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# Medicinal Plants for Prophylaxis and Therapy of Common Infectious Diseases In Poultry–A Systematic Review of *In Vivo* Studies

## Authors
Patricia Farinacci[1,2], Meike Mevissen[1], Hannah Ayrle[2], Veronika Maurer[2], Tina Sørensen Dalgaard[3], Matthias F. Melzig[4], Michael Walkenhorst[2]

## Affiliations
1  Department of Clinical Research and Veterinary Public Health, Division of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Bern, Bern, Switzerland
2  Department of Livestock Science, Research Institute of Organic Agriculture (FiBL), Frick, Switzerland
3  Department of Animal Science, Aarhus University, Aarhus, Denmark
4  Freie Universität Berlin, Institute of Pharmacy, Berlin, Germany

## Correspondence
Dr. med. vet. Michael Walkenhorst
Forschungsinstitut für biologischen Landbau (FiBL)
Ackerstrasse 113, 5070 Frick, Switzerland
Phone: + 41 (0) 6 28 65 72 86, Fax: + 41 (0) 6 28 65 72 73
michael.walkenhorst@fibl.org

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## ABSTRACT
Medicinal plants for prophylaxis and therapy of common infectious diseases in poultry have been studied for several years. The goal of this review was to systematically identify plant species and evaluate their potential in prophylaxis and therapy of common diseases in poultry caused by bacteria and gastrointestinal protozoa. The procedure followed the recommendations of the PRISMA statement and the AMSTAR measurement tool. The PICOS scheme was used to design the research questions. Two databases were consulted, and publications were manually selected, according to predefined in- and exclusion criteria. A scoring system was established to evaluate the remaining publications. Initially, 4197 identified publications were found, and 77 publications remained after manual sorting, including 38 publications with 70 experiments on bacterial infections and 39 publications with 78 experiments on gastrointestinal protozoa. In total, 83 plant species from 42 families were identified. Asteraceae and Lamiaceae were the most frequently found families with *Artemisia annua* being the most frequently found plant, followed by *Origanum vulgare*. As compared to placebo and positive or negative control groups, antimicrobial effects were found in 46 experiments, prebiotic effects in 19 experiments, and antiprotozoal effects in 47 experiments. In summary, a total of 274 positive effects predominated over 241 zero effects and 37 negative effects. Data indicate that *O. vulgare, Coriandrum sativum, A. annua,* and *Bidens pilosa* are promising plant species for prophylaxis and therapy of bacterial and protozoal diseases in poultry.

## Introduction

Effective safeguarding of poultry health is essential to meet the demand for meat and eggs for human consumption [1]. High stocking density, growth, and laying performance as well as different infectious diseases like colibacillosis, salmonellosis, or coccidiosis are leading to an increase in morbidity and mortality in poultry of all ages. Hence, due to multifactorial circumstances, these infectious diseases create major economic losses [2]. It has been reported that the annual loss due to coccidiosis in poultry production was estimated up to 3 billion dollars worldwide [3, 4]. The use of anticoccidial drugs as well as antimicrobials is still the most widespread measure to control coccidiosis and bacterial infections in poultry. In 2011, more than 40% of all antimicrobials

sold in the UK for use in poultry were classified for the control of coccidian parasites, predominantly Eimeria [3]. In cattle and pigs, 20 000 tons of antimicrobial each were used and for poultry the use of 8905 tons has been estimated in 31 countries in the EU in 2017 [5]. Besides pharmacotherapy, antibiotics were also used for prophylaxis and as a growth-promoting agent to increase productivity in livestock [6, 7]. Use and misuse of antimicrobials may lead to the emergence of antimicrobial-resistant pathogens [6, 8]. In 2016, almost 70 % of *E. coli* isolates from poultry from different EU countries showed antibiotic resistance against amoxicillin; in other countries like the USA, China, or Brazil, *E. coli* isolates showed resistances up to 100 % against different antibiotic drugs [9]. A similar problem could be seen with the resistance against anticoccidial drugs: a study in China showed the development of various degrees of resistance of *Eimeria spp.* against most of the 8 anticoccidial drugs tested [7]. Resistance to the available chemicals has become widespread [3, 6, 10]. Due to the emergence of antimicrobial resistance, the EU Commission set a ban on antibiotics as growth promoters in animal feed in 2006, restricting the use of antibiotics to the sole purpose of veterinary treatment [11].

According to the sales data published from 2011 to 2017 by the European Surveillance of Veterinary Antimicrobial Consumption, a yearly decrease in sales of 32.5 % was observed and the use of antibiotics decreased, and the list of highest critically important antibiotics showed fewer antimicrobials [5]. Anticoccidial drugs, however, are still allowed to be fed for prevention and growth promotor use.

In contrast to the amounts of antimicrobials used in poultry, the variety of antimicrobial veterinary medicinal products registered for use in poultry has decreased and is relatively small. In Switzerland, only 11 veterinary medicinal products against bacteria and coccidia are registered based on the official information system for Swiss veterinary medicinal products "CliniPharm" [12] for poultry. Seven of them are antibiotic drugs, with 4 belonging to the category "highest critically important antibiotic drugs".

The most important bacterial infections that were reported to lead to prominent economic losses in poultry production are salmonellosis, colibacillosis, and clostridiosis [2, 13]. The pathophysiology of those infections is accompanied by several clinical symptoms like anorexia, apathy, diarrhea, reduced performance (egg production, daily weight gain, laying or feed conversion rate), or even mortality [14]. Similar problems can be observed on a global scale with protozoal infections like coccidiosis [13, 14]. Links between coccidiosis and increased colonization with pathogenic bacteria of the intestine have been described [3]. Coccidiosis is an infectious disease of the intestinal tract of wild and domestic animals caused by parasites of the phylum Apicomplexa. Especially *Eimeria tenella* remains highly invasive and is most likely the most important Eimeria species causing chicken coccidiosis [15]. The protozoal pathogens attach to intestinal epithelial cells, enter and replicate in the epithelial cell, leading to a rupture of the cells. This causes an interruption of food intake, dehydration, blood loss, increased mortality, poor growth, and reduced performance [4, 10, 14]. Therapeutic or prophylactic treatments of poultry diseases caused by bacterial and protozoal pathogens should have antibacterial, antiprotozoal, antidiarrheal, anti-inflammatory, antiadhesive, and analgesic properties (▶ **Table 1**).

Numerous plant species were traditionally used by farmers in Europe for prophylaxis and therapy of poultry diseases. In Switzerland, 13 plant species were reported to be used by farmers [16–20]. In a recent literature review about European ethnoveterinary practices, 63 plant species were documented for use in poultry in European countries [21], including the treatment of a variety of diseases like parasitosis and gastrointestinal diseases [17, 21]. For the treatment of digestion problems and inflammation of the digestive tract, the use of a variety of medical plants has been described in recent German textbooks about veterinary herbal medicine [22, 23]. Many herbs have been found efficacious in *in vitro, in vivo,* and/or clinical studies for the treatment of gastrointestinal diseases, and many different herbal compounds have been investigated for their potential use as a dietary supplement [10, 24]. A recent systematic review on medicinal plants as a treatment option for gastrointestinal and respiratory livestock diseases showed that a high number of *in vivo* studies were performed on poultry [24].

The goal of this review was to systematically evaluate the current research on medicinal plants used in *in vivo* poultry studies in the context of the most important bacterial and protozoal infectious diseases and to identify the variety and potential of the different plant species studied. Previously published reviews mainly focused on "plant bioactives" or "phytogenics" to enhance productivity in poultry or to improve their performance [25–27], but a systematic analysis on disease control is lacking.

## Material and Methods

The methods of this systematic review are based on the recommendations of the PRISMA statement [28, 29] and the AMSTAR measurement tool [30]. Moreover, they were performed following the design of a recently published study by Ayrle et al. [24]. The PICOS scheme [28] was used to design the research question: the population is poultry and included chickens, quails, turkey, and waterfowl, and the intervention is the administration or feeding of plant-based substances. The comparator is no treatment, placebo, or standard therapy (antibiotic or anticoccidial), and the outcomes are the effects on performance, health, bacteria, and gastrointestinal protozoa. The study design includes only *in vivo* or clinical studies with poultry and no *in vitro* studies. A detailed description of the study protocol is given in supplementary material file 1.

### Selection of published scientific studies
#### Literature search
The literature research was conducted in February 2018 by 1 person, and 2 databases, Web of Science [31] and PubMed [32], were consulted. No specific timeframe of publication years was considered. An additional literature search was done with the same databases for the period from February 2018 to February 2019 by 1 person. The search term in both databases consisted of the name of the animal species and the phytotherapeutic description: (layer* OR hens OR chicken* OR poultry OR fowl* OR duck* OR quail* OR goose* OR turkey*) AND (medicinal plant* OR plant ex-

▶ **Table 1** Challenging infectious diseases in poultry: pathogens, pathophysiology, and resulting demands for prophylaxis and therapy.

| Disease complex | | Pathogens | Pathophysiology (Pp) and clinical signs (Cs) | Demands for prophylaxis and therapy |
|---|---|---|---|---|
| **Bacteria** | | | | |
| Salmonellosis[a] | Paratyphoid Sallmonellae | *S. enteritis, S. typhimurium* | Pp: *S. enteritis* adheres to epithelial cells at the tip of villi, toxin production → changes density and morphology → electrolyte, intestinal fluid are affected; septicemia. Cs: embryo mortality, high mortality on hatch day, rest similar to fowl typhoid and pullorum disease. Adult animals are often symptomless. | Anti-inflammatory, antiadhesive, analgesic, antidiarrheal, prebiotic, improved feed intake, improved feed conversion rate, anti-inflammatory, improved performance |
| | Pullorum disease | *S. pullorum* | Pp: septicemia, focal necrotic lesions of mucosa, liver, and spleens swollen, hemorrhagic streaks Cs: weakness, anorexia, diarrhea, dehydration, reduced growth, reduced feed intake, high mortality, joint infections, blindness, reduced fertility and hatchability, drop in egg production | |
| | Fowl typhoid | *S. gallinarum* | | |
| Necrtic enteritis/clostridiosis[b] | | *Clostridium perfringes* Type A | Pp: adheres to cell, toxin production, gross lesions in the intestine Cs: severe depression, anorexia, reluctance to move, diarrhea and wet litter, ruffled feathers, acute mortality, growth depression | Antibacterial, analgesic, improved feed intake, antiadhesive antidiarrheal, prebiotic, spasmolytic, anti-inflammatory, improved performance |
| Colibacillosis[c] | | avian pathogenic *Escherichia coli* (APEC) and enterotoxigenic *E. coli* (ETEC) | Pp: enters the host through mucosa or directly through breaks in skin → inflammation (serositis, cellulitis, enteritis, salpingitis, synovitis, meningitis, etc.), dehydration, septicemia → synovitis and osteomyelitis Cs: depression, fever, diarrhea, reduced egg production, high mortality | Antibacterial, anti-inflammatory, analgesic, immunostimulatory, antidiarrheal, improved performance |
| Campylobacteriosis[d] | | *Campylobacter jejuni* | Rare/no obvious clinical signs in poultry but in humans | |
| **Gastrointestinal Protozoa** | | | | |
| Coccidiosis[e] | | *Eimeria spp. (E. acervulina, E. brunetti, E. maxima, Eimeria mitis E. necratix, E. praecox, E. tenella)* | Pp: E. adheres to epithelial cells in the intestine, replications intracellular in intestine → rupture of epithelial cell wall → tissue damage, dehydration, blood loss, increased intestinal passage time, intestinal malabsorption, reduced nutrient digestion, villous atrophy, intestinal leakage of plasma proteins, increased intestine activity Cs: reduced weight gain, reduced feed conversion efficiency, reduced feed and water intake, bloody diarrhea, decreased digesta viscosity | Antiadhesive, antiprotozoal, spasmolytic, improved feed intake, improved feed conversion rate, improved weight gain, anti-inflammatory |
| Histomonosis[f] | | *Histomonas meleagridis* | Pp: ulceration and inflammation of cecal walls, inflammation of mesenteric, necrosis of the liver, engorgement of the ceca Cs: yellow feces, drowsiness, anorexia, cyanotic head, increased mortality | Antiprotozoal, anti-inflammatory, improved blood circulation, prokinetic, prebiotic |

a–f [14]; a,c [2]; b,e [13]

tract OR phytogenic feed additive OR herbal OR phytotherapy). In the Web of Science keyword search, the results were refined with the categories "agriculture" or "veterinary science" and only in the languages "English", "German", or "French". In the PubMed keyword research, the results were refined with "other animals", "language" (only in English, French, or German language), "complementary medicine", "dietary supplements", "history of medicine", "systematic reviews", "toxicology and veterinary science", and an additional MeshTerm search was conducted with the terms "phytotherapy", "poultry", and "plant extracts".

### Manual sorting of experiments according to predetermined criteria

After the removal of duplicates, the remaining publications were refined manually by selective screening of the title and the abstract by 2 evaluators. Publications were maintained if they fit

▶ **Table 2** Schematic representation of the scoring system used in the systematic literature search for each parameter measured in each experiment.

| Effects* | Score definition | Experiments that compared a medicinal plant-based treatment only with an antiparasitic, antibacterial, or another treatment** as control. | Experiments that compared a medicinal plant-based treatment at least with a negative control group (placebo treatment or no treatment), sometimes, in addition, with an antiparasitic, antibacterial, or another treatment*** as control. |
|---|---|---|---|
| + | The positive effect (in the case of several dosages of 1 plant material at least 1 dosage showed a positive effect and other dosages showed no effect). | Medicinal plant-based treatment showed a significant positive effect or no difference compared to the control. | Medicinal plant-based treatment showed a significant positive effect compared to the negative control. |
| 0 | No effect | Medicinal plant-based treatment showed a significant negative difference compared to the control. | Medicinal plant-based treatment showed no significant difference from the negative control. |
| − | The negative effect (in case of several dosages of 1 plant material at least 1 dosage showed a negative effect and other dosages showed no effect) | (In this experimental design, it is not possible to distinguish between a lack of effect and a negative effect.) | Medicinal plant-based treatment showed a significant negative effect compared to the negative control. |
| n | No data available | | |
| ? | In the case of experiments with several dosages of 1 plant material: if at least 1 dosage showed a positive and another dosage a negative effect compared to the negative control group. | | |

* as this study was not designed as a meta-analysis but more as a qualitative systematic review, a detailed proof of the statistical methods was not conducted. Only the results that the authors presented as significant were considered; ** in 4 experiments the positive group was a "vaccinated control group", which was compared to a not vaccinated but medicinal plant treated group; *** in 7 experiments instead of an antiparasitic/antibacterial control was a probiotic control group, 2 times vitamin E supplemented group and 3 times a combination of different plants

the predefined inclusion criteria and were sorted according to pathogen-associated categories in an Endnote database.

## Inclusion and exclusion criteria

To be included, publications had to provide an abstract written in English, French, or German. Further, the publications had to include an assessment of oral administration (via feed or drinking water) of plant-based materials in an *in vivo* trial with poultry. In addition, in these trials, a challenge of the poultry with bacteria and/or gastrointestinal protozoa must have been conducted, or a detailed description of the intestinal microflora must have been included. Effects of the medicinal plant-based treatment (e.g., antidiarrheic effects, immunotropic effects, anti-inflammatory effects, antioxidant effects, improved growth, improved feed conversion rate, etc.) must have been described. In addition, a control group (placebo, untreated, and/or positive control groups like antibiotics or anticoccidials) had to be included. Publications without an abstract investigating a mixture of different plant species in a combined preparation or publications that did not distinguish the plant species or did not mention the Latin name of the plant used were excluded. Furthermore, publications reporting studies on vinegar, charcoal, soil, prebiotics, yeast, other animals than chickens, quails, turkeys, or waterfowl; studies with eggs or embryos; studies focusing only on feed, performance, or product quality; and studies on synthetic single substances were also excluded. Publications that fulfilled the inclusion criteria but where no full text was available were excluded.

## Classification

The included publications were divided into 2 main groups: "bacteria" and "gastrointestinal protozoa". Before adding the respective information of the included publications in a table, a distinction between "publication" (as one scientific paper) and "experiment" was made, based on the fact, that some publications included several trials or trials with more than 1 medicinal plant. Other publications referred to more than 1 animal species (e.g., *Artemisia annua* L. tested in turkeys and chickens). Therefore, the following definition of "experiment" was used: Experiment = plant species × animal species × trial × publication. Hence, as an example, a publication referring to 2 controlled trials with 2 animal species (1 with quails and 1 with chickens) and 2 plant species each (3 groups in each trial: 1 with peppermint, 1 with garlic, and 1 control group) would lead to 4 "experiments": garlic × chicken, peppermint × chicken, garlic × quails, and peppermint × quails.

## Assessment

All experiments were evaluated according to the following characteristics: plant species, plant family, a pharmaceutical form of the plant (extract), dosage/concentration, trial specification (on a station/on a farm), poultry species, age of the poultry at the start of the trial, number (n) of individuals per group, distribution of animals to different treatment groups (randomized or not), comparator, issue of the study, way of application, duration of administration, and observation period (from the first day of application) and were entered in a data table (**Table 1S**, Supporting Information). To determine the recent bionomical nomenclature of the plant species used in the trials, the web page "the plant list" [33]

was used. The potential of the plant species was evaluated based on possible effects, improving the expected pathophysiology of the most common, and important bacterial and protozoal infectious diseases in poultry (▶ **Table 1**). The plant-based treatment was screened for the following effects: antibacterial, synergism with antibiotics, antiprotozoal, antiadhesive, antidiarrheic, gut spasmolytic, lung spasmolytic, expectorant (secretolytic/mucolytic/secretomotoric), antitussive, anti-inflammatory, analgesic, antioxidant, immunotropic/stimulation of immune system, intestinal microbiota (prebiotic; predominantly assessed based on the lactobacillus population), improved growth, improved feed intake, improved feed conversion rate, improved egg production or other effects.

## Scoring System

A scoring system was established for each parameter to estimate the plants' potential for prophylaxis or therapy (▶ **Table 2**). The following system was, for example, used for studies with a negative control: if an experiment showed a significant positive effect of a plant-based substance compared to placebo or no treatment (in several dosages or at least in 1 dosage and no dosage showed a negative effect), it was marked as a "+" in the respective data table. If the plant-based substance showed no significant difference, it was marked as "0". In case the plant-based substance showed a significant negative effect (in several dosages or at least in 1 dosage, and no dosage showed a positive effect), it was marked as a "−". A "?" was given if the experiment used different dosages, and at least 1 dosage showed a positive and another dosage a negative effect. The same procedure was used if different durations of administrations had been compared within 1 experiment. An "n" was given if there were no data available on the specific parameter. For plant species with reports from 2 or more experiments, a total score for each "+", "0", and "−" as well as a total summation (counting "+" as 1, "0" as 0, and "−" as − 1) was calculated.

## Results

Database screening resulted in 4197 hits, and 3345 publications remained after the removal of 852 duplicates. After screening the titles of the publications, 3068 publications were excluded because they did not match the defined criteria, and finally a total of 277 publications remained. Out of these, 197 studies were excluded after screening the abstracts of the publications for the defined criteria. Sometimes, as examples, only growth-promoting factors were studied, without a link to bacterial or gastrointestinal protozoal infection, or a mixture of plant species was used in the trial, or no Latin name of the used plant species was given. The remaining 80 publications resulted in 77 included publications, due to lack of full-text availability or language issues in the remaining 3 (▶ **Fig. 1**). These publications were published between 1997 and 2019 and described 148 experiments (**Table 1S**, Supporting Information).

More publications were found between the years 2011 and 2016 compared to the time period ranging from 1997 to 2010. After 2016, the number of publications obtained decreased again (▶ **Fig. 2**).
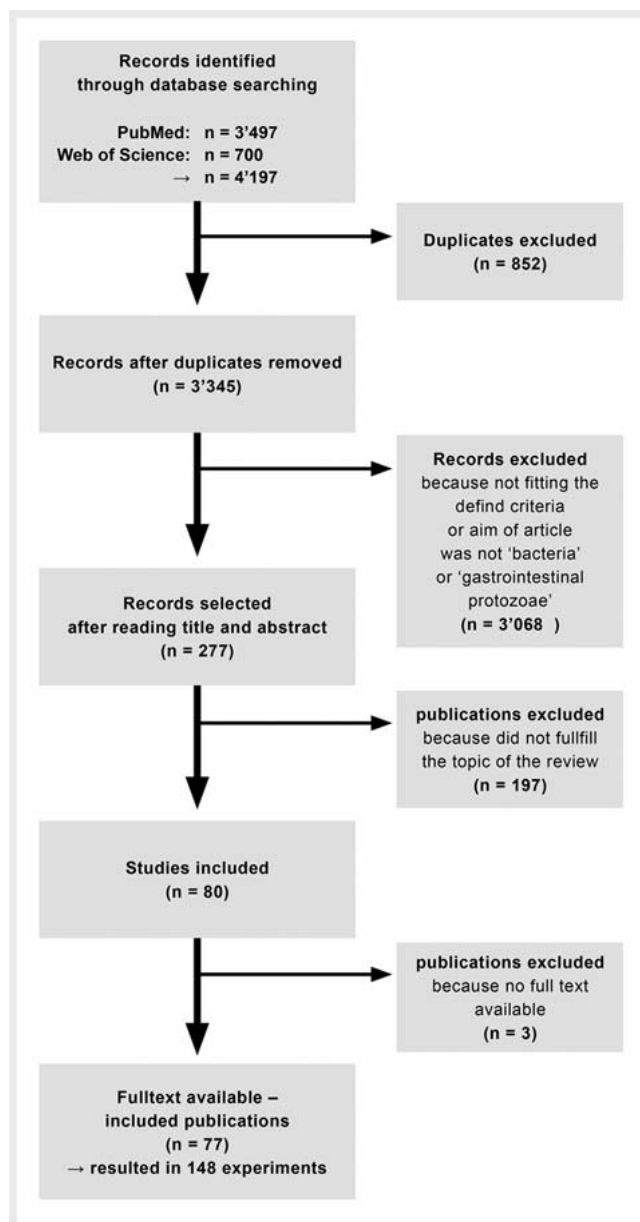


▶ **Fig. 1** Process of the systematic literature search. Source: Simone Bissig, FiBL

Publications were divided into 2 groups, namely "bacterial" and "gastrointestinal protozoal" infections: 38 publications, focusing on "bacteria", comprised 70 experiments, wherein 5 focused on "campylobacter species", 4 on "clostridia species", 16 on "*E. coli*", 5 on "salmonella", 6 on "other mixed bacteria", and 34 experiments on "microbiota". The second group, "gastrointestinal protozoa", included 39 publications and 78 experiments, wherein 72 experiments referred to "coccidia" and 6 to "other protozoa".

The 148 experiments were *in vivo* trials with 83 plant species of 42 plant families (▶ **Table 3**). Most experiments were found for *A. annua* (13), followed by *Origanum vulgare* L. (9). *Artemisia sieberi* Besser was analyzed in 5 experiments, as well as *Rosmarinus officinalis* L. and *Thymus vulgaris* L. *Echinacea purpurea* (L.) Moench,
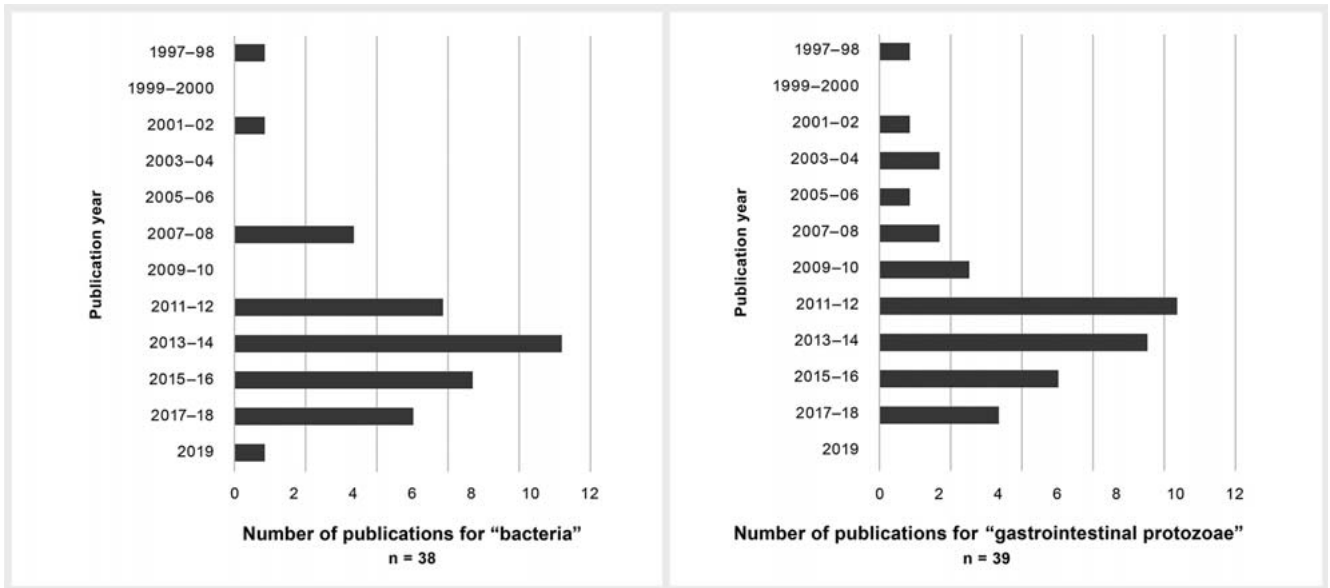
► **Fig. 2** Distribution of the publication dates of all included publications subdivided by pathogen-associated groups "bacteria" and "gastrointestinal protozoa". Source: Simone Bissig, FiBL

*Peganum harmala* L., and *Allium sativum* L. were represented in 4 experiments each. Most experiments (34) included the family Asteraceae, containing 11 plant species, followed by Lamiaceae with 28 experiments and 8 plant species. Apiaceae was included with 10 experiments, containing 9 plant species. Two or more experiments were found for 24 plant species (► **Table 4**). Fifty-nine plant species were only represented with 1 *in vivo* experiment.

The most commonly investigated poultry type in the experiments included in this review was broilers with 102 out of 148 experiments, followed by 39 with laying hens, 5 included turkeys, and 2 used quails. In 106 out of 148 experiments, the birds were randomly allocated to the trial groups; in 4 experiments, the allocation was described as equally distributed according to body weight. In the remaining 38 experiments, information about the method of distribution was missing. At the start of the trial, the age of the animals ranged from 1 day (90 experiments) to 280 days (1 trial with 40-wk old layers). The treatment duration ranged from 1 day up to 49 days.

The most frequently used pharmaceutical preparation consisted of extracts (103 experiments: 20 with alcoholic, 7 with aqueous, and 54 with not further specified extracts, and 22 with essential oils), followed by the crude plant material (40 experiments) and other pharmaceutical preparations (5 experiments). In 102 experiments, administration of plant preparations was via feed, followed by 30 experiments using drinking water for administration. Administration by forced feeding directly into the animals' crop was performed in 16 experiments. In a total of 51 2-armed experiments, 45 had a "negative control group", 2 a "positive control group", and 4 a vaccinated group as control. In 99 experiments, a 3-armed design was chosen, in most cases comprising a "negative and positive control group" with the medicinal plant preparation.

The outcome of the trials resulted in the following scores: 274 "+", 241 "0", and 37 "−" (► **Table 4**). Most of the experiments investigated performance effects (125 on growth or egg production, 69 focused on feed intake and 77 analyzed feed conversion rate), while "antiadhesive", "anti-inflammatory", and "antioxidant" effects were evaluated less frequently (6, 6, 15). Antibacterial activity was tested in 71 experiments, whereof 46 showed a positive effect according to the defined criteria in this review, 24 studies showed no effect compared to the control group, and 1 study had a negative outcome. Prebiotic effects were studied in 46 experiments, resulting in 19 positive and 27 zero effects. Antiprotozoal activity of plants or plant extracts in poultry was investigated in 77 experiments, whereof 49 showed positive effects, 26 found no difference compared to the control group, and in 2 experiments, the plant had a negative effect compared to the control group.

Based on the data of this review with a total of 83 investigated plant species, 19 plant species showed an antibacterial effect, 35 plant species showed an antiprotozoal effect, and 3 plant species had a prebiotic effect (► **Table 4**, Table 1S, Supporting Information). Ten plant species out of the 5 families Amaryllidaceae, Asteraceae, Lamiaceae, Nitrariaceae, and Xanthorrhoeaceae showed both *in vivo* antibacterial and *in vivo* antiprotozoal activities in chicken and turkeys: *A. sativum, Aloe secundiflora* Engl., *Aloe vera* L., *A. annua, A. sieberi, E. purpurea, O. vulgare, Salvia officinalis* L., *T. vulgaris*, and *P. harmala*. Fifteen plant species showed antibacterial as well as prebiotic effects, often detected within the same study.

Regarding the total score for all experiments, the positive outcome for antibacterial (65 %), antiprotozoal (63 %), antiadhesive (67 %), antioxidant (87 %), anti-inflammatory (100 %), and immunotropic (71 %) effects overweighed compared to "zero" and "negative" effects (► **Table 4**). The outcome for the production

▶ **Table 3** Medicinal plants used in *in vivo* trials with bacterial or gastrointestinal protozoal infections in poultry published between 1997 and 2019 in peer-reviewed journals: incidence of plant families and species.

| Family | Number of experiments per family | Number of species per family | Species in alphabetic order (in brackets: experiments per species, if more than 1) |
|---|---|---|---|
| Asteraceae | 34 | 11 | *Achillea millefolium* L. (3), *Ageratum conyzoides* (L.) L, *Artemisia annua* L. (13), *Artemisia asiatica* (Pamp.) Nakai ex Kitam., *Artemisia sieberi* Besser (5), *Artemisia vestita* Wall. ex Besser, *Artemisia vulgaris* L., *Bidens pilosa* L. (3), *Echinacea purpurea* (L.) Moench (4), *Eclipta alba* (L.) Hassk., *Inula helenium* L. |
| Lamiaceae | 28 | 8 | *Mentha x piperita* L. (2), *Mentha spicata* L., *Origanum majorana* L. (2), *Origanum minutiflorum* O.Schwarz & P.H.Davis, *Origanum vulgare* L. (9), *Rosmarinus officinalis* L. (5), *Salvia officinalis* L. (2), *Teucrium polium* L., *Thymus vulgaris* L. (5) |
| Apiaceae | 10 | 9 | *Bupleurum chinense* DC., *Centella asiatica* (L.) Urb, *Coriandrum sativum* L. (2), *Cuminum cyminum* L., *Ferulago angulata* (Schltdl.) Boiss. *Foeniculum vulgare* Mill., *Heracleum persicum* Desf. ex Fisch., C.A.Mey. & Avé-Lall., *Torilis japonica* (Houtt.) DC., *Trachyspermum ammi* (L.) Sprague) |
| Leguminosae | 7 | 7 | *Acacia decurrens* Willd., *Astragalus membranaceus* (Fisch.) Bunge, *Gleditsia japonica* Miq., *Lupinus angustifolius* L., *Sophora flavescens* Aiton, *Styphnolobium japonicum* (L.) Schott, *Trigonella foenum-graecum* L. |
| Xanthorrhoeaceae | 5 | 2 | *Aloe secundiflora* Engl. (2), *Aloe vera* (L.) Burm.f. (3) |
| Amaryllidaceae | 4 | 1 | *Allium sativum* L. (4) |
| Nitrariaceae | 4 | 1 | *Peganum harmala* L. (4) |
| Euphorbiaceae | 3 | 2 | *Euphorbia hirta* L. (2), *Manihot esculenta* Crantz |
| Poaceae | 3 | 1 | *Saccharum officinarum* L. (3) |
| Ranunculaceae | 3 | 2 | *Nigella sativa* L. (2), *Pulsatilla cernua* (Thunb.) Bercht. ex J. Presl |
| Rutaceae | 3 | 3 | *Citrus x bergamia* Risso & Poit., Citrus limon (L.) Osbeck, *Citrus sinensis* (L.) Osbeck |
| Simaroubaceae | 3 | 1 | *Brucea javanica* (L.) Merr. (3) |
| Vitaceae | 3 | 1 | *Vitis vinifera* L. (3) |
| Anacardiaceae | 2 | 2 | *Anacardium occidentale* L., *Rhus coriaria* L. |
| Aquifoliaceae | 2 | 1 | *Ilex paraguariensis* A. St.-Hil. (2) |
| Arecaceae | 2 | 2 | *Areca catechu* L., *Serenoa repens* (W.Bartram) Small |
| Lauraceae | 2 | 1 | *Cinnamomum verum* J.Presl (2) |
| Myrtaceae | 2 | 1 | *Syzygium aromaticum* (L.) Merr. & L.M.Perry (2) |
| Oleaceae | 2 | 2 | *Forsythia suspensa* (Thunb.) Vahl, *Fraxinus ornus* L. |
| Scrophulariaceae | 2 | 2 | *Eremophila glabra* (R.Br.) Ostenf., *Scrophularia striata* Boiss. |
| Theaceae | 2 | 1 | *Camellia sinensis* (L.) Kuntze (2) |
| Altingiaceae | 1 | 1 | *Liquidambar orientalis* Mill. |
| Burseraceae | 1 | 1 | *Commiphora swynnertonii* Burtt |
| Combretaceae | 1 | 1 | *Combretum indicum* (L.) DeFilipps |
| Cucurbitaceae | 1 | 1 | *Cucurbita pepo* L. |
| Ganodermataceae | 1 | 1 | *Ganoderma lucidum* (Curtis) P. Karst. |
| Hydrangeaceae | 1 | 1 | *Dichroa febrifuga* Lour. |
| Lythraceae | 1 | 1 | *Punica granatum* L. |
| Malvaceae | 1 | 1 | *Abelmoschus esculentus* (L.) Moench |
| Marasmiaceae | 1 | 1 | *Lentinula edodes* (Berk.) Pegler |
| Meliaceae | 1 | 1 | *Melia azedarach* L. |
| Menispermaceae | 1 | 1 | *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson |

*continued*

| Family | Number of experiments per family | Number of species per family | Species in alphabetic order (in brackets: experiments per species, if more than 1) |
|---|---|---|---|
| Moringaceae | 1 | 1 | *Moringa olifera* L. |
| Musaceae | 1 | 1 | *Musa paradisiaca* L. |
| Piperaceae | 1 | 1 | *Piper sarmentosum* Roxb. |
| Polygonaceae | 1 | 1 | *Polygonum aviculare* L. |
| Quillajaceae | 1 | 1 | *Quillaja saponaria* Molina |
| Rubiaceae | 1 | 1 | *Morinda citrifolia* L. |
| Schisandraceae | 1 | 1 | *Illicium verum* Hook.f. |
| Taxaceae | 1 | 1 | *Torreya nucifera* (L.) Siebold & Zucc. |
| Tremellaceae | 1 | 1 | *Tremella fuciformis* (Berk.) |
| Ulmaceae | 1 | 1 | *Ulmus macrocarpa* Hance |
| Urticaceae | 1 | 1 | *Urtica dioica* L. |

parameters, including improved growth, feed intake, and feed conversion rate was mostly "zero" (46%, 58%, 57%). Prebiotic effects were found, and positive (41%) and zero (57%) outcomes were almost equally represented. In summary, 274 positive effects (50%) predominated over 241 zero effects (44%) and 37 negative effects (7%).

## Discussion

Detection of an increasing number of antimicrobial-resistant pathogens (against antibiotic as well as anticoccidial drugs) in poultry has resulted in an intensified search for alternative treatment methods. Medicinal plants and their extracts might represent an option for alternative treatments to reduce or replace the common therapy with antimicrobials.

An increase in the number of publications per year was observed around 2010. This outcome could be associated with the EU's ban on antibiotics as growth promoters in livestock feed in 2006, leading to an increasing interest in exploring alternative ways to prevent infectious diseases. Since 2016, the number of publications decreased again, which is difficult to explain, as the problem of antimicrobial input in the worldwide poultry industry has not been resolved yet.

### Evaluation of the methodology

This systematic review was designed according to the PRISMA statement and AMSTAR measurement tool [28–30]. The risk of introducing database bias was reduced by using 2 different and independent databases and by using the Mesh Term functions on PubMed. The deliberately less specific search strategy led to over 3000 hits in the first search, and only around 3% of the references were finally included in the review. However, this is consistent with studies using comparable methodology [24]. To reach a high level of validity, only trials with control groups were included. However, 2 methodological limitations might have led to a certain bias: Besides 106 experiments where a randomized distribution of

the birds to the trial groups was clearly stated, no information about the distribution was available in 38 of the 148 included experiments. Furthermore, blinding is unusual in herbal feeding trials with poultry because in trials with oral administration of plant raw material, essential oils, or simple plant extracts, blinding is hardly possible due to the sensory properties of the used plant material. The scoring system allowed comparisons of a large number of experiments and helped to identify the most relevant plant species. Nevertheless, the total score must be interpreted with caution. Plant species with a large number of experiments and a large number of parameters measured per experiment had *a priori* the highest chance to reach the highest total scores, which might have caused a bias. The median number of parameters measured per experiment was 3 with a range of 1 to 7. Even publications measuring a high number of parameters did not clearly state if a Bonferroni correction was conducted. However, detailed proof of the statistical methods was not conducted, and these studies with a potential flaw in statistical methods were still included because this review was not designed as a meta-analysis but rather as a qualitative systematic review.

The outcomes of different studies regarding the same plant species were often not uniform. One explanation might be the variability of natural products within the same plant species. Environmental factors like climate and geographic conditions, time of the year, soil, method of cultivation, and storage affect the phytochemical composition [34–36]. Therefore, the amounts of active constituents can differ in each product sample as reported, for example, for *S. officinalis* [37] or *A. annua* [36]. Furthermore, it is important to consider that the amounts of active constituents can depend on the type of extract and the extraction method used [38], as well as the parts of the plant used, as described for *Forsythia suspensa* (Thunb.) Vahl or *Aloe spp.* [39, 40]. Unfortunately, detailed information about the natural products compounds of the used plants was broadly missing. Last, the mode and duration of the administration for prophylactic or therapeutic use have an impact on the effectiveness of medicinal plants [41, 42].

▲ **Table 4** Assessment of medicinal plants based on at least 2 *in vivo* experiments with bacterial or gastrointestinal protozoal infections in poultry published between 1997 and 2019 in peer-reviewed journals.

| Plant species (Score) | Antibacterial + | Antibacterial 0 | Antibacterial − | Microbiota/prebiotic + | Microbiota/prebiotic 0 | Microbiota/prebiotic − | Antiprotozoal + | Antiprotozoal 0 | Antiprotozoal − | Antiadhesive + | Antiadhesive 0 | Antiadhesive − | Antidiarrheic + | Antidiarrheic 0 | Antidiarrheic − | Anti-inflammatory + | Anti-inflammatory 0 | Antioxidant + | Antioxidant 0 | Immunotropic + | Immunotropic 0 | Immunotropic − | Improved performance (fattening, laying) + | Improved performance 0 | Improved performance − | Improved feed intake + | Improved feed intake 0 | Improved feed intake − | Improved feed conversion rate + | Improved feed conversion 0 | Improved feed conversion − | Total Score (number of +, 0, −) | Number of experiments/number of publications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Achillea millefolium* L. | 1[1] | 2[2] | | | 3[3] | | | | | | | | | | | | | | | | | | | 3[4] | | | 3[5] | | | 3[6] | | 1 (1,14,0) | 3/2 |
| *Allium sativum* L. | 2[7] | 1[8] | | | | | 1[9] | | | | | | | | | | | | | | | | 2[10] | 2[11] | | 1[12] | 1[13] | 1[14] | 2[15] | 2[16] | | 7 (8,6,1) | 4/4 |
| *Aloe secundiflora* Engl. | 1[17] | | | | | | 1[18] | | | | | | 2[19] | | | | | | | | | | 2[20] | | | | | | | | | 6 (6,0,0) | 2/2 |
| *Aloe vera* (L.) Burm.f. | 1[21] | | | 1[22] | | | 1[23] | | | | | | | | | | | | | 1[24] | 1[25] | | 2[26] | | | 1[27] | | | 1[28] | | | 8 (8,1,0) | 3/2 |
| *Artemisia annua* L. | 1[29] | 1[30] | | | | | 6[31] | 5[32] | | | | | 1[33] | 1[34] | | | | 1[35] | | | | | 2[36] | 4[37] | 4[38] | | 3[39] | 4[40] | 3[41] | 1[42] | 1[43] | 6 (14,16,8) | 13/7 |
| *Artemisia sieberi* Besser | 1[44] | | | | 1[45] | | 4[46] | | | | | | 1[47] | | | 1[48] | | | | | | | 1[50] | 1[51] | 1[49] | | 1[52] | 1[53] | | 2[54] | | 6 (8,5,2) | 5/4 |
| *Bidens pilosa* L. | | | | 1[55] | | | 3[56] | | | | | | 1[57] | | | | | | | | | | 3[58] | | | | | | 2[59] | | | 10 (10,0,0) | 3/3 |
| *Brucea javanica* (L.) Merr. | | | | | | | 2[60] | 1[61] | | | | | 3[62] | | | | | | | | | | | 3[63] | | | | | | | | 5 (5,4,0) | 3/1 |
| *Camellia sinensis* (L.) Kuntze | 1[64] | 1[65] | | | 1[66] | | | | | | | | | | | | | | | | | | 1[68] | | 1[67] | 1[69] | | 1[70] | | | 1[71] | − 1 (2,2,3) | 2/2 |
| *Cinnamomum verum* J. Presl | | 1[72] | | | 1[73] | | | | | | | | | | | 1[74] | | 1[75] | | 2[76] | | | | | | | | | | | | 5 (5,1,0) | 2/2 |
| *Coriandrum sativum* L. | 2[77] | | | | 1[78] | | | | | | | | | | | | | | | 1[79] | 1[80] | | 2[81] | | | 2[82] | | | 2[83] | | | 9 (9,2,0) | 2/2 |
| *Echinacea purpurea* (L.) Moench | 1[84] | | | | 1[85] | | 1[86] | 2[87] | | | | | | | | | | | | 1[88] | | | 1[89] | 1[90] | 1[91] | 1[92] | | | | 2[93] | 1[94] | 3 (5,5,2) | 4/4 |
| *Euphorbia hirta* L. | 2[95] | | | 1[96] | | | | | | | | | | | | | | 1[97] | | | | | | 2[98] | | | 2[99] | | 2[100] | | | 6 (4,0,0) | 2/2 |

*continued*

▲ **Table 4** *Continued*

| Plant species | Antibacterial + | 0 | - | Microbiota/prebiotic + | 0 | - | Antiprotozoal + | 0 | - | Antiadhesive + | 0 | - | Antidiarrheic + | 0 | - | Anti-inflammatory + | 0 | Antioxidant + | 0 | - | Immunotropic + | 0 | - | Improved performance (fattening, laying) + | 0 | - | Improved feed intake + | 0 | - | Improved feed conversion rate + | 0 | - | Total Score (number of +, 0, -) | Number of experiments/number of publications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Ilex paraguariensis* A.St.-Hil. | | 1[101] | 1[102] | | 1[103] | | | | | | | | | | | | | | | | | | | | | 2[104] | | | | | | | −3 (0,2,3) | 2/1 |
| *Mentha x pipierita* L. | 2[105] | | | 1[106] | 1[107] | | | | | | | | | | | 1[108] | | | | | 1[109] | | | 1[110] | 1[111] | | | 2[112] | | | 2[113] | | 6 (6,6,0) | 2/2 |
| *Nigella sativa* L. | 1[114] | 1[115] | | | 1[116] | | | | | | | | | | | | | | | | | | | 2[118] | | 1[117] | | 1[119] | | | | 1[120] | 1 (3,3,2) | 2/2 |
| *Origanum majorana* L. | | 2[121] | | | | | | | | | | | | | | | | | | | | | | | 2[122] | | | 2[123] | | | 2[124] | | 0 (0,8,0) | 2/1 |
| *Origanum vulgare* L. | 4[125] | 2[126] | | 1[127] | 4[128] | | 1[129] | 2[130] | | | 1[131] | | | | | | | | | | 2[132] | | | 3[133] | 4[134] | | | 4[135] | 2[136] | 4[137] | 6[138] | | 9 (12,23,2) | 9/8 |
| *Peganum harmala* L. | 2[139] | 1[140] | | | | | 1[141] | | | | | | 1[142] | | | | | | | | | 3[143] | | 1[144] | | | 1[145] | | | 1[146] | | | 7 (7,4,0) | 4/2 |
| *Rosmarinus officinalis* L. | 2[147] | 2[148] | | 1[149] | 2[150] | | | 1[151] | | | | | | | | | | | | | | 1[152] | | 2[153] | 3[154] | | | 2[155] | 2[156] | 1[157] | 4[158] | | 4 (6,15,2) | 5/4 |
| *Saccharum officinarum* L. | | | | | | | 3[159] | | | | | | 1[160] | | | 1[161] | | | | | 2[162] | | | 3[163] | | | | | | | | | 10 (10,0,0) | 3/2 |
| *Salvia officinalis* L. | 1[164] | | | | | | 1[165] | | | 1[166] | | | | | | | | | | | | 1[167] | | 1[168] | | | | | | | 1[169] | | 4 (4,2,0) | 2/2 |
| *Syzygium aromaticum* (L.) Merr. & L.M. Perry | | 1[170] | | 1[171] | 1[172] | | | | | | | | | | | | | 1[173] | | | 2[174] | | | 1[175] | | | | | | | | | 5 (5,2,0) | 2/2 |
| *Thymus vulgaris* L. | 1[176] | 2[177] | | 1[178] | 2[179] | | 1[180] | 1[181] | | | | | | | | | | 1[182] | | | 1[183] | | | 2[184] | 2[185] | | | 3[186] | | | 4[187] | | 7 (7,14,0) | 5/4 |

*continued*

▸ **Table 4** *Continued*

| Plant species | Antibacterial | | | Microbiota/prebiotic | | | Antiprotozoal | | | Antiadhesive | | | Antidiarrheic | | | Anti-inflammatory | | | Antioxidant | | | Immuno-tropic | | | Improved performance (fattening, laying) | | | Improved feed intake | | | Improved feed conversion rate | | | Total Score (number of +, 0, −) | Number of experiments/number of publications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Score | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | + | 0 | − | | |
| *Vitis vinifera* L. | | | | | | | 1[188] | 2[189] | | | | | | | | | | | 1[190] | | | | | | 2[191] | | | | | | | | | 4 (4, 2, 0) | 3/2 |
| Total of plant species > 2 experiments | 27 | 17 | 1 | 8 | 20 | 0 | 27 | 14 | 0 | 1 | 1 | 0 | 10 | 1 | 0 | 4 | 0 | 0 | 6 | 0 | 0 | 13 | 7 | 3 | 34 | 28 | 8 | 6 | 24 | 10 | 15 | 29 | 4 | (151, 141, 25) | |
| Others: 59 species[192] | 19 | 7 | 0 | 11 | 7 | 0 | 22 | 12 | 2 | 3 | 1 | 0 | 4 | 12 | 0 | 2 | 0 | 0 | 7 | 2 | 0 | 12 | 0 | 0 | 22 | 29 | 4 | 7 | 16 | 6 | 14 | 15 | 0 | (123, 101, 11) | |
| Total | 46 | 24 | 1 | 19 | 27 | 0 | 49 | 26 | 2 | 4 | 2 | 0 | 14 | 13 | 0 | 6 | 0 | 0 | 13 | 2 | 0 | 25 | 7 | 3 | 56 | 57 | 12 | 13 | 40 | 16 | 29 | 44 | 4 | (274, 241, 37) | |

The table shows number of individual experiments with score +, 0 and − (for detailed information, please compare ▸ Table 2). Superscript numbers refer to the specific literature references: [1] [104, 105], [2] [105], [3] [104, 105], [4] [104, 105], [5] [104, 105], [6] [104, 105], [7] [106, 107], [8] [108], [9] [109], [10] [107, 109], [11] [106, 108], [12] [107], [13] [108], [14] [106], [15] [106, 109], [16] [107, 108], [17] [110], [18] [77], [19] [77, 110], [20] [77, 110], [21–22] [111], [23–24] [112], [25] [111], [26] [111, 112], [27–28] [111], [29–30] [63], [31] [41, 64, 66], [32] [41, 42, 65, 113], [33] [66], [34–35] [113], [36] [41, 66], [37] [41, 42, 113], [38] [41, 63, 64], [39] [42, 64, 65], [40] [63, 65], [41] [63, 66], [42] [43], [43] [64], [44–45] [114], [46] [70, 115], [47–48] [115], [49] [114], [50] [116], [51] [114], [52] [116], [53] [114], [54] [114, 115], [55] [117], [56] [117–119], [57] [118], [58] [117–119], [59] [117, 119], [60–63] [120], [64] [121], [65–67] [114], [68] [121], [69–71] [114], [72–73] [122], [74] [123], [75] [122], [76] [122, 123], [77] [124, 125], [78] [124], [79] [124], [80] [125], [81–83] [124, 125], [84] [126], [85] [126], [86] [127], [87] [109, 128], [88] [126], [89] [109], [90] [128], [91] [127], [92] [127], [93] [109, 128], [94] [127], [95] [109, 128], [96] [130], [97] [129, 130], [98] [129, 130], [99] [129, 130], [100] [129, 130], [101–104] [131], [105] [104, 132], [106] [132], [107] [104], [108–109] [132], [110] [104], [111] [132], [112] [104, 132], [113] [104, 132], [114] [121], [115–117] [114], [118] [114, 121], [119–120] [114], [121–124] [105], [125] [133–136], [126] [105], [127] [134], [128] [105, 133, 136], [129] [96], [130] [109, 137], [131] [96], [132] [96, 134], [133] [109, 133, 136], [134] [105, 134, 137], [135] [133, 136, 137], [136] [105], [137] [133], [138] [105, 109, 134, 136, 137], [139–140] [138], [141–142] [139], [143] [138], [144–146] [139], [147] [133, 134], [148] [105], [149] [134], [150] [105], [151] [109], [152] [109, 133, 134], [154] [105, 134], [155] [105, 133], [156] [105, 134], [157] [133], [158] [105, 109, 134], [159] [140, 141], [160] [140], [161] [141], [162–163] [140, 141], [164] [141], [165] [109], [166–167] [142], [168–169] [109], [170] [122], [171] [143], [172–173] [122], [174] [122, 143], [175] [143], [176] [144], [177] [105], [178] [144], [179] [105], [180] [145], [181] [109], [182–183] [144], [184] [105, 109], [185] [105, 144], [186] [105, 144], [187] [105, 109, 144], [188] [146], [189] [145, 146], [190] [146], [191] [145, 146], [192] (n = 59): Altingiaceae (*Liquidambar orientalis* Mill. [147]), Anacardiaceae (*Anacardium occidentale* L. [148], *Rhus coriaria* L. [132]), Apiaceae (*Bupleurum chinense* DC. [113], *Centella asiatica* [L.] Urb [107], *Cuminum cyminum* L. [104], *Ferulago angulata* [Schltdl.] Boiss. [97], *Foeniculum vulgare* Mill. [133], *Heracleum persicum* Desf. ex Fisch., C. A. Mey. & Avé-Lall. [132], *Trachyspermum ammi* [L.] Sprague [122], *Torilis japonica* [Houtt.] DC. [113]), Arecaceae (*Areca catechu* L. [149], *Serenoa repens* [W.Bartram] Small [145]), Asteraceae (*Ageratum conyzoides* [L.] L. [150], *Artemisia asiatica* [Pamp.] Nakai ex Kitam. [113], *Artemisia vestita* Wall. ex Besser [151], *Artemisia vulgaris* L. [42], *Eclipta alba* [L.] Hassk. [152], *Inula helenium* L. [113]), Burseraceae (*Commiphora swynnertonii* Burtt [153]), Combretaceae (*Combretum indicum* [L.] DeFilipps [113]), Cucurbitaceae (*Cucurbita pepo* L. [145]), Euphorbiaceae (*Manihot esculenta* Crantz [42]), Ganodermataceae (*Ganoderma lucidum* [Curtis] P. Karst. [154]), Hydrangeaceae (*Dichroa febrifuga* Lour. [155]), Lamiaceae (*Mentha spicata* L. [156], *Origanum minutiflorum* O.Schwarz & P. H.Davis [157], *Teucrium polium* L. [104]), Leguminosaceae (*Acacia decurrens* Willd. [158], *Astragalus membranaceus* [Fisch.] Bunge [159], *Gleditsia japonica* Miq. [113], *Lupinus angustifolius* L. [160], *Sophora flavescens* Aiton [113], *Styphnolobium japonicum* [L.] Schott [113], *Trigonella foenum-graecum* L. [121]), Lythraceae (*Punica granatum* L. [161]), Malvaceae (*Abelmoschus esculentus* [L.] Moench [162]), Marasmiaceae (*Lentinula edodes* [Berk.] Pegler [159]), Meliaceae (*Melia azedarach* L. [113]), Menispermaceae (*Sinomenium acutum* [Thunb.], Rehder & E.H.Wilson [113]), Moringaceae (*Moringa oleifera* L. [163]), Musaceae (*Musa paradisiaca* L. [164]), Oleaceae (*Forsythia suspensa* [Thunb.] Vahl [102], *Fraxinus ornus* L. [165]), Piperaceae (*Piper sarmentosum* Roxb. [166]), Polygonaceae (*Polygonum aviculare* L. [113]), Quillajaceae (*Quillaja saponaria* Molina [137]), Ranunculaceae (*Pulsatilla cernua* [Thunb.] Bercht. ex J. Presl [113]), Rubiaceae (*Morinda citrifolia* L. [167]), Rutaceae (*Citrus x bergamia* Risso & Poit. [168], *Citrus limon* [L.] Osbeck [168], *Citrus sinensis* (L.) Osbeck [168]), Scrophulariaceae (*Eremophila glabra* [R.Br.] Ostenf. [167]), Schisandraceae (*Illicium verum* Hook.f. [169]), Scrophulariaceae (*Eremophila glabra* [R.Br.] Ostenf. [158], *Scrophularia striata* Boiss. [97]), Taxaceae (*Torreya nucifera* [L.] Siebold & Zucc. [113]), Tremellaceae (*Tremella fuciformis* [Berk.] [159]), Ulmaceae (*Ulmus macrocarpa* Hance [113]), Urticaceae (*Urtica dioica* L. [109])]

## Antibacterial, anticoccidial, and prebiotic active plant species

Several plant species including *A. sativum, A. secundiflora, A. vera, A. annua, A. sieberi, E. purpurea, O. vulgare, S. officinalis, T. vulgaris,* and *P. harmala* showed antibacterial, antiprotozoal, and, in some plant species, also prebiotic activities. In accordance, antimicrobial activities were also shown in these plants in numerous *in vitro* studies [43–56]. Interestingly, no study analyzed the antibacterial and antiprotozoal effect at the same time, even if in practice, pathologies might often be caused by such combined infections.

It is still not obvious why some medical plants act antibacterially concerning pathogens and prebiotic (e.g., by elevation of the lactobacillus population) at the same time. It has been shown or hypothesized that gram-negative and zoopathic bacteria utilize acylated homoserine lactone (AHL) for their communication system [57]. This system has been named quorum sensing (QS), and it has been demonstrated to regulate various activities such as virulence factors, sporulation, and biofilm formation [57, 58]. One way of inhibiting AHL biosynthesis includes effects on LuxI-type synthase and/or LuxR-type receptor proteins as shown for *O. vulgare* and *T. vulgaris* and other Lamiaceae species as well as their direct antibiofilm activity [57], also known for other plant species [59]. Bifidobacteria and Lactobacilli may produce metabolic end-products that lower the gut pH [60, 61] and inhibit the growth of pathogens such as *E. coli, Salmonella thyphimurium,* and *C. perfringens* [61]. Animals fed with antibiotics had a thinned mucosal layer and a decreased gut-weight as well as a decrease in protective microflora: thus, antibiotics were shown to weaken the ecosystem in the gut and facilitate pathogen survival [61, 62]. Powering up the healthy gut microflora with plants with possible prebiotic activities might enhance the nonpathogen bacteria population. The sum of these effects might lead to antibacterial and prebiotic effects at the same time. However, the clinical evidence of such effects is still controversially discussed.

## Some outstanding single plant species

Based on the aim to identify the most promising plant species for future research, species that were represented by a high number of experiments and species that showed a high total score will be discussed in detail in alphabetical order: *A. annua, A. sieberi, A. vera, A. secundiflora, Bidens pilosa, Coriandrum sativum* L., *Mentha x piperita* L., and *O. vulgare*.

*A. annua* was represented in 13 experiments and resulted in a total score of 6 (14 positive, 16 zero, 8 negative effects). In 11 experiments the antiprotozoal effect was evaluated, wherein 6 were positive and 5 showed no effect. Detrimental effects were found especially in performance, related to reduced body weight [41, 63, 64] or reduced feed intake [63–65]. These results might be attributed to the lowered palatability of the feed, due to the bitter and strong taste of *A. annua*, imposed by contained sesquiterpenes, mainly artemisinin [63–65]. In contrast, there is some evidence that *A. annua* improves the feed conversion rate [63, 66]. The anticoccidial effect showed a linear relationship between artemisinin dose used and oocyst output [41, 63]. Overall, antiparasitic effects of artemisinin and its derivates were confirmed in many *in vitro* and *in vivo* studies [67]. Nevertheless, *A. annua* contains a broad spectrum of secondary metabolites [68], which vary depending, for example, on geographic origin [36]. This might be one reason for divergent results in some effects. While it is well documented that artemisinin affects different metabolic pathways of malaria parasites [69], the mode of action in gastrointestinal poultry coccidia is still unknown.

*A. sieberi* was represented with 5 experiments resulting in a total score of 6 (8 positive, 5 zero, and 2 negative effects). Four experiments confirmed antiprotozoal effects. In addition, *A. sieberi* was demonstrated to reveal anti-inflammatory effects. The chemical component responsible for the antiprotozoal and the anti-inflammatory effect might be again artemisinin, similar to the effect of *A. annua* [70]. Artemisinin has been shown to exert immunomodulatory effects through its inhibition of several immune cells and related signaling pathways [71]. *A. sieberi* has been demonstrated to contain sesquiterpene lactones, leading to antimicrobial activity *in vitro* against both gram-negative and gram-positive like *E. coli, Pseudomonas aeruginosa,* and *Staphylococcus aureus* [47]. As already reported for Genus Artemisia, European farmers used *Artemisia absinthum* traditionally in laying hens for its antidiarrheal, intestinal anti-inflammatory, and anti-infective as well as antiparasitic effects. [21].

*A. vera* showed a total score of 8 (8 positive, 1 zero effect) represented in 3 experiments. Besides antibacterial and antiprotozoal effects, improved performance, feed intake, and feed conversion rate, *A. vera* also led to immunotropic and prebiotic effects. Its antimicrobial potential might be attributed, for example, to flavonoids [68, 72], or anthraquinones are likely to inhibit protein synthesis in bacteria [73]. Contained polysaccharides enhance phagocytosis-activity and may therefore be responsible for the *in vivo* antibacterial effect shown in one of the experiments [74]. Contained catechol, a hydroxylated phenol, was reported to exert antimicrobial activities [74]. The immunotropic effect might be given through the polysaccharide acemannan, which has been reported to exert immunostimulating effects *in vitro* [75] and in particular to activate macrophages *in vivo* in chicken [76]. Whole-plant extracts but also several single components of *A. vera* showed anti-inflammatory activities via different modes of action such as inhibition of proinflammatory cytokines or cyclooxygenase pathway [73].

*A. secundiflora*, represented in 2 experiments, showed consistent positive effects (antibacterial, antiprotozoal, antidiarrheic effects, and improved performance) with a total score of 6. The presence of terpenoids, flavonoids, and tannins is responsible for these effects [77].

The Asteraceae *B. pilosa* reached a total score of 10 (10 positive effects) out of 3 experiments. All experiments showed antiprotozoal effects, improved performance, and antidiarrheic and prebiotic effects. *B. pilosa* is an extraordinary source of natural products, containing predominantly polyacetylenes and flavonoids, and these have been demonstrated to be anti-inflammatory [78], antioxidant [79], and antibacterial [79, 80]. Phenols, like luteolin, ethyl caffeate, and polyynes were reported to be the major anti-inflammatory natural products present in *B. pilosa* [81]. *B. pilosa's* potential to exert anticoccidial properties might be caused by cytopiloyne inhibiting the oocyst sporulation and invading into the cell, as demonstrated in *in vitro* and *in vivo* experiments [82].

*C. sativum*, represented with 2 experiments, resulted in a total score of 9 points (9 positive, 2 zero effects). Antibacterial and immunotropic effects, as well as improved performance, have been reported. The essential oil of *C. sativum* has been described to have antibacterial action *in vitro* [83], with its effect on gram-positive and gram-negative pathogens being sometimes more potent than the antibiotic rifaximin [84]. This effect is most probably due to an increase in bacterial membrane permeability and the loss of respiratory activity due to complex interactions between the membrane and several components of the essential oil [85]. Per the outcome of this systematic review, a study on feeding rainbow trouts with *C. sativum* seed extract optimized growth performance [86], possibly through stimulating the secretion of digestive enzymes [87].

Two experiments on *M. x piperita* were found, resulting in a total score of 6 points (6 positive, 6 zero effects). Both experiments confirmed an *in vivo* antibacterial effect. Furthermore, an anti-inflammatory and immunotropic effect could be shown. Interestingly, a plant species from the same genus, *Mentha suaveolens* Ehrh. has been traditionally used by farmers in Spain for antiprotozoal therapeutic action in laying hens [21]. The main components of the essential oil from leaves of *M. piperita* are menthol, menthone, and menthyl acetate, and they were shown to effectively inhibit the growth of 18 multidrug-resistant *S. aureus* strains in an *in vitro* trial [88]. Similar results were found in another *in vitro* trial on pathogenic methicillin-resistant *S, aureus* [89]. Essential oil of *M. piperita* resulted in an antioxidant activity that was analyzed by measuring the reduction of the radical cation [90] and might explain the anti-inflammatory effects also found in the present study. It has been reported that menthol suppresses the expression of prostaglandin E2, leukotriene B4, and interleukin (IL)-$\beta$2 and therefore exerts anti-inflammatory effects [91].

*O. vulgare* was found in 9 experiments, resulting in a total score of 10 (12 positive, 23 zero, 2 negative). Improved performance and antibacterial and anticoccidial properties were measured, and 5 experiments confirmed a prebiotic action. *O. vulgare* has been traditionally used in Switzerland in hens with gastrointestinal disorders [17]. Five experiments used the oregano essential oil, which is rich in phenolic compounds, containing carvacrol as its main compound [90, 92]. Carvacrol has been reported to have antibacterial effects *in vitro* (i.e., due to the phenols containing an isopropyl group at the para-position [93, 94] and via altering the structure of phospholipid membranes of bacteria) [95]. *In vitro*, carvacrol's immunomodulating properties led to a significant decrease in phagocytosis [92], but IL-6 production was not significantly affected. This is in contrast to our assessment, where 1 experiment showed enhanced IgM+ cells [96].

Some plant species were only represented in 1 experiment. Four plant species stood out due to a high total score: *Scrophularia striata* Boiss and *Ferulago angulata* (Schltdl.) Boiss (each 6 scoring points) and *F. suspensa* and *Mentha spicata* L. (each 5 scoring points). None of these plant species resulted in any negative effects. Therefore, they are shortly discussed in the following, although a plant species represented with only 1 experiment is less meaningful.

*S. striata* was shown to be antibacterial *in vivo* against coliform bacteria, prebiotic on Lactobacillus, immunotropic, and causing improved performance in broilers [97]. It is traditionally used for infectious diseases, allergies, and chronic inflammatory diseases [98] and to treat constipation in laying hens [21]. Its action has been reported to be antimicrobial, anti-inflammatory, and antioxidative and is caused by contained gallic acid, flavonoids, and phenylpropanoids [98, 99].

*F. angulata* showed antibacterial, prebiotic, and immunotropic effects and improved fattening, feed intake, and feed conversion rate in broilers [97]. Constituents such as $\alpha$-terpineol, terpenen-4-ol, $\alpha$-pinene, $\beta$-pinene, and $\rho$-cymene have been reported to be anti-inflammatory [100]. $\alpha$-Pinene is high concentrated in *F. angulata* and known for its antimicrobial properties [35], most probably via decreasing the bacterial membrane integrity [101].

*F. suspensa* resulted in antibacterial, antioxidant, immunotropic, and prebiotic effects, improved growth, and improved feed intake in broilers *in vivo* [102]. An *in vitro* trial showed that forsythiaside (a phenylethanoid glycoside) and forsythin (a lignan), 2 recently identified natural compounds (n = 237) of *F. suspensa* [103], inhibited the growth of *E. coli, P. aeruginosa,* and *S. aureus*. The same study also gave evidence for the antioxidant activity of *F. suspensa*. The improved weight gain might be explained by the repression of the growth of *E. coli* and the improved growth of lactobacillus [39].

## Conclusions

Data from this systematic review indicate that medicinal plants have the potential to reduce the use of antibiotics and antiprotozoals in poultry production. *O. vulgare, C. sativum, A. annua,* and *B. pilosa* are promising plant species for prophylaxis and therapy of bacterial and protozoal diseases in poultry. Several further plant species are interesting candidates for future research. Different dosages and phytochemical compositions of the used material may impact the outcome of the systematic review.

A comprehensive and transparent description of the used herbal preparations, as already recommended from the CONSORT group for human clinical trials with herbal interventions nearly 15 years ago, should be considered in future trials with poultry. The missing patentability for phytogenic feed additives might be addressed by phytochemical fingerprints in combination with some overall descriptions and analyses of the used plant material.

### Supporting information

S1: Protocoll of the systematic review. **Table 1S:** Detailed information on the 148 experiments used for the final analysis of the systematic review.

### Contributors' Statement

Conception and design of the work: H. Ayrle, M. Walkenhorst, V. Maurer, M. Mevissen, M. Melzig, T. S. Dalgaard; data collection: P. Farinacci, H. Ayrle; analysis and interpretation of the data: P. Farinacci, H. Ayrle, V. Maurer, M. Walkenhorst, M. Mevissen, M. Melzig, T. S. Dalgaard; statistical analysis: P. Farinacci, M. Walkenhorst, M. Mevissen; drafting the manuscript: P. Farinacci; critical revision of the manuscript: P. Farinacci, H. Ayrle, V. Maurer, M. Walkenhorst, M. Mevissen, M. Melzig, T. S. Dalgaard.

## Conflict of Interest

The authors declare that they have no conflicts of interest. The funding institution was not involved in the study design, collection, analysis, and interpretation of the obtained data or in the writing of the manuscript.

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