. Yang, S. Zhu, G. Song, Salinomycin attenuates liver cancer stem cell motility by enhancing cell stiffness and increasing F-actin formation via the FAK-ERK1/2 signalling pathway, Toxicology 384 (2017) 1–10.
[187] C. Zhang, Y. Lu, Q. Li, J. Mao, Z. Hou, X. Yu, S. Fan, J. Li, T. Gao, B. Yan, B. Wang, B. Song, L. Li, Salinomycin suppresses TGF-β1-induced epithelial-to-mesenchymal transition in MCF-7 human breast cancer cells, Chem. Biol. Interact. 248 (2016) 74–81.
[188] N. Nishida, H. Yano, T. Nishida, T. Kamura, M. Kojiro, Angiogenesis in cancer, Vasc. Health Risk Manag. 2 (2006) 213–219.
[189] T. Li, X. Liu, Q. Shen, W. Yang, Z. Huo, Q. Liu, H. Jiao, J. Chen, Salinomycin exerts anti-angiogenic and anti-tumorigenic activities by inhibiting vascular endothelial growth factor receptor 2-mediated angiogenesis, Oncotarget 7 (2016) 26580–26592.
[190] Y.L. Bi, P.Y. Mi, S.J. Zhao, H.M. Pan, H.J. Li, F. Liu, L.R. Shao, H.F. Zhang, P. Zhang, S.L. Jiang, Salinomycin exhibits anti-angiogenic activity against human glioma in vitro and in vivo by suppressing the VEGF-VEGFR2-AKT/FAK signaling axis, Int. J. Mol. Med. 39 (2017) 1255–1261.
[191] J.L. Dorne, M.L. Fernández-Cruz, U. Bertelsen, D.W. Renshaw, K. Peltonen, A. Anadon, A. Feil, P. Sanders, P. Wester, J. Fink-Gremmels, Risk assessment of coccidostatics during feed cross-contamination: animal and human health aspects, Toxicol. Appl. Pharmacol. 270 (2013) 196–208.
[192] R.G. Boutilier, Mechanisms of cell survival in hypoxia and hypothermia, J. Exp. Biol. 204 (2001) 3171–3181.
[193] J.S. Lagas, R.W. Sparidans, R.A.B. van Waterschoot, E. Wagenaar, J.H. Beijnen, A.H. Schinkel, P-glycoprotein limits oral availability, brain penetration, and toxicity of an anionic drug, the antibiotic salinomycin, Antimicrob. Agents Chemother. 52 (2008) 1034–1039.
[194] J.S. van der Linde-Sipman, T.S. van den Ingh, J.J. van Nes, H. Verhagen, J.G. Kersten, A.C. Beynen, R. Plekkringa, Salinomycin-induced polyneuropathy in cats: morphologic and epidemiologic data, Vet. Pathol. 36 (1999) 152–156.
[195] P. Story, A. Doube, A case of human poisoning by salinomycin, an agricultural antibiotic, N. Z. Med. J. 117 (2004) 799.
[196] Y. Li, J. Fang, S. Wu, K. Ma, H. Li, X. Yan, F. Dong, Identification and quantification of salinomycin in intoxicated human plasma by liquid chromatography-electrospray tandem mass spectrometry, Anal. Bioanal. Chem. 398 (2010) 955–961.
[197] A. Scherzed, S. Hackenberg, K. Froelich, K. Rak, C. Ginzkey, R. Hagen, P. Schendzielorz, N. Kleinsasser, Effects of salinomycin and CGP37157 on head and neck squamous cell carcinoma cell lines in vitro, Mol. Med. Rep. 12 (2015) 4455–4461.
[198] W. Cybulski, L. Radko, W. Rzeski, Cytotoxicity of monensin, narasin and salinomycin and their interaction with silybin in HepG2, LMH and L6 cell cultures, Toxicol. Vitro 29 (2015) 337–344.
[199] K. Resham, P.N. Patel, D. Thummuri, L. Guntuku, V. Shah, R.B. Bambal, V.G.M. Naidu, Preclinical drug metabolism and pharmacokinetics of salinomycin, a potential candidate for targeting human cancer stem cells, Chem. Biol. Interact. 240 (2015) 146–152.
[200] A. Scherzed, S. Hackenberg, K. Froelich, K. Rak, A. Technau, A. Radeloff, U. Nöth, C. Koehler, R. Hagen, N. Kleinsasser, Effects of salinomycin on human bone marrow-derived mesenchymal stem cells in vitro, Toxicol. Lett. 218 (2013) 207–214.
[201] A. Scherzad, S. Hackenberg, K. Froelich, K. Rak, R. Hagen, J. Taeger, M. Bregenzer, N. Kleinsasser, Chronic exposure of low dose salinomycin inhibits MSC migration capability in vitro, Biomed. Rep. 4 (2016) 325–330.
[202] A. Scherzad, S. Hackenberg, C. Schramm, K. Froelich, C. Ginzkey, R. Hagen, N. Kleinsasser, Geno- and cytotoxicity of salinomycin in human nasal mucosa and peripheral blood lymphocytes, Toxicol. Vitro 29 (2015) 813–818.