Review Article

A New Insight Into Salinomycin

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ABSTRACT

Salinomycin is a polyether ionophore antibiotic used as a coccidiostat and growth promoter in veterinary medicine and animal husbandry since the 1980s. It is a promising anticancer drug that targets human cancer stem cells and inhibits tumor cell growth. It can induce autophagy, mitophagy, and mitochondrial polarity in cancer cells. Salinomycin can induce cytotoxicity in cancer cells by generating reactive oxygen species and inhibiting cyclooxygenase-2 activity. It is also lipid-soluble, which can induce toxicity in humans and various animal species, including bovines, sheep, swine, equines, dogs, and birds. Accidental ingestion of high amounts of salinomycin can lead to cardiac toxicity, neural dysfunction, and paralysis in animals. It can also cause liver damage in animals. Studies have shown that different doses of oral salinomycin alter oxidative stress biomarkers, leading to increased inflammatory biomarkers. Treatment for salinomycin toxicosis often involves supportive care and symptomatic therapy. It is crucial to be cautious when using salinomycin, as it can cause harmful side effects due to its severe toxicity.

Keywords: Anticancer drugs, Coccidiostat, Ionophores, Salinomycin, Toxicosis

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Introduction

Salinomycin is an antibiotic widely used in veterinary medicine (Jędrzejczyk et al., 2022). It is a polyether ionophore antibiotic commonly used as an animal coccidiostat and growth promoter (Mousavinasab et al., 2022). It has also been used in animal husbandry since the 1980s as a broad-spectrum antimicrobial agent with activity against gram-positive bacteria and parasites (Zhou et al., 2013). The mechanism of salinomycin action is still unclear. It has been suggested that it acts as a K+ ionophore, affecting mitochondrial bioenergetic performance (Managò et al., 2015). It has been found to induce rapid hyperpolarization, mitochondrial matrix acidification, and decreased respiration in mouse embryonic fibroblasts and cancer stem cells (Managò et al., 2015). Salinomycin is metabolized through monooxygenation, leading to monohydroxy-salinomycin, dihydroxy-salinomycin, and trihydroxy-salinomycin (Radko et al., 2020).

Salinomycin Biosynthesis, Chemical Structure, and Promising Analogs

Salinomycin is biosynthesized by the polyketide synthase (PKS) enzyme complex in *Streptomyces albus* XM211 (Jiang et al., 2012; Zhang et al., 2019). The biosynthesis process involves polyketide assembly and release, oxidative cyclization, modification, export, and regulation (Jiang et al., 2012). This monocarboxylic polyether ionophore is a 751 Da compound (Figure 1) and is weakly acidic.

The chemical structure of salinomycin consists of a unique 1, 6, 8-trioxadispiro [4.1.5.3]pentadec-13-ene core (Luhavaya et al., 2014; Tefas et al., 2021). It has been shown that modifications at specific positions in the salinomycin structure can lead to more active analogs with greater potency (Huang et al., 2016). For example, selective chemical modification at the C20 hydroxyl group yielded analog structures with significantly lower toxicity toward normal cell lines (Luhavaya et al., 2014; Huang et al., 2016).

Structural studies have provided insights into the substrate specificity of the acyltransferase (AT) domains of the salinomycin PKS enzyme (Zhang et al., 2019). The AT domains of the PKS are responsible for selecting and incorporating specific α-carboxy acyl-CoA extension units during salinomycin biosynthesis (Zhang et al., 2019). Crystal structures and molecular dynamics simulations have revealed the enzyme-substrate interactions involved in substrate binding and discrimination among different extension units (Zhang et al., 2019). Analogs of salinomycin with lower toxicity but retained cation-binding properties hold promise for developing targeted therapies (Luhavaya et al., 2014).

Antimicrobial Activity of Salinomycin

Salinomycin has been shown to exhibit antimicrobial activity against various microorganisms, including gram-positive bacteria, coccidian parasites, and trypanosomes (Lavine & Arrizabalaga, 2011; Santos-Beneit et al., 2022). Salinomycin and its derivatives are effective against methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *Staphylococcus epidermidis*, and *Mycobacterium tuberculosis* (Santos-Beneit et al., 2022). However, salinomycin is inactive against fungi such as *Candida albicans* and gram-negative bacteria (Santos-Beneit et al., 2022). The antibacterial mechanism of action of salinomycin is not fully understood, but it has been shown to disrupt the cell cycle of *Toxoplasma gondii* (a food-borne zoonosis) (Mehrabi et al., 2023; Jahantigh et al., 2020) and coccidian parasites, leading to their death (Lavine & Arrizabalaga, 2011).

Salinomycin also influences the mobile resistance gene in gram-positive bacteria and inhibits the in vivo transfer of the tetracycline mobile resistance gene (Hosseinzadeh et al., 2016). In addition, it has been used for myxosporean treatment in fish (Karagouni et al., 2005a). Moreover, results of a study on gilthead seabream infected with *Polysporoplasma sparis* showed that treatment with salinomycin significantly reduced the infection intensity and prevalence rate (Karagouni et al., 2005). Furthermore, salinomycin has been investigated as a potential treatment for bovine mastitis caused by gram-positive pathogens, and it has exhibited bacteriostatic antimicrobial activity against *Staphylococcus* spp. and *Streptococcus* spp. (Hickey et al., 2018). However, further in vivo studies are needed to determine its safety and efficacy.

Salinomycin as an Anticancer Drug and Its Mechanism of Action

It has been demonstrated that salinomycin has potential therapeutic indications in humans, particularly in targeting cancer stem cells (CSCs). It inhibits the growth of various tumor cell types, including breast cancer, prostate cancer, and chemotherapy-resistant cancer cells (Soni et al., 2022; Zhou et al., 2013), and it can also overcome acquired tamoxifen resistance in breast cancer, possibly by inhibiting cancer cell invasion in endocrine-resistant breast cancer (Manmuan et al., 2017).

Studies have demonstrated that salinomycin selectively eliminates human breast CSCs in mice (Naujokat & Steinhart, 2012). Salinomycin may also inhibit the growth of cisplatin-resistant human ovarian cancer cells by activating p38 MAPK (Zhang et al., 2013). It has also been identified as a functional binding target for nucleolin in neuroblastoma stem cells that suppresses neuroblastoma CD34 expression and reduces the CD34+ cell population (Wang et al., 2019).

Salinomycin may be associated with various biochemical changes in different cell types and organisms. One of the biochemical changes induced by salinomycin is the inhibition of Wnt signaling. Salinomycin has been shown to interfere with LRP6 phosphorylation, a key step in the activation of the Wnt/β-catenin pathway (Lu et al., 2011), which can impair the survival of cells depending on this pathway for their growth and development (Lu et al., 2011; Norouzi et al., 2018). Salinomycin may also induce autophagy and mitophagy, affecting mitochondrial polarity in cancer cells (Jangamreddy et al., 2013). It can trigger a massive autophagic response, which acts as a protective mechanism in cancer cells (Jangamreddy et al., 2013). Salinomycin decreases cellular ATP levels and induces mitochondrial membrane potential in a subpopulation of cells (Jangamreddy et al., 2013). These changes in mitochondrial function and energy metabolism contribute to the cytotoxic effects of salinomycin. Furthermore, it has been reported that salinomycin causes cytotoxicity in cancer cells by generating intracellular reactive oxygen species and inhibiting cyclooxygenase-2 activity (Eskandari & Suntharalingam, 2019).

Salinomycin has also been investigated for its potential as a treatment for glioblastoma. It inhibits the growth of glioblastoma cancer stem cells and induces cell death in these cells (Magrath et al., 2020). However, it is important to consider the effect of salinomycin on normal brain tissue, as cases of neural toxicity induced by salinomycin overdoses have been documented in humans and animals (Van der Linde-Sipman et al., 1999; Story & Doube, 2004).

Systemic administration of salinomycin in mammals has been associated with adverse reactions such as tachycardia and myoglobinuria (Qin & Guo, 2022). In terms of its anticancer mechanisms, salinomycin has been found to target CSCs by blocking β-catenin/T-cell factor complex formation, decreasing the expression of Wnt target genes, and inhibiting sphere formation, proliferation, and anchorage-independent growth of cancer cells (Wang et al., 2019b). Salinomycin has also been shown to enhance the efficacy of other anticancer drugs, such as SN38, the active form of irinotecan, against colorectal cancer stem cells (Silva et al., 2021). Additionally, administering salinomycin and doxorubicin improved the therapeutic effectiveness in cancer stem cells, decreased their adverse side effects, and produced high antitumor efficacy for cancer treatment (Anees et al., 2023).

Despite all these effects of salinomycin, it has produced adverse effects in non-rodent preclinical models. Toxicology and pharmacokinetic studies are still required before human tests can be conducted (Qi et al., 2022). Additionally, salinomycin has been found to have neurotoxic effects at micromolar concentrations (Boehmerle & Endres, 2011). Further research is needed to determine the optimal dosage and potential side effects of salinomycin in humans, and more research is needed to fully understand its mechanisms of action and optimize its usage in humans.

Salinomycin Toxicosis in Animals

Salinomycin forms a lipid-soluble complex with cations, leading to the loss of intracellular potassium and subsequent cell death (Pakozdy et al., 2010). It is important to note that salinomycin has a narrow therapeutic index and can induce toxicity in animals (Managò et al., 2015). Cases of salinomycin toxicity have been reported in various animal species, including bovines, sheep, swine, equines, dogs, and birds (Ekinci et al., 2023).

Salinomycin toxicity goes beyond animals, and humans are also highly sensitive. Severe intoxication in humans has been reported, emphasizing caution in its use (Klose et al., 2019). In addition, chronic exposure to low doses of salinomycin via consumption of animal products may pose a risk to human health (Scherzad et al., 2016).

As salinomycin is commonly used as a coccidiostat antibiotic in poultry and also as a feed additive to improve feed efficiency in ruminant animals (Lagas et al., 2008), accidental high-dose ingestion by animals can lead to severe toxicity (Lagas et al., 2008). Various studies have reported different toxic effects of salinomycin in several animal species.

Salinomycin toxicosis in ruminants

Accidental salinomycin intoxication has been reported in sheep, resulting in high mortality rates (Ashrafihelan et al., 2014). The symptoms observed in sheep include anorexia, tachycardia, heart attack, muscle weakness,

and paralysis (Ekinci et al., 2023). Experimental studies in sheep showed that salinomycin does not significantly affect nutrient digestibility or ruminal characteristics (Soares et al., 2023).

Although salinomycin is not officially approved as a feed additive for cattle, it has been shown to enhance feed efficiency and daily weight gain in cattle and sheep (Limede et al., 2021). The toxic effects of salinomycin on cattle manifest in various ways. One study found that cattle-fed salinomycin had a higher dry matter intake, which may have overwhelmed the suppressive effect of salinomycin on acid production, leading to subacute acidosis (Ferreira et al., 2019). Another study observed that salinomycin supplementation in cattle-fed forage-based diets resulted in lower average daily gain than other additives (Limede et al., 2021). Additionally, salinomycin has been shown to alter ruminal fermentation characteristics, including decreased molar proportions of acetate and butyrate and increased propionate (Soares et al., 2023). In some cases, accidental poisoning of animals, such as calves, has been reported due to salinomycin toxicity (Ensley, 2020).

Salinomycin toxicosis and the development of antibiotic resistance in poultry

Salinomycin is commonly used in the poultry industry to control coccidiosis (Naseer et al., 2022). In broiler breeders and turkeys, salinomycin toxicosis has led to severe mortality, decreased egg production, and reduced food consumption (Koutoulis et al., 2013). Salinomycin is often used with other antimicrobial agents, such as bacitracin, to improve growth performance in broiler chickens (Diarra et al., 2007). However, salinomycin indication has been associated with the development of antibiotic resistance in commensal *Escherichia coli* isolates from broiler chickens (Diarra et al., 2007). A study found that chickens receiving feed supplemented with salinomycin exhibit considerably higher levels of gentamicin, spectinomycin, and ceftiofur resistance (Diarra et al., 2007). This finding highlights the potential risk of indication in poultry production and the need for careful monitoring of antibiotic resistance.

Salinomycin toxicosis in horses

Salinomycin toxicosis in horses is a well-documented phenomenon worldwide (Aleman et al., 2007). Horses are susceptible to intoxication by salinomycin as well as other ionophores such as lasalocid (Decloedt et al., 2012). In horses, salinomycin toxicosis can result in severe clinical signs, including acute rhabdomyolysis with muscle weakness and myocardial insufficiency (Croubels & Daeseleire, 2012). The horse is the most sensitive species to toxicosis associated with salinomycin, with concentrations above 8 µg/g (Huang et al., 2011). It should be noted that salinomycin toxicosis in horses is a serious condition causing high mortality rates (Ashrafihelan et al., 2014). In addition to salinomycin, other ionophores, such as monensin and lasalocid, can cause toxicosis in horses (Croubels & Daeseleire, 2012; Decloedt et al., 2012). These ionophores can have short-term and long-term consequences on horses' cardiovascular and neurological systems (Decloedt et al., 2012). Therefore, it is crucial to prevent accidental exposure of horses to ionophores and monitor their feed to avoid potential toxicosis.

Salinomycin toxicosis in small animals

Salinomycin toxicosis in dogs and cats can be a serious condition that requires appropriate treatment. The indication of salinomycin in veterinary medicine has been well documented and is well tolerated among mice, pigs, cats, and dogs. However, high doses of salinomycin can lead to neural dysfunction and paralysis in animals (Jangamreddy, 2015). Cats, for example, have shown symptoms of sensorimotor polyneuropathy, acute hind-limb paralysis, respiratory failure, and even death as a result of food contamination with salinomycin (Van der Linde-Sipman et al., 1999; Rajaian et al., 2009; Pakozdy et al., 2010). Therefore, it is important to carefully monitor the dosage and administration of salinomycin in dogs and cats to avoid toxicity.

Biochemical and Pathological Findings Associated With Salinomycin Toxicosis

Salinomycin may cause liver damage in animals. Although the exact molecular mechanism of salinomycin toxicity is not fully understood, certain biochemical parameters can indicate liver damage. In a study by Hosseini et al. (2013), salinomycin caused a significant increase in the levels of alanine transaminase (ALT), aspartate transaminase (AST), and lactate in sheep.

The effects of salinomycin on oxidative stress biomarkers in sheep have also been investigated. It was found that different doses of oral salinomycin altered oxidative stress biomarkers in sheep, suggesting that salinomycin could induce oxidative stress (Hajimohammadi et al., 2015).

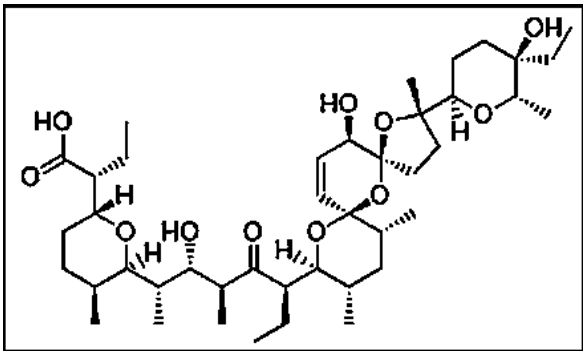

Figure 1. Structure of salinomycin

In calves, administration of toxic levels of salinomycin resulted in a significant increase in the activities of ALT, AST, and creatine kinase (CK). Concentrations of creatinine, potassium, phosphorous, and blood urea nitrogen in the serum were also significantly elevated (Rajaian et al., 2009a). It was demonstrated that administration of salinomycin to sheep increased cardiac troponin I, a specific biomarker in myocardial necrosis. Numerous arrhythmias were recorded, such as sinus tachycardia, supraventricular tachycardia, and supraventricular premature contraction (Hajimohammadi et al., 2014).

Overdosage of salinomycin can lead to a nonspecific inflammatory reaction in the host, which occurs briefly after any tissue injury. The levels of a few plasma proteins, identified as acute phase proteins, were measured by Nazifi et al. (2014). They showed a significant increase in inflammatory biomarkers such as haptoglobin, serum amyloid A, tumor necrosis factor-alpha, interferon-gamma, total sialic acid, lipid-bound sialic acid, and protein-bound sialic acid concentrations in sheep.

In an experimental study of salinomycin toxicity, Rajaian et al. (2013) showed a significant dose-dependent positive correlation between salinomycin toxicity and non-esterified fatty acid concentration and a significant negative correlation between salinomycin toxicity and serum glucose, β-hydroxybutyrate, and cholesterol concentrations in sheep. The results indicated that salinomycin intoxication might cause a negative energy balance.

Khodakaram Tafti et al. (2008) examined the histopathology of salinomycin toxicosis in sheep and showed pulmonary congestion and edema with thrombi in some capillaries, myocardial degeneration, and necrosis. Hepatocytes, renal tubules, sciatic nerves, and muscles were among the other tissues showing histologic changes.

Treatment of Salinomycin Toxicosis

In cases of salinomycin toxicosis, supportive care is often necessary. This care may include intravenous fluids to maintain hydration and electrolyte balance, as salinomycin can cause loss of intracellular potassium and ATP depletion (Pakozdy et al., 2010). Additionally, symptomatic treatment may be required to manage any neurological symptoms that may arise from salinomycin toxicity, such as weakness and decreased reflexes (Jangamreddy, 2015). It is important to be cautious when using salinomycin in stockbreeding, particularly in poultry, as it can have harmful side effects due to its severe toxicity (Scherzad et al., 2016). Researchers have explored potential interventions to mitigate the risks and side effects of salinomycin toxicity, but limited information is available.

A study on adult rabbits investigated the hepatoprotective and renal-protective effects of silymarin, an extract from *Silybum marianum* (milk thistle), against salinomycin-induced toxicity (Salehi et al., 2023). The study showed that silymarin administration reduces the adverse effects of salinomycin (Ghonaim et al., 2022). Hosseinian et al. (2021) also studied the hepatoprotective effect of silymarin. In addition, salinomycin in the diet of laying chickens induces side effects on various parameters, most likely due to oxidative damage. However, adding vitamin E and selenium to pullet diets can reduce the side effects of salinomycin (Rashidi Fathabadi et al., 2022). It has also been reported that administering hypertonic dextrose is partially helpful in treating salinomycin toxicosis in chickens. Hypertonic dextrose decreased mortality by around 44% and decreased the levels of the enzymes AST, ALT, and CK in the serum (Asmarian et al., 2010).

Conclusion

Salinomycin is commonly used in animal husbandry and has demonstrated antimicrobial activity against various microorganisms, including gram-positive bacteria, coccidian parasites, and trypanosomes. Its mechanism of action involves disrupting the cell cycle and activating apoptotic pathways. It can cause severe toxicity in animals and humans. Its toxic effects can vary depending on the animal species and the presence of other drugs or antibiotics. Horses are among the most susceptible species to salinomycin and other ionophores intoxication, so it is important to take preventive measures to avoid accidental exposure. Monitoring feedstuffs for ionophore concentrations and implementing strict control measures can help prevent salinomycin toxicosis. Salinomycin has

also shown the potential to act as an anticancer agent, particularly by targeting cancer stem cells. However, being cautious of its narrow therapeutic index and potential toxicity in animals is important. Additionally, the potential phytotoxic effects and persistence of salinomycin in the environment should be considered. Further research is needed to understand its toxicology and pharmacokinetics better before it can be safely used in human clinical trials.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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مقاله مروری

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چکیده

سالینومایسین یک آنتی بیوتیک آیونوفور پلی اتر است که از دهه ۱۹۸۰ در طب دامپزشکی و پرورش حیوانات مورد استفاده قرار گرفته است. سالینومایسین به عنوان یک داروی ضد سرطان نیز مطرح شده است که در سلول های بنیادین باعث مهار رشد سلول های سرطانی شده است. این دارو توانسته است سبب برانگیختن اتوفاژی، میتوفاژی، و نابودی میتوکندری در سلول های سرطانی گردد. سالینومایسین می تواند با ساخت انواع گونه های کنشگر اکسیژن و مهار فعالیت سیکلواکسیژناز-۲ در سلول های سرطان سمیت ایجاد کند. از طرف دیگر سالینومایسین یک آنتی بیوتیک محلول در چربی است که می تواند سبب بروز مسمومیت در انسان و انواع مختلف حیوانات، از جمله گاو، گوسفند، خوک، اسب، سگ و پرندگان شود.

مصرف تصادفی دوزهای بالایی از این دارو می تواند سبب مسمومیت شدید، نارسائی عصبی و فلجی در حیوانات شود. این دارو همچنین می تواند منجر به آسیب کبدی در حیوانات گردد. مطالعات نشان داده اند که دوزهای متفاوتی از سالینومایسین به صورت خوراکی نشانگرهای استرس اکسیداتیو را تغییر می دهد و باعث افزایش نشانگرهای التهابی می شود. درمان مسمومیت با سالینومایسین اغلب شامل مراقبت های حمایتی و درمان علامتی می باشد. بنابراین بسیار مهم است که در زمان استفاده از سالینومایسین احتیاط لازم رعایت شود، زیرا سمیت آن می تواند عوارض جانبی با علائم خطرناکی به همراه داشته باشد.

کلیدواژه‌ها: داروهای ضد سرطان، کوکسیدیواستات، آیونوفورها، سالینومایسین، مسمومیت

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