Chapter

Phytochemicals as Alternatives to Antibiotics in Animal Production

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Abstract

Despite the continuous improvement of feed diets and recipes, animal health problems persist. For their treatment, antibiotics and chemotherapy have been shown to have side effects hard to control. The antibiotic residues in animal products may endanger human health. Since the antibiotics were restricted in animals' diets, which were previously used to keep under control digestive and respiratory pathologies, as well as allergies, so the researchers began to search for natural alternatives. Thus, it was developed the concept of phytoadditives, and these natural plant extracts are gaining ground in animal farming. Since then, more and more animal breeders and farms are willing to use various types of phytoadditives. This chapter aims to present the most widely used phytochemicals in animal nutrition, their effects on animal production and health, and to make some recommendations on the use of phytochemicals in farm animals' diets.

Keywords: phytochemicals, antibiotics, antimicrobial resistance, poultry, pigs, ruminants

1. Introduction

Antibiotics, since their discovery in the 1920s, have had a significant contribution to the economic growth of animal production. They were used as food supplements in sub-therapeutic doses in order to increase and make food conversion more efficient by preventing infections [1]. The antibiotics used as feed additives in the animal industry have contributed to the intensification of modern animal production. Starting with the intensification of animal husbandry, there is a constant concern regarding the large-scale use of food antibiotics that can lead to the development of the phenomenon of antimicrobial resistance. This represents a potential threat to human health [2, 3].

Due to the emergence of the phenomenon of antimicrobial resistance, the World Health Organization (WHO) established guidelines and recommendations to stop the use of antibiotics as growth promoters in 1997. One year later, in 1998, the EU banned the first phase for poultry, and the use of antibiotics as additives in their feed later in 2006, establishing a complete ban on the use of prophylactic antibiotics in the feed of all animals [4–6].

Consequently, various alternatives were sought to reduce the use of antibiotics in animal production, in order to maintain their health and performance. The types of additives available to increase animal productivity while maintaining the health of the human population include probiotics and prebiotics, plant extracts, essential oils, dietary fiber and enzymes, antimicrobial peptides, functional amino acids, hyperimmune antibodies from eggs, clays, and/or metals [2, 3, 7–10]. The optimal combinations of different compounds, together with good management and breeding practices, can be the key to intensifying the performance and productivity of animals with the aim of reducing and/or replacing antibiotics in the animal industry [3].

Phytochemicals have been used in the past to treat various ailments. Some compounds of plant origin, such as phenols, organosulfur compounds, terpenes, and/or aldehydes, have different properties: antimicrobial (antibacterial, antifungal, antiviral, and antiprotozoal), antioxidant, immunomodulatory, or mycotoxin detoxifying, as well as maintaining the integrity of the intestinal mucosa and maintaining the balance of the digestive microbiota [10–13]. Phytochemical substances are characterized by the fact that they have low residues, do not develop resistance or side effects, and can be used for prophylactic or therapeutic purposes against pathogenic bacteria. It has also been shown to act as functional additives by improving animal health and growth performance.

Phytochemical compounds have great potential as substitutes for classic antibiotics and can enter the structure of feed additives with a promising effect on animal production. Developing new classes of antibiotics around a phytochemical core may be the best solution to the growing antibiotic resistance crisis [10, 14].

2. The most common types of potentially pathogenic bacterial species

Several studies carried out in order to evaluate the antimicrobial activity of plants have demonstrated their effectiveness against different pathogens. The use of plant extracts aims to obtain natural additives with antimicrobial properties that could be used in the feed mixture, to determine the reduction of antibiotic consumption and the use of more natural diets for animals [15].

According to the European Food Safety Authority (EFSA) report in 2012 on zoonotic pathogens of food origin, *Campylobacter jejuni*, *Salmonella*, *Escherichia coli,* and *Listeria monocytogenes* have been described with increased incidence in animal flocks and raw animal products [16].

Campylobacter can be found in the intestinal tract of animals and in the oral cavity of humans, having the ability to cause disease in both hosts [17]. *Campylobacter* infection in human populations results from the handling or ingestion of undercooked poultry contaminated with this pathogen. In the United Kingdom, it is estimated that 80% of raw meat is contaminated with these bacteria [6, 18]. Thus, *C. jejuni* was the cause of the majority of confirmed zoonotic cases in humans in 2010, registering a significant increase in human campylobacteriosis reported by the European Union. The main reservoir for these zoonoses continues to be chicken meat, in the European Union 30% of fresh chicken meat units are positive for *Campylobacter*, with a variation between 3.1% and 90.0% [16].

Salmonella, the causative agent of the disease salmonellosis, is usually found in the intestinal tract of animals and humans, where it infects foods, such as poultry and eggs. Salmonellosis, as a disease transmitted through the food of animal origin, is known as a public health problem due to its high morbidity and mortality among humans [6]. Although in recent years, a reduction in salmonellosis cases has been observed, through good management of the control programs of this infection, salmonellosis still remains an important disease with an economic impact, by affecting the productive performance of animals and by making the human population sick due to consumption of contaminated eggs and meat [15, 19]. *Salmonella* is most often detected in the fresh carcass of broilers. In the European Union, the proportion of positive samples for *Salmonella* varies between 0.2% and 27.8%, with an average value of 1.2%. In humans, cases of *Salmonella enteritidis* disease are most commonly associated with the consumption of contaminated eggs and poultry meat, while *Salmonella typhimurium* cases are mostly associated with the consumption of contaminated meat from pork, poultry, and cattle [16].

E. coli (*E. coli*) is normally part of the natural intestinal microbiota of humans and animals, being the most dominant aerobic bacteria with 10^6–10^9 colony forming units (UFC) per cm of the intestine of poultry (chicken and turkey). This bacterium is one of the first species to colonize the human and animal intestine [6, 20]. Ingestion of animal foods containing antibiotic-resistant *E. coli* becomes a source of antimicrobial-resistant bacteria in the human gut, and this may affect the use of medicinal antibiotics or cause opportunistic diseases in the future [21]. In 2005, at the European level, 3314 cases of *E. coli* VTEC illnesses were reported, mainly associated with the consumption of fresh beef [22]. Therefore, there is a need for alternative control measures, such as the use of natural phytochemicals, that do not develop resistance [6].

The genus *Listeria* has 17 species, of which only two species are considered pathogenic, producing the disease called listeriosis. *L. monocytogenes* is considered pathogenic for humans and several animal species, while *Listeria ivanovii* is pathogenic, especially for ruminants and occasionally for humans [23, 24]. Due to the increased risk of infection with *L. monocytogenes* for the unborn, infants, and the elderly, it is considered one of the most important zoonotic agents with implications for food safety through the consumption of processed preparations of animal origin [25]. As a result of poor-quality control measures during food processing/handling and packaging, contamination with *L. monocytogenes* can occur, creating public health concerns, considering that 4.9% of pre-prepared animal products are contaminated with this bacterium [24–27].

One of the biggest challenges in the meat industry is keeping products safe without being contaminated with pathogens. Before slaughtering the animals, a number of measures are used to reduce the intestinal passage of pathogens, such as careful formulation of the diet regarding the macronutrient content, the use of antibiotics and additives that stimulate animal growth, phenolic antimicrobial compounds, organic acids, and acidifying products in animal feed, used on a large scale throughout the world [28]. It has been shown that some plants and their extracts stimulate the growth of certain bacteria, having a prebiotic effect. This effect, combined with the antimicrobial action of some extracts or essential oils, changes the intestinal microflora and reduces the microbial load by suppressing the proliferation of bacteria. There are some claims that some phytochemicals increase the turnover of the intestinal mucosa and prevent the attack of pathogenic bacteria by maintaining a healthier commensal population. In this context, it is very interesting to consider the use of natural plant extracts, essential oils, or some of their components as indispensable ingredients in the formulation of diets for animals, in order to reduce the excretion of pathogenic bacteria [6].

3. The most common plants with antimicrobial activity

The extensive, inappropriate, irregular, and indiscriminate use of antibiotics has led to the emergence of antimicrobial resistance [29]. Antibiotic resistance can lead to the inability to medically treat various infectious diseases [30, 31]. This situation is worrying and considered by the World Health Organization (WHO) as perhaps the most urgent problem facing medical science [32, 33]. Considering the lack of a new generation of antibacterials, as well as the increase in resistance of the existing generations of antibiotics, plants could represent a solution to this shortcoming [31].

According to the World Health Organization (WHO), there are more than 1340 plants with defined antimicrobial activity and more than 30,000 antimicrobial compounds that have been isolated from plants [32, 34]. Plants have the ability to develop secondary metabolites with various functions for the plant, such as a role in defending against pests, adapting to the environment, or providing the plant with a specific smell and taste. These compounds can be classified from a chemical point of view into three classes, recognized for their biological activity: terpenoids, phenolics, and alkaloids [31, 35, 36]. Thus, plants can represent an almost unlimited source of bioactive compounds and their use as antimicrobial agents can be exploited in different ways, considering that natural antimicrobial agents can act alone or in different combinations (**Table 1**) [37–39].

Currently, there is more and more research on the antimicrobial effect of plant extracts from different regions of the world. Most studies have analyzed a group of plants or even a single plant, regarding their effect on various infectious diseases in various species of animals, either with a curative or preventive effect. Further, the most common species of plants recognized as having antibacterial action are presented.

Echinacea purpurea is a plant from the daisy family, frequently used in traditional medicine for its multiple health benefits [40]. The genus *Echinacea* has medicinal value due to the contained chemical components [41]. The compounds can be isolated from the roots or aerial parts of plants and are mainly represented by volatile compounds, alkyl amides, polyphenols, caffeic acid derivatives, polysaccharides, alkaloids, and many other different structures [42–44]. Regarding the volatile compounds, the essential oils are considered as potential medicinal agents [44]. For *E. purpurea*, the main compounds found in the essential oils of leaves and roots include germacrene D (18.1% and 20.3%), naphthalene (7.8% and 6.4%), caryophyllene oxide (11.3% and 12.2%), α-phellandrene (6.9% and 6.6%), α-cadinol (9.1% and 5.9%), and caryophyllene (4.5% and 4%) [45]. It can be highlighted that the essential oils obtained from *E. purpurea* present a great variability of compounds in their chemical composition. However, the sesquiterpene germacrene D is the most abundant compound [44].

The medicinal importance of *Echinacea* derives from its antimicrobial properties against bacteria, fungi, and opportunistic diseases, so that it constitutes a valuable alternative to semisynthetic antibiotics. These properties are due to its ability to stimulate the immune system, producing more white blood cells. Echinacein, caffeic acid, and chicory are the components that produce this stimulation. It has also been proven its ability to stimulate the production of interferon, a protein that the body itself produces to neutralize viruses [46].

Echinacea has proven to be effective in treating various animal diseases. Some pathologies respond to *Echinacea* treatment, either through the direct antiviral or antibacterial effect, or through the anti-inflammatory effect. In addition, some organisms, especially bacteria, such as *Salmonella* and *Campylobacter* species, can

Common name	Scientific name	Compound	Classic	Activity
Alfalfa	*Medicago sativa*	—		Gram-positive organisms
Allspice	*Dioica allspice*	Eugenol	Essential oil	General
Aloe	*Aloe barbadensis*, *Aloe vera*	Latex	Complex mixture	*Corynebacterium, Salmonella, Streptococcus*
Apple	*Malus sylvestris*	Phloretin	Flavonoid derivatives	General
Ashwagandha	*Withania somniferum*	Withaferin A	Lactones	Bacteria, fungi
Aveloz	*Euphorbia tirucalli*	—		*S. aureus*
Bael tree	*Aegle marmelos*	Essential oil	Terpenoid	Fungous
Pear conditioner	*Bites the charantia*	—		General
Barberry	*Berberis vulgaris*	Berberine	Alkaloid	Bacteria, protozoa
Basil	*Ocimum basilicum*	Essential oils	Terpenoids	*Salmonella*
Bay	*Laurus nobilis*	Essential oils	Terpenoids	Bacteria, fungi
Betel pepper	*Betel pepper*	Catechols, eugenol	Essential oils	General
Black pepper	*Piper nigrum*	Piperine	Alkaloid	Fungi, *E. coli Lactobacillus*
Blueberries	*Vaccinium* spp.	fructo	Monosaccharides	*E. coli*
Brazilian pepper tree	*Schinus terebinthifolius*	Terebinthone	Terpenoids	General
Buch	*Barosma setulina*	Essential oil	Terpenoid	General
Burdock	*Arctium lappa*		Polyacetylenes, tannins, terpenoids	Bacteria, fungi, viruses
Buttercup	*Ranunculus bulbosus*	Protoanemonin	Lactones	General
Carraway	*Carum carvi*		Coumarins	Bacteria, fungi, viruses
Cascara Sagrada	*Rhamnus purshiana*	Tannins	Polyphenols	Viruses, bacteria, fungi
Cashews	*Anacardium pulsatilla*	Salicylic acids	Polyphenols	*Propionibacterium acnes,* Bacteria, fungi
Castor bean	*Ricinus communis*	—		General
Ceylon cinnamon	*Cinnamomum verum*	Essential oils, others	Terpenoids, tannins	General
Chamomile	*Matricaria chamomilla*	Anthemic acid	Phenolic acid	*Mycobacterium tuberculosis, S. aureus, Salmonella typhi*
		—	Coumarins	Viruses

Common name	Scientific name	Compound	Classic	Activity
Chaparral	*Larrea tridentata*	Nordihydroguaiaretic acid	Lignans	Skin bacteria
Chili peppers, paprika	*Capsicum annuum*	Capsaicin	Terpenoid	Bacteria
Cloves	*Syzygium aromaticum*	Eugenol	Terpenoid	General
Dough	*Erythroxylum coca*	Cocaine	Alkaloid	Bacteria
Cockles	*Agrostemma githago*	—		General
Coltsfoot	*Tussilago farfara*	—		General
Coriander, cilantro	*Coriandrum sativum*	—		Bacteria, fungi
Cranberries	*Vaccinium* spp.	Fructo	Monosaccharides	Bacteria
Dandelions	*Taraxacum officinale*	—		*C. albicans, Saccharomyces cerevisiae*
Dill	*Anethum graveolens*	Essential oil	Terpenoid	Bacteria
Echinacea	*Echinaceae angustifolia, E. purpurea*	—		General
Eucalyptus	*Eucalyptus globulus*	Tannin	Polyphenol	Bacteria, viruses
		—	Terpenoid	
fava bean	*Faba bean*	Fabian	Thionin	Bacteria
Gamboge	*Garcinia hanburyi*		Resin	General
Garlic	*Allium sativum*	Allicin, ajoene	Sulfoxides	General
			Sulfated terpenoids	
Ginseng	*Panax notoginseng*		Saponin	*E. coli*, *Sporothrix schenckii*, *Staphylococcus*,
Glory lily	*Glorious gorgeous*	Colchicine	Alkaloid	General
Goldenseal	*Hydrastis canadensis*	Berberine, hydrastine	Alkaloids	Bacteria, *Giardia duodenale,* trypanosomes, Plasmodia
gotu kola	*Centella asiatica*	Asiatocosides	Terpenoid	*Mycobacterium leprae*
Grapefruit peel	*Citrus paradise*		Terpenoid	Fungous
Green tea	*Camellia sinensis*	catechins	Flavonoids	General, *Shigella, Vibrio, S. mutans, Viruses*
Harmel, rue	*Peganum harmala*	—		Bacteria, fungi
Hemp	*Cannabis sativa*	β-Resercyclic acid	Organic acid	Bacteria and viruses
Henn	*Lawsonia inermis*	Gallic acid	Phenolic	*S. aureus*

Common name	Scientific name	Compound	Classic	Activity
Whoops	*Humulus lupulus*	Lupulonehumulone	Phenolic acids	General
		—	(Hemi)terpenoids	
Horseradish	*Rustic armor*		Terpenoids	General
Hyssopi	*Hyssopus officinalis*	—	Terpenoids	Viruses
(Japanese) herb	*Rabdosia trichocarpa*	Trichorabdal A	Terpenes	*Helicobacter pylori*
Lantana	*Lantana chamber*	—		General
—	*L.*	Lawson	Quinones	*M. tuberculosis*
Lavender-cotton	*Santolina chamae cyparissus*	—		Gram-positive bacteria, *Candida*
Lemon balm	*Melissa officinalis*	Tannins	Polyphenols	Viruses
Lemon verbena	*Aloysia triphylla*	Essential oil	Terpenoid	*E. coli*, *M. tuberculosis*, *S. aureus*, *Ascaris*
Licorice	*Glycyrrhiza glabra*	Glabrol	Phenolic alcohol	*S. aureus*, *M. tuberculosis*
Lucky nut, yellow	*Thevetia peruviana*	—		*Plasmodium*
Poppy, nutmeg	*Myristica fragrans*	—		General
Marigold	*Calendula officinalis*	—		Bacteria
Mesquite	*Prosopis juliflora*	—		General
Mountain tobacco	*Arnica montana*	Helanins	Lactones	General
Oak	*Quercus rubra*	Tannins	Polyphenols	General
		Quercetin	Flavonoids	
Olive oil	*Olea europaea*	Hexanal	Aldehydes	General
Onion	*Allium onion*	Allicin	Sulfoxides	Bacteria, *Candida*
Orange peel	*Citrus sinensis*	—	Terpenoid	Fungous
Oregon harrows	*Mahonia aquifolia*	Berberine	Alkaloid	*Plasmodium*, Trypanosomes, general
Pao d'arco	*Tabebuia*	Sesquiterpenes	Terpenoids	Fungous
Papaya	*Carica papaya*	Latex	Mix of terpenoids, organic acids, alkaloids	General
Pasque-flower	*Anemone pulsatilla*	Anemonins	Lactones	Bacteria
Peppermint	*Peppermint*	Menthol	Terpenoid	General
Periwinkle	*Vinca minor*	Reserpines	Alkaloid	General
Peyote	*Lophophora williamsii*	Mescaline	Alkaloid	General
The poinsettia	*Euphorbia pulcherrima*	—		General

Common name	Scientific name	Compound	Classic	Activity
Poppy	*Papaver somniferum*	Opium	Alkaloids and others	General
Potato	*Solanum tuberosum*	—		Bacteria, fungi
Prostrate knotweed	*Polygonum aviculare*	—		General
Purple prairie clover	*Petalostemum*	Petalostemumol	Flavonoids	Bacteria, fungi
Quinine	*Cinchona* sp.	Quinine	Alkaloid	*Plasmodium* spp.
Rauvolfia, chandra	*Rauvolfia serpentina*	Reserpines	Alkaloid	General
Rosemary	*Rosmarinus officinalis*	Essential oil	Terpenoid	General
Sainfoin	*Onobrychis viciifolia*	Tannins	Polyphenols	Ruminal bacteria
Sassafras	*Sassafras albidum*	—		Helminths
Savory	*Mountain saturation*	Carvacrol	Terpenoid	General
Senna	*Cassia angustifolia*	Rhein	Anthraquinone	*S. aureus*
Smooth hydrangea, seven barks	*Hydrangea arborescens*	—		General
Snake plant	*Rivea corymbosa*	—		General
St. John's wort	*Hypericum perforatum*	Hypericin, others	Anthraquinone	General
Sweet flag, calamus	*Acorus calamus*	—		Enteric bacteria
Tansy	*Tanacetum vulgare*	Essential oils	Terpenoid	Helminths, bacteria
Tarragon	*Artemisia dracunculus*	Caffeic acids, tannins	Terpenoid, Polyphenols	Viruses, helminths
Thyme	*Thymus vulgaris*	Caffeic acid	Terpenoid	Viruses, bacteria, fungi
		Thymol	Phenolic alcohol	
		Tannins	Polyphenols	
		—	Flavones	
Tree bard	*Podocarpus nagi*	Totarol	Flavonoids	*P. acnes*, other gram-positive bacteria
		Nagilactone	Lactones	Fungous
Tua-Tua	*Jatropha gossyphiifolia*	—		General
Turmeric	*Curcuma longa*	Curcumin	Terpenoids	Bacteria, protozoa
		Turmeric oil		
Valerian	*Valeriana officinalis*	Essential oil	Terpenoid	General

Common name	Scientific name	Compound	Classic	Activity
Willow	*Salix alba*	Salicin	Phenolic glucosides	General
		Tannins	Polyphenols	
		Essential oil	Terpenoid	
Wintergreen	*Gaultheria procumbens*	Tannins	Polyphenols	General
Woodruff	*Gallium odoratum*	—	Coumarin	General, Viruses
Yarrow	*Achillea millefolium*	—		Viruses, helminths
Yellow dock	*Rumex crispus*	—		*E. coli, Salmonella, Staphylococcus*

Selection of data from reference [39].

Table 1.
Plants with antimicrobial activity.

also be important sources of infection for humans through contaminated food. Some researchers, through numerous published studies, have emphasized the importance of evaluating herbal preparations as substitutes for antibiotics that are frequently used in farm animals [46–48]. *Echinacea* extracts have a modern tradition of veterinary applications [49, 50] existing studies similar to those described for human pathologies, or even controlled studies in animals. Thus, it was concluded that *Echinacea* treatments are safe and free of significant side effects. This conclusion is also supported by studies in mice and rats in which no toxic effects were observed [46, 51]. In addition to controlling infections in animals, herbal preparations have also proven their effectiveness in stimulating immunity, supporting growth, and improving performance [46, 52].

Ginger, the rhizome of *Zingiber officinale*, frequently used as a spice is also used to cure various diseases [53]. It plays an important role in cancer prevention by inactivating and/or activating different molecular pathways. Different studies highlight the therapeutic role of ginger in the management of infectious diseases by modulating biological activities, through anti-inflammatory and antioxidant activities [54]. Ginger contains many active ingredients, including terpenes and oleoresin, included in the generic name of ginger oil. Ginger also contains volatile oils of approximately 1–3% and non-volatile components with a pungent smell and taste—oleoresin [55]. The major components identified from the terpene category are sesquiterpene hydrocarbons and phenolic compounds, such as gingerol and shogaol. Also, lipophilic extracts of rhizomes have been isolated, with the production of potentially active gingerol, which can be converted into shogaol, zingerone, and paradol [54].

Previous research has shown that ginger and its compounds play a vital role in preventing microbial growth or acting as an antimicrobial product. The studies carried out support the antimicrobial activity of ginger against *E. coli*, *Salmonella typhi*, and *Bacillus subtilis*. It has also been proven that ginger also has antifungal properties, the ethanolic extract from a ginger powder having a pronounced inhibitory action against *Candida albicans* [54, 56, 57]. The main constituents, such as gingerol, showed antibacterial activity against oral bacteria, proving to be an active inhibitor for *Mycobacterium avium* and *Mycobacterium tuberculosis* [54, 58, 59].

There are studies on the use of natural extracts based on ginger and its derivatives in animal feed, as feed additives for their effects on growth performance, production quality, health as well as economic efficiency [60, 61]. The ginger essential oil has proven strong antimicrobial action against most pathogenic microorganisms, bacterial (*Staphylococcus aureus*, *E. coli,* and *Pseudomonas aeruginosa*) and fungal (*Aspergillus niger* and *C. albicans*) [62]. Thus, ginger and its compounds can be considered harmless because they do not present acute toxicological side effects. According to several studies, it can be concluded that feed supplements based on ginger positively influence animal growth and carcass development, with a reduction in the amount of abdominal fat. It can also be emphasized that food supplements with ginger have a positive influence on immune and antioxidant function in animals [60, 61].

Oregano (*Origanum vulgare* subsp. *hirtum*) is a plant widely used in cooking, as an aromatic plant, and also frequently used in traditional medicine. The chemical analysis of oregano essential oil highlighted the presence of several ingredients, most of them proving important antioxidant and antimicrobial properties [63]. Carvacrol and thymol, the two main phenols that make up about 78–85% of oregano essential oil, are mainly responsible for antimicrobial activity. Other minor constituents, such as the monoterpene hydrocarbons γ-terpinene and p-cymene, further contribute to the antibacterial activity of the oil [64]. In the scientific literature, there are many publications related to the chemical composition and antimicrobial properties of the essential oil obtained from different species of oregano and their use in different commercial preparations as antibiotics and antioxidants [65–67].

The different species of oregano are one of the most studied herbs used for their antimicrobial activity- antibacterial, antifungal, and antiviral. Among the activities and applications of oregano essential oil reported in the livestock industry and meat production are antioxidant, preservative, antimicrobial, and anticoccidial effects, as well as improving the production of digestive enzymes, stimulating digestion and blood circulation, and improving immune status [68–70]. The improvement of feed utilization efficiency and animal rearing performance could be determined by changes in intestinal morphology, such as the increase in the height of intestinal villi or the intensification of enzyme activity, with the improvement of protein digestibility due to the intervention of chymotrypsin and by the prevention of parasitosis [70–72]. Thus, it can be concluded that oregano essential oil used as a feed additive has beneficial effects on animal health and production.

Rosmarinus officinalis, L. is an aromatic plant with a unique taste and aroma, recognized for its antioxidant properties. Rosemary extracts have been used in the treatment of various diseases due to their hepatoprotective, antiangiogenic effect, or as a curative treatment in Alzheimer's disease [73, 74]. On the other hand, it can be used in food preservation, preventing oxidation and microbial contamination, thus being a potential substitute for reducing synthetic antioxidants in food [75, 76]. EFSA (European Food Safety Authority) analyzed the safety of rosemary extracts [77]. It was concluded that it can be used in considerable amounts, ranging from 0.09 (elderly) to 0.81 (children) mg/kg per day of carnosol and carnosic acid. Currently, in the European Union, rosemary extracts are added to foods and beverages at levels up to 400 mg/kg (as the sum of carnosic acid and carnosol) [78].

R. officinalis is a rich source of phenolic compounds, and their properties are derived from its extracts and essential oils. The polyphenolic profile of this plant is characterized by the presence of carnosic acid, carnosol, rosmarinic acid, and hesperidin as major components. Rosemary essential oil contains mainly 1,8-cineole

(46.4%), camphor (11.4%), and α-pinene (11.0%) [78, 79]. Thus, rosemary oil, thanks to its phytochemical compounds (mainly caffeic acid, rosmarinic acid, and carnosic acid) has antibacterial, antifungal, and antioxidant properties. To support these bioactivities, there are studies that have demonstrated the antibacterial activity of rosemary oil against *E. coli*, *Bacillus cereus*, *S. aureus*, *Clostridium perfringens*, *Aeromonas hydrophila,* and *Salmonella choleraesuis* [78].

Animal studies have proven that rosemary used in smaller amounts in the feed mixture has beneficial effects on the gastrointestinal microbiota ecosystem. Another hypothesis is that the beneficial effects of essential oils result not only from their antimicrobial properties but also from their interference with digestive and absorption processes and with the immune system, improving the productive performance of animals and the state of health, in general [80]. In cows, rosemary leaves can be used to modulate the rumen microbiome and its function, being able to influence the abundance of rumen microbial populations responsible for protein and fiber degradation, and influencing methane and ammonia production [81]. In general, it can be concluded that rosemary extracts and essential oil can be used with confidence as feed additives, as a result of their multiple bioactivities with a favorable influence on production, product quality, and animal quality of life.

Thyme, a species of the genus *Thymus*, is an aromatic and medicinal plant, which includes two representative species *Thymus serpyllum* (wild thyme) and *T. vulgaris* (common thyme) [82]. The essential oil of *T. vulgaris* contains up to 30 monoterpenes, having a different chemical composition of the oils, depending on the area of origin of the plants. Thyme oil is of great commercial interest, being in the top 10 oils worldwide, used as a natural food preservative and aromatic additive to a wide variety of foods and beverages. It has considerable antioxidant, antibacterial, and antifungal effects, and is used as a flavoring in personal care products (soaps, cosmetics, perfumes, etc.) [83, 84].

Thyme essential oil has remarkable antibacterial effects associated with the presence of phenolic components, carvacrol, and thymol. Being rich in phenolic substances, thyme essential oil has the ability to modify both the permeability and the function of cell membrane proteins by penetrating the phospholipid layer of the bacterial cell wall, binding to the proteins, and blocking their normal activity. Due to the variety of molecules in thyme extracts, the antimicrobial activity cannot be attributed to a single mechanism, but to a number of diverse actions at different sites of the bacterial cell components, thus affecting the functions of the cell membrane, cytoplasm, enzymes, fatty acids, proteins, ions, and metabolites. Thus, this essential oil has been shown to have strong bacteriostatic and bactericidal effects against *C. jejuni*, *E. coli*, *S. enteritidis*, *L. monocytogenes,* and *S. aureus* [82].

The composition of thyme essential oil leads to antiseptic, antibacterial, antifungal, antioxidant properties and antimicrobial, anticoccidial, and anti-inflammatory actions in animals as well. Thyme essential oil has been shown to increase the production of digestive enzymes, which in turn improve the digestion of nutrients. This will result in increased weight gain, feed intake, and a better feed conversion ratio [85]. In numerous studies, thyme oil has proven its antibacterial effect, even for multidrug-resistant strains of *Salmonella*, *E. coli*, *Listeria,* or *Campylobacter* [86, 87]. The treatment with thymol oil determines the improvement of the general condition of the animals, through the bacterial balance established at the intestinal level. This fact leads to the obtaining of healthy animal products intended for human consumption.

Therefore, due to an increased demand to develop natural antimicrobial products capable of replacing classic antibiotics and not developing resistance, phytochemical extracts are gaining more and more ground. Thus, researchers are increasingly concerned with isolating and identifying new bioactive chemical compounds from plants to solve the problem of microbial resistance. Currently, approximately 50% of pharmaceutical and nutraceutical preparations are natural compounds and their derivatives [88]. Medicinal plants are an almost unlimited source of bioactive substances, and their capacity as antimicrobial agents can be exploited in different ways [29].

4. The use of plant additives in animals

Phytochemical substances are also called phytobiotic or phytogenic. These are natural bioactive compounds derived from plants and administered in animal feed to increase productivity. Natural alternatives to antibiotics should have the same beneficial effects on growth performance, ensure optimal production, and increase nutrient availability by improving the feed conversion rate based on the modulation of the gut microbiome and immunity [2]. The main bioactive compounds of phytochemicals are polyphenols, and their composition and concentration vary depending on the plant species, plant parts, geographical origin, harvesting season, and environmental factors [2, 3].

Recently, phytochemicals are increasingly used as natural growth promoters in the livestock industry. There are numerous studies that have tested a wide variety of essential oils or plant extracts from different herbs and spices in the diets of farm animals, ruminants, pigs, and poultry, proving a concrete improvement in health by developing innate immunity and reducing the effects negative effects of enteric pathogens, as well as a constant improvement of feed utilization efficiency and animal growth and production performance [89–92].

The mechanism of action of phytochemical substances is very diverse, depending on the concentration of active substances in the finished product used. Their beneficial effects are mainly attributed to their antimicrobial and antioxidant action. By including phytochemical substances in animal diets, the intestinal microbial population is modified and stabilized and the amount of potentially toxic microbial metabolites in the intestines is reduced. Also, due to their direct antimicrobial properties, including against various species of pathogenic bacteria, intestinal stress is reduced, as well as immune stress, thus improving animal performance [93]. Another important benefit of the use of phytoadditives in the current diet is the reduction of oxidative stress, and implicitly, the increase of antioxidant activity at the tissue level, which determines a significant improvement in health status [94]. Phytochemical substances show, including immunomodulatory action, through the rapid proliferation of immune cells, the development of antibody production, and the modulation of cytokines [3, 89, 93].

4.1 The use of phytoadditives in poultry

Until recently, in the poultry industry, enteric diseases, such as necrotic enteritis or coccidiosis, were traditionally controlled with classical antibiotics introduced into animal feed. As a result of the regulation of the use of natural growth promoters, the control of these diseases requires new prevention and treatment strategies with alternative natural sources without antibiotics. A growing number of scientific publications have emphasized the fact that the most important health-supporting action of phytoadditives is represented by their ability to improve the host's defense possibilities against microbial infections [3].

A wide variety of herbs, such as thyme, oregano, rosemary, marjoram, oregano, garlic, ginger, green tea, black cumin, coriander, or cinnamon, have been used in poultry as alternative solutions to stimulate growth. Various other essential oils, such as thymol, carvacrol, eugenol or coriander, garlic, ginger, star anise, cumin, basil, rosemary, turmeric, lemon, and sage, have been used either individually or in mixtures to improve the health and performance of animal husbandry [2]. Also, the use of a mixture based on thymol, cinnamaldehyde, and star anise essential oil improved body weight gain in broilers and improved feed utilization efficiency by improving feed conversion rate [89, 90].

Another method of maintaining health in poultry is represented by the ability of phytochemicals to increase the host's resistance to enteric diseases of various etiologies. An example of such phytoadditives is a mixture of phytonutrients containing carvacrol, cinnamaldehyde, and capsicum, which is the first commercial phytochemical product approved by the EU for use in animal feed. Research that used this product proved a development of innate immunity, and implicitly, an increase in resistance to the actions of enteric pathogens, resulting in a visible improvement in growth performance in broilers, including by improving the efficiency of feed use, nutrient conversion rate, and mortality reduction [2, 89, 92]. Moreover, the phytochemical substances in Hooker chives determined the amplification of the intestinal barrier function, by increasing the expression of proteins at the level of the intestinal mucosa in broiler chickens fed with lipopolysaccharides [95].

Regarding the ability of medicinal plants to activate the immune system, some extracts of dandelion, mustard, and safflower determined the stimulation of innate immunity and the inhibition of the growth of tumor cells in the tested poultry [3]. In another study, it was observed that the most important genetic effect induced by the use of cinnamaldehyde in poultry feed is correlated with the presence of the antigen and the developed humoral immunity, as well as the developed anti-inflammatory response in the case of enteric diseases [96].

The combination of several phytochemicals develops synergistic effects to counteract the negative consequences of enteric infections. The addition of a mixture of capsicum, lentinus, and curcuma to the broiler diet led to a better body mass gain, an increase in the production of serum antibody titers against profilin, as well as a reduction in the number of oocysts eliminated through feces in infected poultry with *E. acervulina*, compared to chicks, fed the control diet [97]. Detailed research on the effects of carvacrol, cinnamaldehyde, and capsicum extract highlighted a regulation of the expression of genes associated with the immunological, physiological, and metabolic status of the investigated chickens [98].

Many studies have demonstrated the beneficial consequences of phytochemicals in preventing diseases or improving the immune response, but few have analyzed the mechanisms underlying these effects. Some phytochemicals inhibit the innate immune response by targeting effects on pathogen pattern recognition receptors or their later developed signaling molecules [3]. In this context, future studies are needed to present the molecular and cellular mode of action of phytochemical substances for the control of diseases in industrial growth.

4.2 The use of phytoadditives in pigs

The weaning period is one of the most difficult and critical stages in the industrial breeding of pigs. The manifestation of its effects depends on several factors, including animal behavior, environmental factors, disease states, immune status, and nutritional balance. During this vulnerable period, the piglets are subjected to an accumulation of stress factors that result in health imbalances, with diarrheal manifestations, which can lead, in a short time, to the death of individuals [99]. In this context, numerous researchers have tried to highlight the beneficial effects of using phytochemical supplements in the feed of weaning pigs. Various studies in pigs have shown that phytochemicals improve intestinal health. The use of a mixture of phytochemical compounds containing carvacrol, cinnamon, and capsicum resulted in the identification of an increase in the amount of stomach contents, which suggests an increased gastric retention time, also obtaining an increased *Lactobacillus*: *Enterobacteria* ratio [3].

During the weaning period, diarrhea produced by *E. coli* is a frequent cause of death in pigs. This frequent pathology causes significant economic losses due to increased morbidity, decreased growth rate, drug treatment costs, and as the case may be, recorded mortality. *E. coli* enterotoxigenic variant is the most dominant and pathogenic type of *E. coli* that causes this type of diarrheal pathologies in piglets during weaning and after weaning [100]. Various phytochemical compounds, including capsicum, turmeric, or garlic extract, were tested in studies of infection with pathogenic *E. coli* in order to evaluate the beneficial effects in improving diarrhea and maintaining intestinal health in weaned pigs [101]. Studies have shown that supplementation with phytochemicals reduced the frequency of diarrhea in pigs, which underlines the fact that the inclusion of phytochemical extracts in pig diets increases the animals' disease resistance. Supplementation with phytochemicals also improved microflora balance and intestinal health, which indicated a reduced score of diarrheal diseases. Also, research on this topic indicates that the inclusion of low doses of phytochemicals in food reduces both systemic and local inflammation caused by *E. coli* infection. Other research on the most common viral infections encountered in pigs has shown that the inclusion of phytoadditives in the daily feed improves the immune response, reduces the viral load, and serum concentrations of inflammatory mediator factors, and decreases the duration of fever in infected individuals [102].

In conclusion, phytochemicals are the ideal compounds to replace antibiotics in order to obtain better health and growth performance in pigs. The potential positive effects of phytochemical extracts may differ due to a very varied chemical composition of the types of plant extracts. This situation requires the selection of suitable phytoadditives according to the purpose for which we want to use them and for the function we want them to fulfill in the body, as alternative sources to classic antibiotics, in the intensive breeding of pigs.

4.3 The use of phytoadditives in ruminants

In ruminants, host and ruminal microorganisms establish a symbiotic relationship through which the animal provides nutrients and fermentation processes suitable for the survival of the microbial population, and the microorganisms synthesize microbial proteins and degrade fibers as protein and energy sources for the host. Volatile fatty acids, resulting from the fermentation of carbohydrates, represent the key element in maintaining the microbial balance at the ruminal level. The possibilities of manipulating the proportions of volatile fatty acids through the use of phytochemical compounds ensure the ruminal health of cows and certify the increase in production for these species [103]. Protein degradation is important to ensuring the nitrogen requirement for the growth and development of the ruminal microbial population. When ammoniacal nitrogen is in excess, it is absorbed through the ruminal wall, converted into urea in the liver, and then excreted through urine. In general, in intensive production systems, as a result of nutritional imbalances, ammoniacal nitrogen in the rumen is produced in excess of the capacity of microorganisms to use it. This results in high production costs and an increase in the amount of nitrogen released into the environment. Therefore, the control of proteolysis, peptidolysis, and deamination are considered elements of interest regarding the modulation of ruminal fermentation [104].

Improving the efficiency of digestion processes in ruminants proves to be the best strategy for developing animal production performance. Therefore, the industry is looking for alternative feeding strategies and/or natural additives that allow to maintain or improve the production level without increasing the cost. Phytochemical substances from plants, including the diet, have the possibility to modify the nutritional value of feed by modulating the digestibility of nutrients in the digestive tract or by improving systemic metabolism. Those phytonutrients that have a strong antimicrobial activity and could cause imbalances in the ruminal microflora should be avoided. Research on alternative sources to antibiotics used as cattle feed supplements needs to be developed based on the use of phytochemical molecules and doses that induce only minor changes in microbial metabolism, but improve their growth rate, resulting in the improvement of the profile of fermentation [103, 104].

If studies on ruminal microbial vitality and action under the effect of phytoadditives have been intensively studied, there are less data on the effects of phytochemicals on productive performance in cows. Cinnamaldehyde supplementation and/or in combination with eugenol can improve milk production in cows, even if the increases are not significant [105]. On the other hand, the capsicum extract has the ability to modulate the immune function in animals by increasing the number of neutrophils and decreasing the lymphocytes when cattle receive their feed capsicum supplements with ruminal protection. In these cases, significant increases in milk production are also recorded, through the influence on carbohydrate metabolism and the redirection of glucose to the mammary gland [106]. This very interesting new application of phytochemical additives presents an opportunity to improve production, not only by reducing the use of classical antibiotics, but also by offering an alternative to the use of synthetic hormones.

These findings show the importance of the ability to establish clear objectives in the identification of alternative natural sources as growth promoters, through the identification of phytoadditives that can maintain the normal functioning of the rumen without affecting the decomposition of nutrients, the balance of the ruminal microbial population or the production of cows.

Finally, it can be emphasized that, although in human medicine, chemical substances derived from plants with strong medicinal properties are frequently used in various clinical studies for the treatment of a wide variety of diseases in humans and in veterinary medicine, research on the beneficial effects of phytochemicals on animal diseases are becoming increasingly widespread, many researchers being more and more interested in testing these substances [2, 3].

5. Conclusions

The antimicrobial activity of plant extracts represents a new hope for combating the danger of establishing the phenomenon of antimicrobial resistance. Through the phytochemical compounds that the plant products contain, they have the ability to fight against microbial agents, through the bactericidal or bacteriostatic action they exert, being also supported by the fact that they do not develop antimicrobial resistance. Phytochemical substances as alternative sources to antibiotics have been intensively studied and seem to be a promising solution due to the beneficial effects on animals and the possibility of eliminating the phenomenon of antibiotic resistance. It must be taken into account, however, that in some cases the effectiveness of phytochemical compounds has only been tested experimentally, outside the real conditions of raising animals, from intensive farms. Thus, it is considered that for the objective evaluation of plant extracts and to be able to take into account the recommendations to be used as phytoadditives, it would be necessary to select those researches carried out under farm conditions, repeated and tested by several authors and which certify close results. In this sense, the testing of phytoadditives should be supported by the management of intensive animal breeding farms in such a way that their practical applicability highlights concrete results. Also, the acceptance of the research results by the competent authorities and the development of a legal basis for use, according to a standardized method, would be imperatively necessary.

Plant extracts have proven great efficiency in supporting growth processes, intensifying productions, preventing illnesses, or treating various pathologies. But, in this continuous mediatization process of increasing the use of phytoadditives, the chemical characteristics of plant compounds and their mode of action, individual or synergistic, must be taken into account. In this sense, animal breeders are recommended to inform themselves very well or to request the advice of specialists before taking the decision to include some phytoadditives in animal diets, especially those with antimicrobial action. A lack of training can cause negative effects on animal health or production, which can also include an economic decline.

In this context, we recommend the use of phytochemicals as feed additives in animal feed, in order to replace antibiotics, eliminate antimicrobial resistance, intensify production, preserve animal welfare and protect animal and human health, after a rigorous analysis of the farm's needs and the expected effects.

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Conflict of interest

The authors declare no conflict of interest.

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