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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 cancer stem cells in humans 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 (ROS) and inhibiting cyclooxygenase-2 (COX-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

1-Introduction

Salinomycin is an antibiotic widely used in veterinary medicine (Jędrzejczyk et al., 2022). It is a polyether ionophore antibiotic that is commonly used as a coccidiostat and growth promoter in animals (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 action of salinomycin is still not fully understood. 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 a decrease in respiration in mouse embryonic fibroblasts and cancer stem cells (Managò et al., 2015). Salinomycin is primarily metabolized through monooxygenation, leading to the formation of monohydroxy-salinomycin, dihydroxy-salinomycin, and trihydroxy-salinomycin (Radko et al., 2020).

2. 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 polyketide synthase (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 the biosynthesis of salinomycin (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). Analogues of salinomycin with lower toxicity but retained cation-binding properties hold promise for the development of targeted therapies (Luhavaya et al., 2014).

3. Antimicrobial activity of salinomycin

Salinomycin has been shown to exhibit antimicrobial activity against a variety of microorganisms, including Gram-positive bacteria, coccidian parasites, and trypanosomes

(Lavine and Arrizabalaga, 2011; Santos-Beneit et al., 2022). Salinomycin and its derivatives have been found to be effective against methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), 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 and 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 in this context.

4. Salinomycin as an anticancer drug and its mechanism of action

It has been demonstrated that salinomycin has potential therapeutic indication 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 and Steinhart, 2012). Salinomycin may also inhibit the growth of cisplatin-resistant human ovarian cancer cells through the activation of 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, mitophagy, and affect 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 (ROS) and inhibiting cyclooxygenase-2 (COX-2) activity (Eskandari and 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 and Doube, 2004).

Systemic administration of salinomycin in mammals has been associated with adverse reactions such as tachycardia and myoglobinuria (Qin and Guo, 2022). In terms of its anticancer mechanisms, salinomycin has been found to target cancer stem cells (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, the administration of 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 and 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.

5. 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 is not limited to animals, so humans are also highly sensitive. Severe intoxications in humans have 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 coccidiostatic 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.

5.1. 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 (Bortolanza 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 (DM) 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 compared to other additives (Limede et al., 2021). Additionally, salinomycin has been shown to alter ruminal fermentation characteristics, including a decrease in molar proportions of acetate and butyrate and an increase in propionate (Soares et al., 2023). In some cases, accidental poisoning of animals, such as calves, has been reported due to salinomycin toxicity (Ensley, 2020).

5.2. Salinomycin toxicosis and the development of antibiotic resistance in poultry

Salinomycin is commonly used in the poultry industry for the control of 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 in combination 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 exhibited considerably higher levels of gentamicin, spectinomycin, and ceftiofur resistance (Diarra et al., 2007). This highlights the potential risk of indication in poultry production and the need for careful monitoring of antibiotic resistance.

5.3. Salinomycin toxicosis in horses

Salinomycin toxicosis in horses is a well-documented phenomenon around the world (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 and Daeseleire, 2012). The most sensitive species to toxicosis associated with salinomycin is the horse, with concentrations in excess of 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 also cause toxicosis in horses (Croubels and Daeseleire, 2012; Decloedt et al., 2012). These ionophores can have short-term and long-term consequences on the cardiovascular and neurological systems of horses (Decloedt et al., 2012). Therefore, it is crucial to prevent accidental exposure of horses to ionophores and to closely monitor their feed to avoid potential toxicosis.

5.4. 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.

6. 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, there are certain biochemical parameters that can indicate liver damage. In a study by Hosseini et al. (2013), salinomycin caused a significant increase in the levels of ALT, AST, and LDH 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).

In calves, administration of toxic levels of salinomycin resulted in a significant increase in the activities of ALT, AST, and 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 (cTnI), a specific biomarker in myocardial necrosis. Numerous arrhythmias were also recorded, such as sinus tachycardia, supraventricular tachycardia, sinus arrhythmia, 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 (APPs), were measured by Nazifi *et al.* (2014). They showed a significant

increase in inflammatory biomarkers such as haptoglobin (*Hp*), serum amyloid A (SAA), tumor necrosis factor alpha (TNF-α), interferon gamma (*IFN-γ*), total sialic acid, lipid-bound sialic acid, and protein-bound sialic acid concentrations in sheep (Nazifi et al., 2014).

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 (NEFA) concentration and a significant negative correlation between salinomycin toxicity and serum glucose, β-hydroxybutyrate (BHB), and cholesterol concentrations in sheep. The results indicated that salinomycin intoxication might cause a negative energy balance (Rajaian et al., 2013).

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 (Khodakaram Tafti et al., 2008).

7. Treatment of salinomycin toxicosis

In cases of salinomycin toxicosis, supportive care is often necessary. This 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). To mitigate the

risks and side effects of salinomycin toxicity, researchers have explored potential interventions, but there is limited information available.

A study conducted on adult rabbits investigated the hepatoprotective and renal-protective effects of silymarin, an extract from *Silybum marianum* (milk thistle) (Salehi et al., 2023) against salinomycin-induced toxicity. The results of the study showed silymarin administration reduces the adverse effects of salinomycin (Ghonaim et al., 2022). The hepatoprotective effect of silymarin have also been studied by Hosseinian et al (2021). In addition, salinomycin in the diet of laying chickens induces side effects on various parameters, most likely as a result of 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 the administration of hypertonic dextrose is partially useful in the treatment of 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 species of animal and the presence of other drugs or antibiotics. Horses are among the most susceptible species to intoxication by salinomycin and other ionophores, 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, it is important to be cautious of its narrow therapeutic index and potential toxicity in animals. Additionally, the potential phytotoxic effects and persistence of salinomycin in the environment should be taken into account. Further research is needed to better understand its toxicology and pharmacokinetics before it can be safely used in human clinical trials.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

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بینشی جدید در مورد سالینومایسین

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خلاصه

سالینومایسین یک آنتی بیوتیک آیونوفور پلی اتر است که از دهه 1980 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-2 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.

کلمات کلیدی: داروهای ضد سرطان، کوکسیدیواستات، آیونوفورها، سالینومایسین، مسمومیت

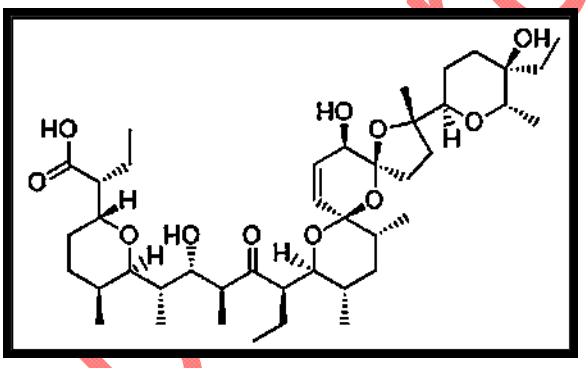

Figure 1. Structure of salinomycin