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IONOPHORE ANTIBIOTICS AND HOP CONES AS REGULATORS OF DIGESTION AND METABOLISM IN RUMINANTS

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The general characteristics of ionophore antibiotics and the mechanisms of their antimicrobial action were analyzed.

Two types of ionophore antibiotics are known: those that transport ions across the membrane, and those that form a channel in the cell membrane through which ions pass. Ionophore antibiotics used in animal husbandry belong to the former group (monensin, lasalocid, salinomycin, narasin). They are synthesized by bacteria of the *Streptomyces* genus.

Bacterial cells and rumen fluid differ in ionic composition, which is regulated by active ion transport. As a result, the cytoplasm of bacteria contains more potassium ions, while the rumen fluid, on the contrary, has more sodium ions. Ionophores transport potassium inside the cell and remove sodium outside. The bacteria try to correct this imbalance and require ATP energy to carry out this process. Eventually, energy deficit develops in the bacterial cell and it dies.

Ionophore antibiotics affect only the Gram-positive bacteria in the rumen of ruminants, because they cannot penetrate through the cell wall of Gram-negative bacteria. Thus, there is a selective destruction of some types of bacteria, the most sensitive among which are the so-called hyper-ammonia-producing bacteria (HAB).

Ionophore antibiotics, which change the breakdown of protein and carbohydrates, change the ratio of volatile fatty acids by increasing the proportion of propionic acid and thus inhibit methanogenesis in the rumen. Ionophore antibiotics are an important antiketotic agent because they reduce the concentration of β-hydroxybutyrate and non-esterified fatty acids in the blood of ruminants.

During the transition period, cows have metabolic disorders so they are more prone to infectious diseases due to a decrease in resistance. The use of ionophore antibiotics affects the immune function and resistance to inflammatory processes, which is caused by an indirect influence associated with a lower pathological effect of ketosis and steatosis.

Ionophore antibiotics reduce the negative energy balance and its pathological impact on metabolism. The influence of ionophore antibiotics on cow's milk productivity is mostly absent or insignificant.

The study presents characteristics of biologically active substances of hop cones. Hop cones contain biologically active components similar to ionophore antibiotics by action. These are prenylated flavonoids: humulone (α-acid), lupulone (β-acid) and their derivatives. These components of hop cones can be regarded as a potential substitute for ionophoric antibiotics. In particular, lupulone and some other components of hop cones inhibit the activity of Gram-positive bacteria, causing reactions similar to ionophore antibiotics. In addition, hop cones have many other biologically active compounds: phenols, essential oils, and resins, which have antimicrobial, antioxidant, sedative, phytoestrogen, insulin stimulating, immunomodulatory, and antitumor effects.

Keywords: ruminants, rumen, ionophore antibiotics, hop cones

INTRODUCTION

Ionophore antibiotics are a group of carboxyl polyether antibiotics produced by bacteria of the genus *Streptomyces* (Ensley, 2020) and some unicellular algae (Dembitsky, 2022).

According to the mechanism of ion transport, there are two types of ionophore antibiotics: those that bind to ions and transport them across the membrane and those that form a continuous channel between the intracellular and extracellular spaces through which ions move (Roy & Talukdar, 2021). The main ionophore antibiotics used in animal husbandry (monensin, lasalocid, salinomycin, narasin) belong to the first group.

Monensin is produced by *Streptomyces cinnamonensins*, lasalocid – by *Streptomyces lasaliensis*, salinomycin – by *Streptomyces albus*, narasin – by *Streptomyces aureofaciens*. Ionophores of this group are capable of binding a fairly wide range of ions with some differences in selectivity. Monensin – $Na^+ > K^+$, $Li^+ > Rb^+ > Cs^+$; lasalocid – Ba^{++}, $K^+ > Rb^+ > Na^+ > Cs^+ > Li^+$; salinomycin – Rb^+, $Na^+ > K^+ >> Cs^+$, Sr^+, Ca^{++}, Mg^+; narasin – $Na^+ > K^+$, Rb^+, Cs^+, Li^+ (Nagaraja, 1995; Marques, 2021). However, in general, the mechanisms of action of these antibiotics are the same.

In addition, many ionophore antibiotics are currently synthesized chemically (Liu *et al.*, 2019). They are lipophilic compounds and have high adhesive ability. As a result, ionophore antibiotics pass across the plasma membrane of Gram-positive bacteria, transport anions into the cell, which disrupts the ion balance and produces an antibacterial effect. A bacterial wall surrounds Gram-negative bacteria, so the antimicrobial properties of ionophore antibiotics do not affect them or are expressed slightly (Marques & Cooke, 2021). However, the sensitivity of different types of bacteria to ionophore antibiotics has some exceptions. In particular, some Gram-positive bacteria of the rumen (*Lachnospira multiparus*, *Ruminococcus albus*, *Ruminococcus flavefaciens*, *Butyvibrio fibrisolvens*) are resistant to the action of ionophore antibiotics (Marques & Cooke, 2021). The mechanisms of this resistance have not yet been determined, but it should be taken into account that the ionophore producers (*Streptomyces* spp.) themselves belong to Gram-positive bacteria and are not sensitive to their action. Individual Gram-negative bacteria may have temporary sensitivity to ionophore antibiotics, but with longer contact, they develop resistance (Russell & Houlihan, 2003).

Cytoplasm of bacteria contains more potassium ions than sodium, while in rumen fluid, on the contrary, there are more sodium ions than potassium ions. To maintain a functionally optimal concentration ratio of these chemical elements, plasma membrane of eukaryotes utilizes a special enzyme – Na^+/K^+-ATPase (sodium-potassium pump). ATPase actively transports K^+ ions into the cell, while Na^+ ions are transported out. The energy source for this is ATP, the energy of which is used for the active transport of ions against the concentration gradient. In bacteria, these processes are more complicated, with the participation of a number of enzyme complexes, separate for sodium and potassium, but the general principle is similar – the transfer of potassium to the inside and the removal of sodium to the outside of the cell using ATP energy (Kevin II *et al.*, 2009).

Under the action of ionophore antibiotics, the concentration of sodium and potassium ions in bacterial cells and rumen fluid begins to equalize, that is the amount of sodium in the cytoplasm increases excessively. Na^+/H^+-ATPases try to remove Sodium ions outside the cell, thereby consuming ATP. Deficiency of ATP leads to a lack of energy for other metabolic processes in the bacterial cell and its death (Marques & Cooke, 2021).

Hundreds of species of microorganisms inhabit the rumen of ruminants. Microorganisms of the rumen ferment the nutrients of the feed, breaking down some of them and transforming the other. In particular, feed carbohydrates in the rumen are almost completely split into acetic, propionic, butyric and lactic acids, protein into amino acids and ammonia, unsaturated fatty acids are transformed into saturated and trans isomers. Volatile fatty acids are absorbed into the blood and participate in synthetic processes. Amino acids and ammonia are used for bacterial protein synthesis, but excessive ammonia is absorbed into the blood and converted into urea in the liver. Trans-isomers of fatty acids are included in the lipids of bacterial membranes. Bacteria, together with fodder masses, enter the abomasum and intestines, where they are digested, providing the animal with a bacterial protein with a balanced amino acid composition. Different bacteria have their specific enzymatic features: some form mainly acetic acid, some propionic acid, others butyric acid, still others lactic acid. The same goes for protein: some bacteria break down protein into amino acids, and others into ammonia. Therefore, when the vital activity of certain types of bacteria is selectively inhibited, the composition of fermentation products in the rumen of a ruminant animal changes, which affects further metabolism in its body.

Ionophore antibiotics, acting selectively on the vital activity of the microflora of the rumen, change the course of ruminal fermentation by influencing the breakdown of carbohydrates and proteins and related metabolic links (Azzaz *et al*., 2015; Duffield *et al.*, 2012). Ionophore antibiotics reduce the formation of ammonia in the rumen by selectively affecting Gram-positive bacteria, which include hyper-ammonia producing bacteria (HAB) (Mullins *et al.*, 2012). They also suppress the activity of lactic acid bacteria (LAB), thus stimulating the formation of the precursor of glucose – propionic acid (Compton *et al.*, 2015). Given the almost complete fermentation of feed carbohydrates in the rumen, propionate for ruminants is one of the main substrates for endogenous glucose synthesis (NASEM, 2016). At the same time, the activities of cellulolytic bacteria are slightly suppressed, which reduces the formation of acetate and inhibits the synthesis of milk fat. Therefore, ionophores modulate the fermentation of carbohydrates, changing the ratio of volatile fatty acids formed in the rumen. As a result, the part of propionate increases and the parts of acetate and butyrate decrease in the rumen volatile fatty acids composition (Duffield *et al.*, 2012; Azzaz *et al*., 2015; Golder & Lean, 2016; Limede *et al.*, 2021; Polizel *et al.*, 2020; Bell *et al*.,2017).

Because of the effect on the microbiota, enzymatic processes in the rumen are changed, which affects the animal metabolism and productivity. (Ensley, 2020; Golder & Lean, 2016; Beck *et al.*, 2016).

The productive effect of ionophore antibiotics depends on the animal physiological state and diet composition. In particular, if ionophore antibiotics are used for fattening cattle kept on a concentrate diet with a high content of non-structural easily fermentable carbohydrates, an increase in gains and a decrease in feed consumption are observed (Duffield *et al.*, 2012; Azzaz *et al*., 2015). When ionophore antibiotics are added to a diet with a high fiber content, gains also increase, but without influence on dry matter consumption (Limede *et al.*, 2021; Polizel *et al.*, 2020).

An important aspect of the ionophore action in the rumen is their effect on methanogenesis (Appuhamy *et al.*, 2013). Methane synthesis requires carbon dioxide and molecular hydrogen. During the fermentation of feed carbohydrates to acetate and butyrate, in addition to the specified volatile fatty acids, CO_2 and H_2 are formed. Methane-synthesizing bacteria use these two substrates for methane formation (Ellis *et al.*, 2012). Unlike acetate and butyrate, during fermentation of carbohydrates to propionic acid, carbon dioxide and molecular hydrogen are not formed, which contributes to reducing the methane release into the atmosphere thus reducing the greenhouse effect. In addition, methanogenesis is accompanied by additional energy costs, so the change of fermentation to the formation of propionate somewhat increases the efficiency of feed utilization (Ellis *et al.*, 2012; Golder & Lean, 2016). This is important for beef cattle breeding, where the use of ionophore antibiotics helps to increase live weight gains (Azzaz *et al*., 2015). In dairy cows, the productive effect is ambiguous in view of the reduction in milk fat content, so it is advisable to feed ionophore antibiotics to cows only in the transition period to equalize the energy balance and for prevention and treatment of ketosis.

IONOPHORE ANTIBIOTICS

Ionophore antibiotics are not used in human medicine. In veterinary medicine, the following ionophores that transport ions through the plasma membrane of bacteria are used: monensin, lasalocid, salinomycin, narasin. Since the mechanism of their action is similar, we will consider it using the example of the most widely used ionophore antibiotic – monensin.

In recent years, the use of monensin to prevent subclinical ketosis has become widespread (Raboisson & Barbier, 2017). Monensin affects ruminal fermentation in ruminants, especially this effect is pronounced in transition cows (Mezzetti *et al.*, 2019; Schären *et al.*, 2017; Drong *et al.*, 2016; Mullins *et al.*, 2012).

Monensin mainly targets Gram-positive bacteria. It changes the ratio of sodium and potassium in Gram-positive bacteria and causes an increase in the use of energy resources by bacterial cells to restore the anion balance. This leads to a slowdown in the growth of the microbial mass and to the death of part of Gram-positive bacteria (Schären *et al.*, 2017). Monensin has virtually no impact on feed intake (Drong *et al.*, 2016; Mullins *et al.*, 2012). Proteolytic bacteria are mostly Gram-positive, thus, when monensin enters the rumen, a decrease in the concentration of ammonia is observed as a consequence of less effective breakdown of feed protein. Accordingly, there is an increase in the proportion of protein that is digested in the small intestine, which is more energetically beneficial for the animal (Mezzetti *et al.*, 2019). Other studies did not reveal changes in rumen ammonia concentration (Drong *et al.*, 2016; Schären *et al.*, 2017), so this aspect of the effect of ionophore antibiotics on proteolysis needs further study.

Data on the effect of monensin on the production of volatile fatty acids in the rumen and pH of rumen fluid indicate the influence of various factors on these processes, in particular the consumption of feed, its composition and digestibility (Drong *et al.*, 2016; Schären *et al.*, 2017).

The results of many studies have not shown differences in the total content of volatile fatty acids in the rumen when monensin is administered to cattle (Mezzetti *et al.*, 2019; Schären *et al.*, 2017; Drong *et al.*, 2016). However, its effect on the ratio of volatile fatty acids was noted. Ionoforic antibiotics increase the part of propionic acid by reducing the proportion of acetic and butyric acids, resulting in the reduction of acetate/propionate ratio (Drong *et al.*, 2016; Schären *et al.*, 2017). An increase in the proportion of valeric, capronic and enanthic acids was also shown (Mezzetti *et al.*, 2019). Thus, the selective inhibition of Gram-positive bacteria functioning changes the course of fermentative processes in the rumen and modulates the formation of individual volatile fatty acids, which are the products of complex catabolism of feed components of different bacterial groups (Drong *et al.*, 2016; Schären *et al.*, 2017).

According to the data of some researchers, monensin increases the pH indicator, which is explained by the inhibition of lactic acid production in the rumen. On the other hand, some studies indicate no effect of monensin on the pH of the rumen fluid (Mullins *et al.*, 2012; Mezzetti *et al.*, 2019).

With long-term use of monensin, temporary bacterial resistance may occur, which disappears after several generations of bacteria. There were no cases of cross-resistance between monensin and other antibiotics (Nesse *et al.*, 2015). According to the European Medicine Agency, the use of monensin for farm animals does not have a negative impact on human health (European Medicine Agency, 2019).

Most studies indicate a decrease in the concentration of ketone bodies, mainly β-hydroxybutyrate, in the blood of cows after calving under the influence of monensin. Such effect is also observed in dry cows but to a lesser degree (Fiore *et al.*, 2021; Kasap *et al.*, 2020; Mezzetti *et al.*, 2019; Drong *et al.*, 2016; Compton *et al.*, 2015; McCarthy *et al.*, 2015; Mullins *et al.*, 2012).

After calving, cows have a negative energy balance associated with glucose deficiency, which is compensated by an increased use of fatty acids from adipose tissue to balance the body's energy needs. Monensin affects the blood concentration of these key energy substrates, but this effect is less pronounced than the effect on the concentration of ketone bodies, and the detected changes are not always statistically significant (Fiore *et al.*, 2021; Kasap *et al.*, 2020; Mezzetti *et al.*, 2019; Drong *et al.*, 2016; McCarthy *et al.*, 2015; Markantonatos & Varga, 2017). Nevertheless, monensin mainly increases the concentration of glucose and decreases the concentration of NEFA in the blood of cows with ketosis. Separate studies indicate that monensin does not have any effect on glucose and NEFA metabolism, but none of them showed a negative effect – a decrease in glucose concentration or an increase in NEFA concentration (Mammi *et al.*, 2021).

The liver of high-yielding cows is prone to excessive accumulation of triacylglycerols, which leads to its fatty degeneration. Monensin reduces the concentration of NEFA in the blood and triacylglycerols content in the liver (McCarthy *et al.*, 2015; Mullins *et al.*, 2012), which is important both for lipid metabolism in general and for maintaining the liver function. The hepatoprotective effect of monensin is also evidenced by a decrease under its influence in the activity of transaminases in the blood of ketotic cows (Fiore *et al.*, 2021).

Thus monensin as an ionophore antibiotic inhibits the vital activity of proteolytic bacteria, its administration reduces protein breakdown in the rumen and increases the intake and assimilation of protein by the small intestine (Mezzetti *et al.*, 2019). This, in many cases, leads to an increase in the concentration of urea in the blood (Kasap *et al.*, 2020) and milk (McCarthy *et al.*, 2015; Mullins *et al.*, 2012).

In the transition period, due to metabolic disorders, cows are prone to infectious diseases as a result of a decrease in resistance (Bradford *et al.*, 2015). The use of monensin affects the immune function and cows' resistance to inflammatory processes. Such an indirect effect is associated with a lower pathological impact of the negative energy balance that leads to ketosis and steatosis (Mammi *et al.*, 2021). The introduction of monensin into the rumen stimulates anti-inflammatory mechanisms in the body of cows, in particular, it affects the expression of acute phase proteins and haptoglobin (McCarthy *et al.*, 2015), but this effect is not always present (Mullins *et al.*, 2012; Mezzetti *et al.*, 2019; Drong *et al.*, 2017). However, when monensin is used for ketosis treatment, less evidence of mastitis, metritis and litter retention is observed (Compton *et al.*, 2015).

The effect of monensin on milk productivity of cows is mostly absent or insignificant. The productive effect is manifested by an increase in milk yield with a simultaneous decrease in milk fat. In most cases, this effect is noticeable at the beginning of lactation in the presence of metabolic disorders in cows, that is, monensin reduces the negative effect of negative energy balance and its pathological effect on metabolism. This improves the general condition of the body and, accordingly, restores milk productivity of cows (McCarthy, Pelton *et al.*, 2015; Robinson, 2020).

HOP CONES

In recent years, there has been a tendency to limit the use of antibiotics in animal husbandry for prophylactic and productivity-stimulating purposes. Therefore, an intensive search for compounds capable of replacing them is being conducting now. Without doubt, biologically active substances of plant origin are less active than antibiotics, but they can be regarded as potential substitutes for antimicrobial drugs. Some plants contain relatively active antimicrobial components. These include hops, the cones of which contain compounds that are similar in biological activity to ionophore antibiotics (Sachko, 2023).

Hops have been used as a plant with medicinal properties since ancient times (Koetter & Biendl, 2010), however, due to the presence of an extremely wide range of biologically active substances in its composition, research into possible ways of its use continues (Nowak *et al.*, 2020; Zugravu *et al.*, 2022; Macchioni *et al.*, 2022). Hop cones contain biologically active components similar in action to ionophore antibiotics. These are prenylated flavonoids: lupulone, humulone and their derivatives (Weiskirchen *et al.*, 2015; Flythe *et al.*, 2017). The specified components of hop cones can be regarded as a potential substitute for ionophoric antibiotics (Flythe, 2009). In addition, hop cones contain a number of other biologically active substances: phenols, essential oils and resins, which have antimicrobial, antioxidant, sedative, phytoestrogenic, insulin-stimulating, immune-modulatory and antitumor effects (Astray *et al.*, 2020; Karabín *et al.*, 2016; Zugravu *et al.*, 2022). Biologically active hop compounds regulate carbohydrate-lipid metabolism by increasing catabolism and lowering the level of glucose and lipids in the blood (Girisa *et al.*, 2021; Vudmaska *et al.*, 2021), reduce the accumulation of lipids in the liver and adipose tissue and suppress the proliferation of adipocytes through the regulation of PPARγ function (Paraiso *et al.*, 2021; Zhang *et al.*, 2021).

Ionophoric antibiotics and hop acids have a similar spectrum of biological activity, that is, they inhibit the vital activity of most Gram-positive microorganisms in the rumen (Flythe & Aiken, 2010; Flythe *et al.*, 2017; Almaguer *et al.*, 2014). In particular, lupulone inhibits the activity of Gram-positive bacteria *S. bovis*, which are one of the main producers of lactate. However, some Gram-positive bacteria are not sensitive to lupulone, such as bacteria of the class *Negativicutes* (Flythe & Aiken, 2010). A member of this class, *M. elsdenii*, is an important producer of propionate in the rumen. Therefore, under the action of biologically active acids of hop cones in the rumen, the production of lactic acid decreases. The quantitative production of propionic acid mostly does not change, but due to a certain decrease of acetate, the proportion of propionate in the rumen fluid becomes larger (Flythe & Aiken, 2010). Similarly to ionophore antibiotics, hop cones decrease the concentration of ketone bodies, reduce proteolytic activity and inhibit ammonia formation and methanogenesis in the rumen (Sachko, Vudmaska, 2019; Blaxland *et al.*, 2021; Vudmaska *et al.*, 2021).

The most abundant biologically active components of hop cones are hydrophobic α- and β-acids, otherwise referred to as “bitter acids”, which are produced by the lupulin glands of the cones. α-Acids are represented by six compounds, including humulone (35–70 %), cohumulone (20–55 %), adhumulone (10–15 %), as well as minor components: posthumulone, prehumulone, and adprehumulone (Karabín *et al.*, 2016). β-acids include lupulone (30–55 %), colupulone (20–55 %), adlupulone (5–10 %), prelupulone and postlupulone (Karabín *et al.*, 2016). α-Acids are important in brewing, they are the main components for which hops are used to produce beer. In contrast, β-acids are much less important for brewing, but they are of interest as compounds with antimicrobial and antioxidant properties.

Another large group of biologically active substances of hop cones are essential oils, which are also produced by the lupulin glands. Essential oils of hop cones have a different chemical structure; they include hydrocarbons (monoterpenes, sesquiterpenes, and aliphatic hydrocarbons), oxygen-rich compounds (terpene alcohols, sesquiterpene alcohols), and sulfur-rich compounds (thioesters, sulfides). The main representatives of essential oils, which are present in hop cones in the largest amount, are monoterpenes: α-pinene, β-pinene, myrcene and limonene and sesquiterpenes: α-humulene, α-selinene, β-farnesene, β-caryophyllene, β-selinene.

Hop cones also contain polyphenolic components, the amount of which is relatively small (3–6 %), but they have significant biological activity. This is a large group of compounds, among which prenylflavonoids have the greatest pharmaceutical value: xanthohumol, isoxanthohumol, desmetylxanthohumol and 8-prenylnaringenin (Karabin *et al.*, 2015).

Among the components of hops, the highest antimicrobial activity is observed in α- and β-acids, with functional characteristics similar to those of ionophore antibiotics, and β-acids are more effective then α-acids. These acids are embedded in the cell membrane of Gram-positive bacteria and transport undissociated protonated molecules into the cytoplasm. As a result, H^+ protons accumulate in the cytoplasm and the cell dies (Gerhäuser, 2005). Gram-negative bacteria and fungi are mostly not sensitive to the antimicrobial action of α- and β-acids (Karabín *et al.*, 2016). *Iso*-forms of these acids are less active against bacteria, however, taking into account their better solubility, the effectiveness of antimicrobial action is relatively high (Sakamoto & Konings, 2003). Antimicrobial activity increases at lower pH (Karabín *et al.*, 2016). Bacteria of the genera *Lactobacillus*, *Streptococcus*, *Staphylococcus*, *Micrococcus*, *Bacillus*, *Pediococcus*, *Helicobacter*, *Clostridium*, and *Listeria* are sensitive to the action of bitter acids (Karabín *et al.*, 2016).

Other antimicrobial components of hops are polyphenol compounds (Gerhäuser, 2005; Daglia, 2012). They act in the following two ways: through accumulation in microbial cells, and violation of the cell membrane integrity. Among hop polyphenols, flavonols and tannins show the highest activity (Daglia, 2012). Like α- and β-acids, polyphenolic compounds affect mainly Gram-positive bacteria, in particular on *Staphylococcus aureus*, *Lactobacillus acidophilus*, *Actinomyces naeslundi*, *Streptococcus mutans*, *Clostridium perfringens* (Sendamangalam *et al.*, 2011). But some Gram-negative bacteria, for example *Prevotella oralis*, *Prevotella melaninogenica*, *Fusarium nucleatum*, *Escherichia coli* are also sensitive to polyphenolic compounds (Karabín *et al.*, 2016). Other phenols: gallic, caffeic, ferulic and some other acids have lower activity, but show a moderate effect on some Gram-positive and Gram-negative bacteria (Díaz-Gómez *et al.*, 2014; Rozalski *et al.*, 2013). Polyphenols of the prenylflavonoid group are characterized by relatively high activity on Gram-positive bacteria, some fungi and protozoa (Mukai, 2018), and also have an antiviral effect (Zhang *et al.*, 2010).

Antimicrobial activity is also present in essential oils of hops, but is much less pronounced than the action of bitter acids and polyphenols (Karabín *et al.*, 2016). This aspect is important because most plants contain essential oils and their extracts are often proposed as antimicrobial agents. In addition to essential oils, hops contain other antimicrobial substances with a much stronger effect. Nevertheless, essential oils of hops have antimicrobial properties, which adds to the overall antimicrobial effect. Hop cones contain the following biologically active essential oils that belong to terpenes: linoleol, geraniol, terpineol, limonene, caryophyllene, humulene, myricene, cadinene, pinene, and others (Bassolé & Juliani, 2012; Yap *et al.*, 2014; Hsu *et al.*, 2013). Substances present in hop cones have significant antioxidant properties (Zugravu *et al.*, 2022). The highest antioxidant effect is characteristic of hop polyphenols, which effectively neutralize active forms of oxygen, in particular hydroxyl, peroxyl, superoxide, and peroxide radicals and singlet oxygen (Sandoval-Acuña *et al.*, 2014). In addition, polyphenols inhibit enzymes involved in the generation of active forms of oxygen: NADPH oxidase, cyclooxygenase, xanthine oxidase, lipoxygenase (Karabín *et al.*, 2016). Among flavonoids, quercetin, myricetin and kaempferol show the highest antioxidant effect (Quiñones *et al.*, 2013). The antioxidant activity of hop phenolic compounds such as gallic acid, quercetin, and catechin exceeds that of ascorbic acid (Kim *et al.*, 2002), and xanthohumol has a higher antioxidant activity than α-tocopherol (Miranda *et al.*, 2000). A high antioxidant activity is also characteristic of α- and β-acids (humulone and lupulone); in terms of the effectiveness of their antioxidant activity, they approach α-tocopherol and ascorbic acid (Karabín *et al.*, 2016). Antioxidant properties were also found in hop leaves (Muzykiewicz *et al.*, 2019; Macchioni *et al.*, 2022).

The sedative effect of hop cones has long been known (Karabín *et al.*, 2016). The main principle of the sedative effect of hop cones and their extracts lies mainly in the allosteric modulation of specific neurotransmitter receptors by biologically active substances, such as essential oils or resins. More attention is paid to the interaction with GABA (γ-aminobutyric acid) receptors, although the interaction of essential oils of hops with N-methyl-D-aspartate (NMDA) receptors has also been studied (Sigel & Steinmann, 2012).

Hop polyphenols, especially xanthohumol, have antitumor properties (Girisa *et al.*, 2021; Jiang *et al.*, 2018). When taken *per os*, xanthohumol in the course of digestion is transformed into a number of biologically active substances that inhibit neoplastic growth. The mechanism of action of xanthohumol and its metabolites consists in inhibiting the two signaling pathways Akt and NF-κB, inducing of tumor cells apoptosis due to an increased expression of Bax, PARP, caspase-3, -8, -9 and inhibiting the expression of Notch1, mTOR, STAT3, FAK and MMP-2 (Girisa *et al.*, 2021; Jiang *et al.*, 2018). Interestingly, even though xanthohumol mainly exhibits antioxidant properties, in tumor cells this compound often exhibits a pro-oxidant effect, which contributes to the anti-carcinogenic effect (Wei *et al.*, 2018). An increase in the level of free radicals suppresses the activity of NF-κB, which induces apoptosis (Fouani *et al.*, 2019). Xanthohumol prevents the occurrence of metastases by inhibiting ERK/MAPK and PI3/AKT signaling pathways (Sławińska-Brych *et al.*, 2021).

CONCLUSION

Ionophores are carboxyl polyether antibiotics used for birds as coccidiostat, and for ruminants to regulate fermentation in the rumen and treat metabolic disorders, in particular ketosis.

In animal husbandry, ionophore antibiotics belonging to the group of those that transport ions through the bacterial plasma membrane have become widespread: monensin, lasalocid, salinomycin, narasin. The most common of them is monensin.

Ionophores are active against Gram-positive bacteria, while Gram-negative bacteria are not sensitive to their action, because ionophores cannot penetrate the bacterial cell wall.

Ionophores disrupt the intracellular ion balance, reducing the concentration of potassium and increasing the concentration of sodium in the bacterial cell. Na^+/H^+-ATP-ases try to remove excess of sodium ions from the cell consuming the ATP supply, which leads to the death of bacteria. Ionophores, selectively affecting the species composition of rumen microflora, change the protein and carbohydrates fermentation, reduce the formation of ammonia, lactate and methane and increase the formation of propionic acid. At the same time, the concentration of glucose in the blood of a ruminant animal increases and the concentration of β-hydroxybutyrate decreases. This effect improves the general condition of the animal and prevents the occurrence of metabolic disorders.

Hop cones contain a significant amount of metabolically active components, including substances with ionophoric action, so they can be considered as a potential substitute for ionophoric antibiotics. Other components of hop cones, such as phenols, essential oils, and resins have antimicrobial, antioxidant, sedative, phytoestrogenic, insulin-stimulating, immunomodulatory, and anititumor properties.

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Conflict of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualization, [I.V.]; methodology, [-]; validation, [-]; formal analysis, [I.V.; Yu.S.]; investigation, [-]; resources, [-]; data curation, [-]; writing – original draft preparation, [I.V.; Yu.S.; S.S.]; writing – review and editing, [I.V.; Yu.S.; S.S.]; visualization, [-]; supervision, [I.V.; Yu.S.]; project administration, [Yu.S.]; funding acquisition, [-].

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ІОНОФОРНІ АНТИБІОТИКИ ТА ШИШКИ ХМЕЛЮ ЯК РЕГУЛЯТОРИ ТРАВЛЕННЯ Й ОБМІНУ РЕЧОВИН У ЖУЙНИХ ТВАРИН

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Проаналізовано загальну характеристику іонофорних антибіотиків і механізми їхньої антимікробної дії.

Відомі два типи іонофорних антибіотиків: ті, що транспортують іони крізь мембрану, і ті, що утворюють канал у клітинній мембрані, через який іони проходять. До першої групи належать антибіотики-іонофори, які застосовують у тваринництві (монензин, лазалоцид, саліноміцин, наразин). Вони синтезуються бактеріями роду *Streptomyces*.

Бактеріальні клітини та рідина рубця відрізняються іонним складом, який регулюється активним транспортом іонів. У результаті цитоплазма бактерій містить більше іонів калію, а рідина рубця, навпаки, – більше іонів натрію. Іонофори транспортують калій усередину клітини та видаляють натрій назовні. Бактерії намагаються виправити такий дисбаланс, і цей процес використовує енергію АТФ. У бактеріальної клітини виникає дефіцит енергії, і вона гине.

Іонофорні антибіотики діють лише на грампозитивні бактерії рубця жуйних тварин, оскільки не можуть проникнути крізь клітинну стінку грамнегативних бактерій. Отже, відбувається селективне знищення деяких видів бактерій, найчутливішими серед яких є т. зв. гіперамонійпродукуючі бактерії (ГАБ).

Іонофорні антибіотики – це важливий антикетотичний засіб, оскільки вони знижують концентрацію β-гідроксибутирату і неетерифікованих жирних кислот у крові жуйних.

У перехідний період у корів порушується обмін речовин і знижується резистентність, тому вони більш схильні до інфекційних захворювань. Застосування іонофорних антибіотиків впливає на імунну функцію та стійкість до запальних процесів, що обумовлено опосередкованим впливом, пов'язаним із меншим патологічним ефектом, спричиненим кетозом і стеатозом.

Антибіотики-іонофори зменшують негативний енергетичний баланс і його патологічний вплив на обмін речовин. Впливу іонофорних антибіотиків на молочну продуктивність корів переважно не фіксують або він незначний.

Дано характеристику біологічно активних речовин шишок хмелю. Шишки хмелю містять біологічно активні компоненти, близькі за дією до іонофорних антибіотиків. Це пренільовані флавоноїди: гумулон (α-кислота), лупулон (β-кислота) та їхні похідні. Ці компоненти шишок хмелю можна розглядати як потенційну заміну іонофорних антибіотиків. Зокрема, лупулон і деякі інші компоненти шишок хмелю також пригнічують життєдіяльність грампозитивних бактерій, викликаючи реакції, подібні до іонофорних антибіотиків. Крім того, шишки хмелю містять багато інших біологічно активних сполук: феноли, ефірні олії, смоли, що мають протимікробну, антиоксидантну, седативну, фітоестрогенну, інсуліностимулюючу, імуномодулюючу та протипухлинну дію.

Ключові слова: жуйні, рубець, іонофорні антибіотики, шишки хмелю

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