Secondary plant compounds to reduce the use of antibiotics?

by Dr Inge Heinzl and Dr Thilo Borchardt, EW Nutrition.

The discovery of penicillin in 1929 by Alexander Fleming was the starting point for the triumph of antibiotics. But even then, during an interview with the New York Times, Fleming already pointed out the possibility of resistance.

Antibiotics were and are the method of choice against bacterial diseases and they additionally show a positive influence on the performance parameters like daily gain and feed conversion in farm animals.

These effects are particularly ascribed to the change of the gut flora. The composition of the intestinal flora influences the development of the gut as well as the immune system of the animal. From the 1950s onwards antibiotics were routinely used in animal husbandry to increase performance.

Antibiotics enabled us to treat formerly lethal, bacterial diseases. Nowadays infectious diseases do not play a decisive role with regard to the most frequent causes of death in the industrialised world (1-5%). In developing countries, in contrast, with up to more than 40%, they are still the most common cause of death.

Whilst we are aware of this problem and are trying to reduce the use of antibiotics, yet antibiotics are still needed. We should not let this powerful weapon become blunt.

Antibiotics are promoting the development of resistance:

- Pathogenic bacteria possessing resistance genes are conserved and competitors that do not possess these genes are killed.
- Useful bacteria possessing the resistance genes are conserved and serve as a gene pool of antibiotic resistance for others.
- Useful bacteria without resistance, which probably could keep the pathogens under control, are killed.

"Without urgent, coordinated action by many stakeholders, the world is headed for a post-antibiotic era, in which common infections and minor injuries which have been treatable for decades can once again kill. Effective antibiotics have been one of the pillars allowing us to live longer, live healthier, and benefit from modern medicine. Unless we take significant actions to improve efforts to prevent infections and also change how we produce, prescribe and use antibiotics, the world will lose more and more of these global public health goods and the implications will be devastating."

Dr Keiji Fukuda, WHO's Assistant Director-General for Health Security (WHO Report, April 2014).

In this article laboratory trials are presented which show the good efficacy of secondary plant compounds against commonly occurring pathogens in farm animals.

Antibiotic resistance

Some bacteria, due to mutations, are less sensitive to certain antibiotics than others. That means that, if these special antibiotics are used, the insensitive ones survive.

Due to the fact that their competitors have been eliminated, they are able to reproduce better. This resistance can be transferred to daughter cells by means of 'resistance genes'.

Other possibilities are the intake of these resistance genes from dead bacteria (1), through a transfer of these resistance genes by viruses (2) or from other bacteria by means of horizontal gene transfer (3) (see Fig. 1).

Every application of antibiotics causes a selection of resistant bacteria. A short term use or an application at low dosage give the bacteria a better chance to adapt, promoting the generation of resistance.

Measures

In the EU about 25,000 people die of infections from resistant germs every year, but the estimated number of unreported cases is probably a lot higher because of incomplete documentation.

In 2011, antibiotic resistance was the main agenda point of the World Health Day organised by the WHO. In August last year the US Food and Drug Administration held a general meeting with the topic 'Antimicrobial Resistance Monitoring in the Food Supply'.

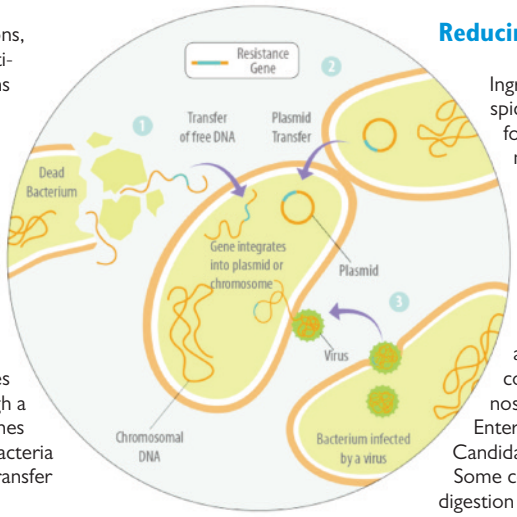

Fig. 1. Resistance genes.

Since 2006 antibiotic growth promoters have been banned in the EU, but already starting from 2000 certain growth promoters were prohibited successively or have not been used anymore because of lack of acceptance by the consumer.

There are already comprehensive regulations in place concerning the use of antibiotics in farm animals. Stated in these directions is that such important treatment tools must no longer be applied prophylactically to healthy animals.

Yet, the metaphylactic use of antibiotics is still allowed. This means that, if there is one animal in one production unit showing signs of sickness, the others can be treated prophylactically with the antibiotic.

If 50,000 broilers are kept together in one barn, the possibility that one chick becomes sick, is rather high. One possibility to limit the development of new resistance is the global restriction of antibiotic use in animal production to pure therapeutic application.

This requires a very good hygiene management, as veterinary medicine here often has to compensate deficits. It has often been demonstrated that the worse hygienic conditions are, the better the effects when antibiotics are applied.

Reducing antibiotics

Ingredients from herbs and spices have already been used for centuries in human medicine. In modern animal husbandry they are also on the rise. A lot of secondary plant compounds have antimicrobial characteristics, for example carvacrol and cinnamon aldehyde. They effectively act against salmonella, E. coli, Pseudomonas aeruginosa, Klebsiella pneumoniae, Entero- and Staphylococcus and Candida albicans.

Some compounds influence digestion and others act as antioxidants. An optimal combination has both – positive influence on health and performance.

Comprehensive knowledge about the single ingredients, their possibly negative but also positive interaction (synergies) is essential for solution orientated developments. Today secondary plant compounds are offered on the market as granulates or as microencapsulated and liquid products respectively.

Granulates and microencapsulated products are suitable for the addition to feed. In acute situations, however, a liquid version would be

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	Secondary plant compounds (Activo liquid)		
Central poultry diagnostic laboratory, Kondapur, Hyderabad, India	10%	2%	1%
E. coli	++	+	+
Proteus vulgaris	+	+	+
Pseudomonas fluorescens	++	+	-
Salmonella pullorum	++	++	+
Salmonella gallinarum	++	++	+
Staphylococcus aureus	+++	++	++
Zone of inhibition: +++ = 22-29mm	++ = 15-21mm	+ = 10-14mm	– = <10mm

Table 1. Inhibition of field isolated standard pathogens by different concentrations of Activo liquid (Agar Diffusion Test).

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more appropriate for a quick application in the waterline.

The antimicrobial effects of secondary plant compounds against reference livestock pathogens in vitro

In so called 'agar diffusion tests' (method available on request), the sensitivity of reference strains – representative for different species of pathogens relevant for farm animals – were evaluated with different concentrations of a special blend of secondary plant compounds.

The effectiveness of the active substances was determined by the extent to which they prevent the development of bacterial overgrowth.

The diameter of a bacteria free zone around an applied substance can be translated into the antimicrobial efficacy against a densely grown bacterial population on a petri dish.

The bigger the bacteria free zone, the higher the antimicrobial effect.

In this trial, the blend of secondary plant compounds and organic acids (Activo liquid) showed an antimicrobial effect on all tested bacteria occurring in farm animals.

The degree of growth inhibition positively correlated with the concentration of Activo liquid (see Table 1).

Sensitivity of antibiotic resistant field pathogens to Activo liquid in vitro

It cannot be excluded that resistant pathogens not only acquired effective weapons to render antibiotics harmless, but also developed general mechanisms to get rid of otherwise harmful substances. In a follow up laboratory trial we evaluated whether the Activo liquid composition is as effective against ESBL producing E. coli and Methicillin resistant S. aureus as to non-resistant members of the same species.

Trial design

Farm isolates of four ESBL producing E. coli and two Methicillin resistant Staphylococcus aureus strains were compared to non resistant reference strains of the same species with respect to their sensitivity against Activo liquid.

In a Minimal Inhibitory Concentration Assay (MIC) under approved experimental conditions (Vaxxinova Diagnostic, Muenster, Germany) the antimicrobial efficacy of Activo liquid in different concentrations was evaluated.

The efficacy of secondary plant compounds (Activo liquid) against the tested strains could be demonstrated in a concentration dependent manner with antimicrobial impact at higher concentrations and bacteriostatic efficacy in dilutions up to 0.1% (ESBL) and 0.2% (MRSA) (Table 2).

Conclusion

In order to contain the emergence and spread of newly formed resistance mechanisms it is of vital importance to reduce the use of antibiotics.

A general rethinking is necessary to rise to the challenge and give new approaches a chance.

These approaches however, will only be successful in combination with good management practices.

Antibiotics must not be used for growth promotion or metaphylactic treatment, but only as a pure curative instrument.

In in vitro trials the liquid blend of secondary plant compounds and organic acids (Activo liquid) showed promising antimicrobial effects against prevalent livestock pathogens.

This indicates the possibility to use secondary plant compounds for prophylaxis and for metaphylaxis and to reduce the use of antibiotics with their help.

The positive influence on performance parameters, as shown in many other trials, is an additional incentive for farmers to use these flavouring substances in the feed.

The high efficacy of secondary plant compounds against ESBL producing Escherichia coli and MRSA can be a further step towards the reduction of antibiotic use.

Due to the specific mode of action of antibiotics, resistance mechanisms are likely to emerge, since only subtle changes in the pathogen can lead to the generation of antibiotic resistance. Secondary plant compounds, however, normally act via several modes of action making it more difficult for bacteria to develop resistance. Therefore they can be a safe supplement for the control of pathogenic organisms. ■

Table 2. Efficacy of secondary plant compounds against ESBL-producing E. coli and MRSA (Minimal Inhibitory Concentration Assay; MIC).

	Secondary plant compounds (Activo liquid)			
Laboratory: Vaxxinova, Muenster, Germany	0.1%	0.2%	0.4%	1%
E. coli reference ATCC25922	+	++	++	++
ESBL 1 (Pig)	-	++	++	++
ESBL 2 (Pig)	+	++	++	++
ESBL 3 (Poultry)	+	++	++	++
ESBL 4 (Poultry)	-	++	++	++
S. aureus reference ATCC29213	-	+	+	++
MRSA 1 (Pig)	-	+	+	++
MRSA 2 (Pig)	-	+	+	++
	- No effect	+ Growth inhibiting	++ Bactericide