Antiviral Medicinal Plants of Veterinary Importance: A Literature Review#

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ABSTRACT

Viruses have a high mutation rate, and, thus, there is a continual emergence of new antiviral-resistant strains. Therefore, it becomes imperative to explore and develop new antiviral compounds continually. The search for pharmacological substances of plant origin that are effective against animal viruses, which have a high mortality rate or cause large economic losses, has garnered interest in the last few decades. This systematic review compiles 130 plant species that exhibit antiviral activity on 37 different virus species causing serious diseases in animals. The kind of extract, fraction, or compound exhibiting the antiviral activity and the design of the trial were particularly considered for review. The literature revealed details regarding plant species exhibiting antiviral activities against pathogenic animal virus species of the following families–*Herpesviridae, Orthomyxoviridae, Paramyxoviridae, Parvoviridae, Poxviridae, Nimaviridae, Coronaviridae, Reoviridae*, and *Rhabdoviridae*–that cause infections, among others, in poultry, cattle, pigs, horses, shrimps, and fish. Overall, 30 plant species exhibited activity against various influenza viruses, most of them causing avian influenza. Furthermore, 30 plant species were noted to be active against Newcastle disease virus. In addition, regarding the pathogens most frequently investigated, this review provides a compilation of 20 plant species active against bovine herpesvirus, 16 against fowlpox virus, 12 against white spot syndrome virus in marine shrimps, and 10 against suide herpesvirus. Nevertheless, some plant extracts, particularly their compounds, are promising candidates for the development of new antiviral remedies, which are urgently required.

Introduction

Viruses are unavoidable intracellular parasites that use the host's cellular machinery to survive and multiply [1], often leading to serious diseases in both animals and humans. Antiviral drug resistance is an increasing concern in the immunocompromised patient population, where ongoing viral replication and prolonged drug exposure result in the emergence of resistant strains [2]. The ever-increasing need for antiviral drugs is even more pronounced presently owing to unsatisfying and limited treatment modalities. Hence, medicinal plants with their diversified secondary plant compounds have promising potential to provide a solution regarding this.

In the underdeveloped regions of the world, herbal medicines still play a crucial role in the treatment of sick animals because of the lack of educated veterinarians and financial resources, as well

Dedicated to Prof. Wolfgang Kubelka on the occasion of his 85th birthday.

ABBREVIATIONS

AMPV	avian metapneumovirus (*Pneumoviridae*)
AcNPV	*Autographa californica* nuclear polyhedrosis virus (*Baculoviridae*)
ARV	avian reovirus = avian orthoreovirus (*Reoviridae*)
AIV	avian influenza virus (*Orthomyxoviridae*)
BCV	bovine coronavirus (*Coronaviridae*)
BoHV-1	bovine herpesvirus type 1 (*Herpesviridae*)
BoHV-2	bovine herpesvirus type 2 (*Herpesviridae*)
BoHV-5	bovine herpesvirus type 5 (*Herpesviridae*)
BPXV	buffalopox virus (*Poxviridae*)
BRV	bovine rotavirus (*Reoviridae*)
BQCV	black queen cell virus in honeybee (*Dicistroviridae*)
BVDV	bovine viral diarrhea virus (*Flaviviridae*)
EAV	equine arteritis virus (*Arteriviridae*)
EDSV	egg drop syndrome virus (*Flaviviridae*)
EHSV	equine herpes simplex virus (*Herpesviridae*)
FWPV	fowlpox virus (*Poxviridae*)
GPV	goose parvovirus (*Parvoviridae*)
GTPV	goat poxvirus (*Poxviridae*)
IBDV	infectious bursal disease virus (*Birnaviridae*)
IBV	avian infectious bronchitis virus (*Coronaviridae*)
IHNV	infectious haematopoietic necrosis virus (*Rhabdoviridae*)
ILTV	infectious laryngotracheitis virus (*Herpesviridae*)
KHV	koi herpesvirus (*Alloherpesviridae*)
NDV	Newcastle disease virus (*Paramyxoviridae*)
OMV	oncorhynchus masou virus (*Herpesviridae*)
PPMV-1	paramyxovirus type 1 (*Paramyxoviridae*)
PPV	porcine parvovirus (*Parvoviridae*)
PRRSV	porcine respiratory and reproductive syndrome virus (*Arteriviridae*)
RABV	rabies virus (*Rhabdoviridae*)
RPV	Rinderpest virus (*Paramyxoviridae*)
SIV	swine influenza virus (*Orthomyxoviridae*)
SuHV-1	suide herpesvirus type 1 (*Herpesviridae*)
VHSV	viral haemorrhagic septicaemia virus (*Rhabdoviridae*)
WHV	woodchuck hepatitis virus (*Hepadnaviridae*)
WNV	West Nile Virus (*Flaviviridae*)
WSSV	white spot syndrome virus in marine shrimp (*Nimaviridae*)
YHV	yellow head virus in shrimp (*Roniviridae*)

as the low availability of modern pharmaceuticals [3,4]. Therefore, medicinal plants and products have been used since ancient times in ethnomedicine and ethnoveterinary medicine [3], often without knowledge of the pathogen or the mode of action of the remedies. Nevertheless, the search for plant substances effective against animal viruses that cause high mortality or significant economic losses has garnered interest in the last few decades.

Domesticated animals, particularly pigs, poultry, and horses, and more recently, dogs and cats, have been noted to experience influenza infections that have the potential to transmit across species to other animals, as well as humans. Swine influenza virus infections are frequently detected among humans with exposure to pigs and become transmissible between humans more often than avian influenza viruses [5]. The current research is focused on antiviral substances against viruses that transmit across species, such as the coronavirus causing severe acute respiratory syndrome (SARS) during the 2002–2003 pandemic or the recent coronavirus outbreak originating from China (SARS-CoV-2).

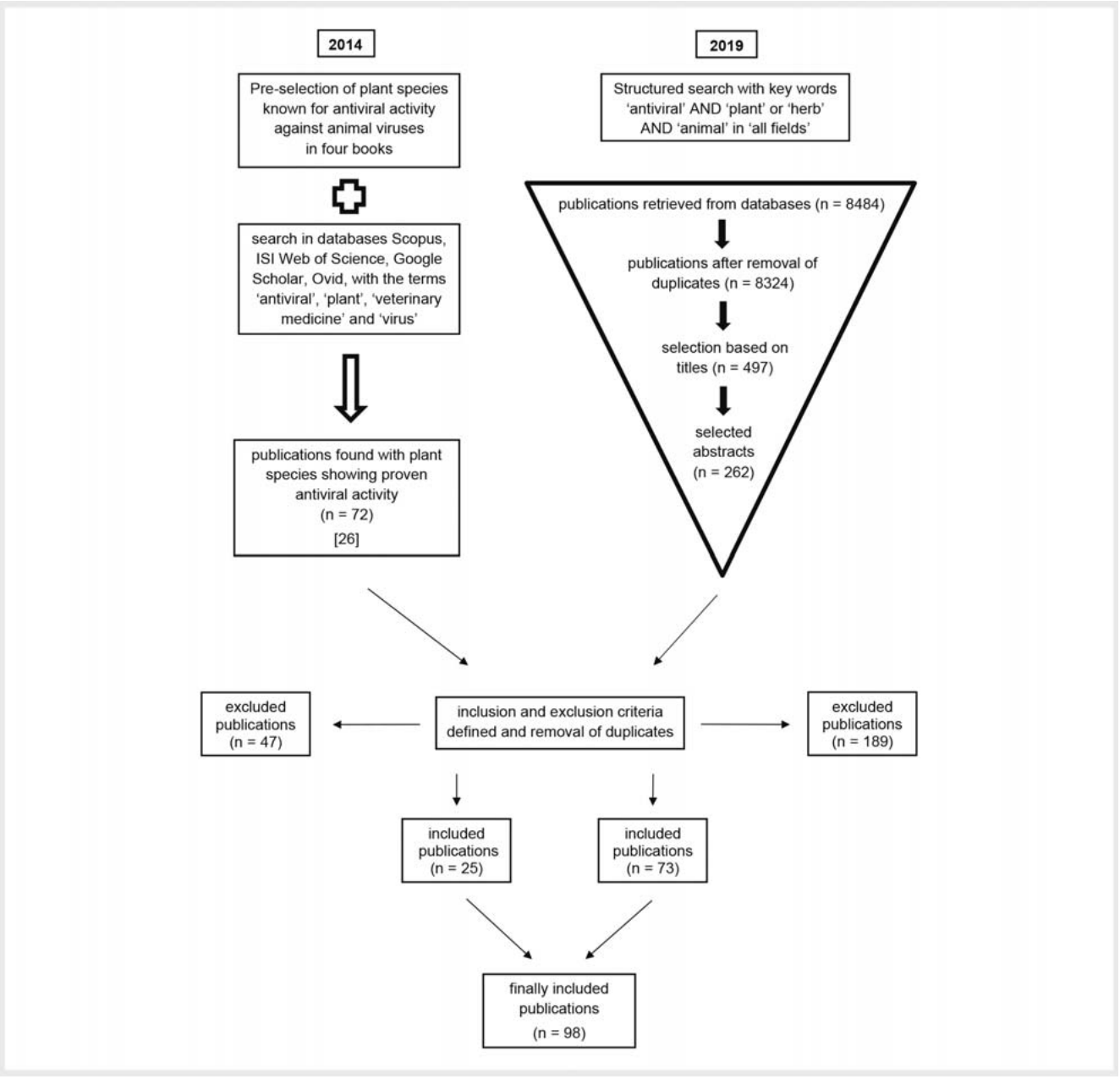
The second half of the 20th century discovered the antiviral activities of some vegetable tannins and flavonoids [6,7], such as the polyphenols of *Melissa officinalis* L. (Lamiaceae) [8] and triterpenoids like dammaradienol and ursonic acid [9]. The antiviral activity of flavonoids was soon determined to be effective against adenoviruses, Rous sarcoma virus, Sindbis virus, pseudorabies virus [10,11], severe acute respiratory syndrome coronavirus (SARS-CoV), respiratory syncytial virus, and influenza A virus H1N1 [12]. Epigallocatechin gallate, a compound of tea (*Camellia sinensis* (L.) Kuntze, Theaceae), has exhibited a broad range of activity against DNA and RNA viruses [13]. Several plant species, such as *Vaccinium angustifolium* Aiton (Ericaceae), *Vitis vinifera* L. (Vitaceae), and *Cinnamomum* species (Lauraceae), contain procyanidins that were shown to inhibit the replication of influenza A virus at various stages of the life cycle [14]. However, bioavailability and bioefficacy studies of polyphenols in humans revealed a wide variability of the data of different polyphenols after ingestion. Gallic acid and isoflavones are the most well-absorbed polyphenols, followed by catechins, flavanones, and quercetin glucosides, but with different kinetics. The least absorption was found for proanthocyanidins, galloylated tea catechins, and anthocyanins [15]. But these data cannot be directly transferred to animals. Bioavailability and bioefficacy of polyphenolic compounds has to be studied in each animal species separately.

Prominent modes of action against viruses are inhibition of viral entry and its replication in the host cell via different mechanisms. Some of these plant compounds could inhibit cellular receptor kinases, thereby interfering with cellular signal transduction [1]. The challenges of drug treatment involve low efficiencies, cytotoxic effects, and development of viral resistance against them.

Over the last decade, the antiviral activity of several biological substances could be proven *in vitro* because of new testing methods. Even though several studies exist regarding the antiviral activities of plant extracts against human viruses, mainly HIV and herpesviruses [16–18], similar studies concerning animal viruses are scarce. Therefore, the objective of this review was to survey plant species with activities against viruses causing serious diseases, particularly those with high infection rates leading to a high mortality or large economic losses. The review primarily focused on the kind of extract, fraction, or isolated substance of a specific plant part and the design of the trial conducted.

Methods

The methods of this systematic review were based on the recommendations of the PRISMA statement [19,20] and the AMSTAR measurement tool [21].



▶ **Fig. 1** Process of the literature search.

The literature research for this review was performed in 2 periods. The first period ranged from February to end of August 2014, and 1 person screened 4 books on ethnoveterinary medicine [22–25] for antiviral plant species, as well as searched in databases, such as Scopus, Ovid, ISI Web of Science, and Google Scholar by using the search words "antiviral", "plant", "veterinary medicine", and "virus" [26].

In the second period in 2019, 1 person used Ovid (Medline) and CAB Direct for a structured search. The keywords used for the search in January 2019 were "antiviral" AND "plant" or "herb" AND "animal". In order to select the information about specific animal viruses in the following months, combinations of keywords consisting of the scientific abbreviation or the full name of an animal virus causing a serious animal disease (such as "NDV", "BoHV", etc.) AND "antiviral" AND "plant" were used. Notably, only English key words were applied. Moreover, a manual search was performed based on the bibliographic references of the articles found. The search was not limited by year of publication. Not all publications published in 2019 concerning the relevant virus species could be covered in this review, because the search of combination of keywords as described above was performed over several months. Search in December 2019 included a slightly longer period than in January 2019. The titles and abstracts of the obtained publications (▶ **Fig. 1**) were screened manually and read

by 1 person. Inclusion or exclusion was performed per the predefined inclusion and exclusion criteria, and duplicates generated in both searches in 2014 and 2019 were removed.

The publications were included based on the following criteria:

1. Only peer-reviewed publications with an abstract written in English were considered.
2. Publications had to describe assays testing plant species *in vitro, in ovo*, or *in vivo* for their antiviral effects against virus species causing serious infections in pigs, birds, ruminants, horses, shrimps, fish, or bees.
3. Publications that indicated the scientific name of the virus and its abbreviation.
4. Those that confirmed the identification of the used plant species.
5. Publications that described the method of extraction, fractionation, or isolation of compound(s) of the plant species.
6. Publications with proven antiviral activities of the plant species against viruses causing notifiable diseases [27, 28] or diseases with high infection rate leading to high mortality or large economic losses.

Publications without an abstract, presented only in conferences, and not in peer-reviewed journals, investigating a mixture of different plant species or extracts in a combined preparation or evaluating blends of several essential oils or mixtures of commercially available pure essential oil compounds were excluded. Furthermore, publications dealing with viruses that primarily caused infections of humans; publications studying the improvement of the immunity through immune stimulatory or immune boosting activities of plant extracts without explicit antiviral effects in infected animals; publications dealing with enhancement of immune responses to virus vaccine by supplementation of plant extract; studies testing the antiviral activity of a plant extract, fraction, or compound without success, as well as those testing viruses in a mouse or rat model, were excluded from the present review. Full text was retrieved of the publications that were eventually included.

In some publications, extracts, fractions, or compounds of numerous plant species were tested. Only those plant species that exhibited a proven antiviral activity against a specific animal virus species causing a serious disease are listed in ▶ **Table 1** and **Table 1S**, Supporting Information. Those plant species that were investigated but did not exhibit any antiviral activity were not mentioned in this review. In many publications, several extracts of different plant species were investigated against 1 or more virus species and in some of them even with different methods (*in vitro, in ovo*, or *in vivo*).

Results and Discussion

Overall, 72 publications related to 79 plant species with proven antiviral activities against animal virus species could be identified in 4 ethnoveterinary regions (24 plant species in Africa, 11 in Asia, 13 in Latin America, and 31 in Western Countries, including Europe, USA, and Canada) in the first part of the search [26] (▶ **Fig. 1**).

From OVID (n = 5097) and CAB Direct (n = 3387) databases, 8484 publications were retrieved after the literature search in 2019 (second part of the search) by using the following combination of key words in "all fields": "antiviral" AND "plant" AND "animal". Removal of duplicates yielded 8324 publications. Restricting the search of the same terms to only the abstracts yielded titles of 497 publications, which were then manually screened, and 262 abstracts were selected (▶ **Fig. 1**). After inclusion or exclusion per the predefined inclusion and exclusion criteria and removal of duplicates generated in both searches, 25 publications of the search in 2014 and 73 of the search of 2019 were included in this review.

Even though all databases used for the searches delivered several useful results, CAB Direct, including the databases CAB Abstracts and Global Health, which specializes in applied life sciences, provided the best results by using the most specific indexing terms in its databases.

In summary, 130 plant species with antiviral activity on 37 different animal virus species were compiled. This review noted several plant species that were active against virus species causing serious diseases in birds. The antiviral medicinal plant species exhibiting activities against serious veterinary viral pathogens are presented in **Table 1S**, Supporting Information. The literature review revealed 46 plant species that were active against pathogenic virus species of the virus family *Herpesviridae*, 31 plant species with antiviral activity against *Paramyxoviridae*, 30 against *Orthomyxoviridae*, 19 against *Poxviridae*, and 12 against *Nimaviridae*. Furthermore, this review included 9 plant species with activity against *Reoviridae*, 7 against *Flaviviridae*, 5 against *Coronaviridae*, 5 against *Baculoviridae*, 4 against *Rhabdoviridae*, and 1 to 3 plant species against viruses of 8 other virus families. Notably, some members of these virus families cause diseases with significant economic losses. However, the research interest varies among the different ethnoveterinary groups concerning the animals, plants, and viruses occurring in various areas and climates. For example, several African medicinal plants were tested for their effects against NDV (*Paramyxoviridae*), whereas numerous Asian and Latin American medicinal plants were tested against bovine herpes viruses (*Herpesviridae*).

Nevertheless, the present review only included plant species exhibiting an antiviral effect against virus species causing notifiable diseases per the World Organisation of Animal Health (OIE) [27] and the Austrian legislation [28]. A list of these diseases and the virus species causing them is provided in ▶ **Table 2**. Virus species causing these notifiable diseases are marked in bold in ▶ **Table 1** and **Table 1S**, Supporting Information. ▶ **Table 1** provides a compilation of the plant species that are active against more than 1 specific virus species, as well as informs regarding the plant part used in the preparation of the specific extract, fraction, or compound(s), the power of the antiviral activity, and the design of the trial (*in vitro, in vivo*, or *in ovo*). Direct comparison of the strength of the antiviral activity of different plant extracts is often difficult, because various testing methods were used. Therefore, if available, the 50 % inhibitory concentration (IC_{50}) and the maximal nontoxic concentration (MNTC) of the plant extract found in *in vitro* and *in ovo* tests as well as the administered doses and the survival rate (SR) or the 50 % effective concentration (EC_{50}) in *in vivo* trials were listed in ▶ **Table 1**. In some cases, antiviral activity was determined only at 2 nontoxic concentrations of the plant extract.

▶ **Table 1** Compilation of plant species exhibiting antiviral activity against more than 1 animal virus causing notifiable diseases (virus marked in bold) or diseases with high infection rate leading to high mortality or large economic losses; plant family; abbreviation of virus species; reference; plant part used for obtaining extracts, fractions or compound(s); power of activity; and design of the trial.

Plant species	Plant family	Virus species	Ref.	Extract/fraction/ compound(s)	Plant part	Activity	Design of trial
Acacia nilotica (L.) Delile	Leguminosae	**BoHV-1**	[40]	hot aqueous extract	leaf and pod	L: prot: 61.1 % (0.156 mg/mL), 43.2 % (0.078 mg/mL); P: prot: 22.1 % (0.039 mg/mL), 14.4 % (0.019 mg/mL)	*in vitro*
		GTPV	[83]	aqueous extract	leaf	EC_{50}: 3.75 µg/mL, TI: 127.1	*in vitro*
Allium sativum L.	Amaryllidaceae	**NDV**	[43]	aqueous extract	bulb	EID_{50}: no infection; garlic extract: 25 mg/mL; 50 mg/mL	*in ovo*
		IBV	[76]	aqueous extract	clove	EI: 1296 ± 269 (v. d. 10^{-2}), 2604 ± 1251 (v. d. 10^{-3}); garlic extract: 400 mg/mL	*in ovo*
		AIV H9N2	[84]	aqueous extracts	clove	HPS: 2.0; 15 % dry extract of 10 g cloves in 100 mL	*in ovo*
Aloe hijazensis = *Aloe castellorum* J. R. I. Wood	Xanthorrhoeaceae	**AIV H5N1**, **NDV**, EDSV	[85]	ethanolic extracts	leaf, flower, root	CC_{50}: > 500–800; IC_{50}: ≤ 5–9; TI: 62.5–160	*in ovo*
Aristolochia bracteolate Lam.	Aristolochiaceae	**NDV**, FWPV	[57]	MeOH extract	leaf, fruit	HAI: L/F: 7/15 % (100 µg/mL); 57.5/22.5 % (200 µg/mL)	*in ovo*
Avicennia marina (Forssk.) Vierh.	Acanthaceae	**NDV**, FWPV	[57]	MeOH extract	leaf, stem	HAI: L/S: 7/7 % (100 µg/mL); 22.5/22.5 % (200 µg/mL)	*in ovo*
Azadirachta indica A. Juss.	Meliaceae	**BoHV-1**	[39]	aqueous extract, pectic arabinogalactan and derivative	leaf	IC_{50}: 31.12–105.25 µg/mL; CC: > 1600–1440 µg/mL	*in vitro*
		FWPV	[86]	aqueous extract	leaf	n. a.	*in vitro*
		IBDV **NDV**	[87]	different extracts	leaf, fruit	CC_{50}: > 200–900 µg/mL; IC_{50}: ≤ 3–9 µg/mL; TI: > 66–120	*in vitro* and *in ovo*
Banisteriopsis variabilis B. Gates	Malphigiaceae	**BoHV-1**, ARV	[31]	crude aqueous extract	leaf	CC: 624–125 µg/mL; VII: 2.79/2.69; IP: 99/99 %	*in vitro*
Bumelia sertorum Mart.	Sapotaceae	**BoHV-1**, **SuHV-1**	[38]	crude aqueous extract	leaf	CC: 250 µg/mL; VII: ≥ 1.5	*in vitro*
Byrsonima intermedia A. Juss.	Malphigiaceae	**BoHV-1**, ARV	[31]	crude aqueous extract	leaf	CC: < 125 µg/mL; VII: 2.67/1.50; IP: 99/97 %	*in vitro*
Camellia sinensis (L.) Kuntze	Theaceae	**AIV H7N3**	[88]	hot aqueous green tea extract	leaf	IC: 80 mg/mL	*in ovo*
		AIV H5N2	[89]	hot aqueous black tea extract	leaf	log_{10} reduction: ≥ 3.7	*in vitro*
		BRV	[75]	several theaflavins	leaf	EC_{50}: 0.125–251.39 µg/mL	*in vitro*
		BCV	[75]	aqueous green tea extract	leaf	EC_{50}: 34.7 µg/mL	*in vitro*
		ILTV	[90]	hot aqueous extract, epi-gallocatechin-3-gallate	leaf	MNCC: 90 µM; EC_{50}: 4.22 µM	*in vitro*

continued

▶ **Table 1** *Continued*

Plant species	Plant family	Virus species	Ref.	Extract/fraction/ compound(s)	Plant part	Activity	Design of trial
Campomanesia xanthocarpa (Mart.) O. Berg	Myrtaceae	**BoHV-1**, ARV	[31]	crude aqueous extract	leaf	CC: 624–125 µg/mL; VII: 2.08/1.50; IP: 99/97 %	*in vitro*
Caralluma retrospiciens (Ehrenb.) N. E.Br.	Apocynaceae	**NDV**, FWPV	[57]	MeOH extract	herb	HAI: 22.5 % (100 and 200 µg/mL)	*in ovo*
Castanea spp.	Fagaceae	ARV, AMPV	[73]	Silvafeed (ENC, ENC400, CE) 77–91 % hydrolysable tannins	wood	CC_{50}: 243–272 µg/mL; IC_{50}: 38–59 µg/mL	*in vitro*
Cissus quadrangularis L.	Vitaceae	**NDV**, FWPV	[57]	MeOH extract	herb	HAI: 22.5 % (100 µg/mL); 7 % (200 µg/mL)	*in ovo*
Coffea arabica L.	Rubiaceae	**BoHV-1, SuHV-1**	[38]	crude aqueous extract	leaf	CC: 250 µg/mL; VII: ≥ 1.5	*in vitro*
Diospyros mespiliformis Hochst. ex A.DC.	Ebenaceae	**NDV**, FWPV	[57]	MeOH extract	bark, leaf	HAI: 100 %, (100 and 200 µg/mL)	*in ovo*
Echinacea purpurea (L.) Moench	Asteraceae	**AIV (H5N1, H7N7)**, SIV H1N1	[47]	Echinaforce, EtOH (65 %)	herb, root	MIC_{100}: 0.32 µg/mL for 10^2 PFU/mL; 7.5 µg/mL for 10^5 PFU/mL virus	*in vitro*
Emilia sonchifolia (L.) DC. ex DC.	Asteraceae	**WSSV, YHV**	[64]	acetone extract and fractions, 1 containing 2,4-di-tert-butylphenol	leaf	100 µg/mL	*in vitro*
Endopleura uchi (Huber) Cuatrec.	Humiriaceae	**BoHV-1, SuHV-1**	[38]	crude aqueous extract	leaf	CC: 250 µg/mL; VII: ≥ 1.5	*in vitro*
Eugenia jambolana Lam. = *Syzygium cumini* (L.) Skeels	Myrtaceae	BPXV	[91]	aqueous extract	leaf	MNTC: 1999.73 µg/mL; EC_{50}: 134 µg/mL; TI: 56.47	*in vitro*
		GTPV	[83]	aqueous extract	leaf	EC_{50}: 46.5 µg/mL, TI: 162.7	*in vitro*
Excoecaria agallocha L.	Euphorbiaceae	IBDV, FWPV, **RPV**	[92]	latex	n. a.	n. a.	*in vitro*
Glycyrrhiza glabra L.	Leguminosae	**NDV**	[44]	aqueous extract	n. a.	0.6 mg/mL	*in ovo*
		PPMV-1	[34]	spray dried aqueous solution of extract	root	300 or 500 mg/kg BW, 7 dpi; viral RNA copy number in livers and kidneys 4-fold lower than in control group	*in vivo*
Guiera senegalensis J. F. Gmel.	Combretaceae	FWPV	[58–60]	aqueous decoctions, aqueous acetone extract	gall	*in vitro*: CC_{50}: 90 µg/mL; EC_{50}: 15.6 µg/mL; SI: 5.8; *in ovo*: MNTC: 250 µg/mL; 1.9 log reduction of virus titre at 25 µg/mL and 2.9 log at 250 µg/mL; *in vivo*: 100 mg/kg BW	*in vitro, in ovo, in vivo*
		EHSV	[93]	fractionated ethanolic (80 %) extract	leaf	EC: 20 µg/mL, 75 % inhibition	*in vitro*
Harrisonia abyssinica Oliv.	Rutaceae	**NDV**, FWPV	[57]	MeOH extract	leaf, fruit	HAI: L/F: 30 %/15 % (100 µg/mL); 7 %/7 % (200 µg/mL)	*in ovo*
Hypericum perforatum L.	Hypericaceae	**PRRSV**	[29, 94, 95]	extract, hypericin, pseudohypericin	n. a.	*in vivo*: extract: 200 mg/kg BW	*in vitro* and *in vivo*
		AIV H5N1	[96, 97]	liquid extract, hypericin	n. a.	n. a.	*in vitro* and *in vivo*

continued

▶ **Table 1** *Continued*

Plant species	Plant family	Virus species	Ref.	Extract/fraction/ compound(s)	Plant part	Activity	Design of trial
Isatis tinctoria L. = Isatis indigotica Fortune	Brassicaceae	PPV	[54]	n. a.	root	310–630 µg/mL	*in vitro*
		AIV (H6N2, H7N3, H9N2)	[98]	root-derived clemastanin B	root	IC_{50}: 88–370 µg/mL	*in vitro*
		GPV	[56]	root derived poly-saccharides	root	72 h p. i. 40 µg polysaccharides, 2^3 highest dilution of pos. allantoic fluid; average survival time 192 h with survival rate 6/6	*in ovo*
Lantana camara L.	Verbenaceae	**AIV (A/H9N2, A/H5N1)**	[14]	extract according to Chinese Pharmacopoeia	procyanidin	n. a.	*in vitro*
		WSSV	[63]	aqueous extract	n. a.	150 mg/kg BW	*in vivo*
Lavandula coronopifolia Poir.	Lamiaceae	**NDV**, FWPV	[57]	MeOH extract	herb	HAI: 100%, (100 and 200 µg/mL)	*in ovo*
Leandra purpurascens (DC.) Cogn.	Melastomataceae	**BoHV-1, SuHV-1**	[38]	crude aqueous extract	leaf	CC: 125 µg/mL; VII: ≥ 1.5	*in vitro*
Lippia graveolens Kunth	Verbenaceae	BoHV-2	[42]	commercial essential oil	n. a.	CC_{50}: 568 µg/mL; EC_{50}: 58.4 µg/mL; SI_{50}: 9.7	*in vitro*
				carvacrol	pure substance	CC_{50}: 215 µg/mL; EC_{50}: 663 µg/mL; SI_{50}: 0.3	*in vitro*
		BVDV	[42]	commercial essential oil	n. a.	CC_{50}: 568 µg/mL; EC_{50}: 78 µg/mL; SI_{50}: 7.2	*in vitro*
				carvacrol	pure substance	CC_{50}: 215 µg/mL; EC_{50}: 50.7 µg/mL; SI_{50}: 4.2	*in vitro*
Maerua oblongifolia (Forssk.) A. Rich.	Capparaceae	**NDV**, FWPV	[57]	MeOH extract	leaf	HAI: 15% (100 µg/mL); 7% (200 µg/mL)	*in ovo*
Melissa officinalis L.	Lamiaceae	**NDV**	[8]	aqueous extract	leaf	n. a.	*in vitro, in ovo*
		AIV H9N2	[99]	essential oil	leaf	5 µg/mL reduced $TCID_{50}$ to 1.9 (log 10); 500 µg/mL to 0.98 (log 10) in pre-infection stage	*in vitro*
		KHV	[100]	aqueous dry extract	leaf	extract in feed: 1.62%, SR: 45% (9/20)	*in vivo*
Momordica charantia L.	Cucurbitaceae	**WSSV**	[63]	methanol extract	n. a.	150 mg/kg BW	*in vivo*
		IHNV, OMV	[101]	n. a.	n. a.	PRR: IHNV: 68%; OMV: 47%	*in vitro*
Nigella sativa L.	Ranunculaceae	**NDV**, FWPV	[57]	methanolic extract	seed	HAI: 100%, (100 and 200 µg/mL)	*in ovo*
		ILTV	[90]	hot aqueous extract, thymoquinone	seed	MNCC: 80 µM; EC_{50}: 35 µM	*in vitro*
Olea europaea L.	Oleaceae	**VHSV**	[102]	extract, oleuropein	leaf	VHSV: conc.: n. a.; IR: extract 10%; oleuropein 30%	*in vitro*
		ILTV	[103]	aqueous extract	leaf	CC_{50}: 1250 µg/mL; IC_{50}: 5.89 µg/mL	*in vitro*

continued

▶ **Table 1** *Continued*

Plant species	Plant family	Virus species	Ref.	Extract/fraction/ compound(s)	Plant part	Activity	Design of trial
Origanum vulgare L.	Lamiaceae	EAV	[104]	ethanolic extract, isolated compounds (phenolic acids, kaempferol, apigenin, quercetin)	leaf	NTC: 12.5 µg/mL; $\log_{10}$ $TCID_{50}$/100 µL extract: 1.25; quercetin: 0.6, control: 6.08	*in vitro*
			[105]	aqueous (AE) and ethanolic extract (EE)	leaf	NTC: AE: 1600 µg/mL; EE: 600 µg/mL; $\log_{10}$ $TCID_{50}$/100 µL: AE: 2.09; EE: 0.79, control: 5.42	*in vitro*
		SuHV-1	[38]	crude aqueous extract	leaf	CC: 62.5 µg/mL; VII: ≥ 1.5	*in vitro*
Phyllantus amarus Schumach & Thonn.	Phyllantaceae	**WSSV**	[63]	aqueous extract	n. a.	150 mg/kg BW	*in vivo*
			[65, 66]	acetone and petroleum ether extracts	leaf	dose: n. a., SR: 100% (9/9)	*in vivo*
			[101]	n. a.	n. a.	SR: 58%	*in vivo*
		IHNV, OMV	[101]	ethanolic extract	n. a.	CC_{50}: 1.237 µg/mL; PRR: 100%	*in vitro*
		YHV	[101]	n. a.	n. a.	SR: 100%	*in vivo*
Prosopis chilensis (Molina) Stuntz	Leguminosae	**NDV**, FWPV	[57]	MeOH extract	leaf	HAI: 30% (100 µg/mL); 15% (200 µg/mL)	*in ovo*
Psidium cattleianum Afzel. ex Sabine	Myrtaceae	**BoHV-1, SuHV-1**	[38]	crude aqueous extract	leaf	CC: 62.5 µg/mL; VII: ≥ 1.5	*in vitro*
Schinopsis spp.	Anacardiaceae	ARV, AMPV	[73]	Silvafeed NutriQ, 94% condensed tannins	wood	CC_{50}: 254 µg/mL; IC_{50}: 21–66 µg/mL	*in vitro*
Synadenium glaucescens Pax	Euphorbiaceae	IBDV, FWPV	[61]	ethanolic extract	root bark	200 µg/mL; SR: 100% (5/5); significantly higher mean embryo weight	*in ovo*
Uncaria tomentosa (Willd. ex Schult.) DC.	Rubiaceae	**BoHV-1, SuHV-1**	[38]	crude aqueous extract	leaf	CC: 500 µg/mL; VII: ≥ 1.5	*in vitro*
Zizyphus spina-christi (L.) Desf.	Rhamnaceae	**NDV**, FWPV	[57]	MeOH extract	leaf, bark	HAI: L/B: 22.5/100% (100 µg/mL); 0/100% (200 µg/mL)	*in ovo*

CC: cytotoxic concentration, dpi: day post infection, EC: effective concentration, EI: embryo index, EID: egg infective dose, HAI: hemagglutination inhibition, HPS: histopathological score, IC_{50}: 50% inhibitory concentration, IP: inhibition percentage, IR: infectivity reduction, MNCC: maximal noncytotoxic concentration, MNTC: maximal nontoxic concentration, prot: protection, PRR: plaque reduction rate, n. a.: information not available, SI_{50}: selectivity index (CC_{50}/IC_{50}), SR: survival rate, TI: therapeutic index (CC_{50}/IC_{50}), v. d.: virus dilution, VII: viral inhibition index

▶ **Table 2** List showing notifiable diseases per the World Organisation of Animal Health (OIE) [27] and the legislation in Austria [28], virus species and their abbreviations, as well as virus family causing the particular disease in a specific host and number of plant species found active against the named virus.

Disease	Virus species	Abbreviation of virus	Family of virus	Host	Plant species
avian influenza	avian influenza virus	AIV	*Orthomyxoviridae*	poultry	26
infectious bovine rhinotracheitis (IBR), infectious pustular vulvovaginitis (IPV), and infectious balanoposthitis (IBP)	bovine herpesvirus type 1	BoHV-1	*Herpesviridae*	cattle	20
rotaviral diarrhea	bovine rotavirus	BRV	*Reoviridae*	cattle	1
bovine viral diarrhea	bovine viral diarrhea virus	BVDV	*Flaviviridae*	cattle	5
goatpox	goat poxvirus	GTPV	*Poxviridae*	goat	2
infectious hematopoietic necrosis infection	infectious hematopoietic necrosis virus	IHNV	*Rhabdoviridae*	fish	2
koi herpesvirus disease	koi herpesvirus	KHV	*Alloherpesviridae*	koi	2
Newcastle disease	Newcastle disease virus	NDV	*Paramyxoviridae*	poultry	30
rabies	rabies virus	RABV	*Rhabdoviridae*	multiple species	1
Rinderpest infection	Rinderpest virus	RPV	*Paramyxoviridae*	multiple species	1
pseudorabies	suide herpesvirus type 1	SuHV-1	*Herpesviridae*	pig	10
viral hemorrhagic septicemia infection	viral hemorrhagic septicemia virus	VHSV	*Rhabdoviridae*	fish	1
West Nile fever	West Nile virus	WNV	*Flaviviridae*	multiple species	1
white spot syndrome virus infection	white spot syndrome virus	WSSV	*Nimaviridae*	Crustacea	12
yellow head virus genotype 1 infection	yellow head virus genotype 1	YHV	*Roniviridae*	Crustacea	2

Table 1S, Supporting Information, provides similar information regarding all plant species that were noted to be active against the virus species, based on the inclusion and exclusion criteria. A closer look into the design of the studies shows that 94 plant species were investigated *in vitro*, 37 *in ovo* on embryonated eggs, and 24 *in vivo*. A significant part of the *in vivo* studies was performed on poultry, shrimps, and crayfish. Only 1 study dealt with experimental infections of PRRSV on piglets [29] and 1 with hepatitis viruses on woodchuck [30]. The aqueous extract of *Phyllanthus niruri* L. (Phyllantaceae) was effective when administered i. p. in reducing and eliminating both the surface antigen titer and DNA polymerase activity in serum after experimental infections with WHV in woodchuck [30]. Notably, *in vivo* studies on mouse and rat models were excluded from the present review. The strategy to include in this review only the plant species found active against a specific virus in a cited study might produce a certain positive bias. It possibly happened only in a very few cases that a plant extract was tested against the same virus species with the same method and found active in 1 study and inactive in another study. However, even in those cases, it seems worth listing the plant species and the antiviral activity found against a specific animal virus in **Table 1S**, Supporting Information, and ▶ **Table 1**, in order to encourage the scientific society to confirm or deny these activities in further studies.

In the present review, it is not possible to describe the antiviral assays performed for each plant species. So that the reader gets an idea about the assays performed, usual work flows for *in vitro, in ovo*, and *in vivo* studies are described. Cytotoxicity assays were performed *in vitro* by exposure of cell strains (*e.g.*, Madin-Darby bovine kidney [MDBK] or Vero cells) to the plant extracts in different concentrations following incubation in microtiter plates. Cell alterations were monitored microscopically or with specific dyes entering only dead cells to determine the MNTC compared to an untreated control. Then cells were incubated for a defined period of time with the plant extracts in dilutions corresponding to the MNTC and inoculated with dilutions of viruses corresponding to tissue culture infective dose ($TCID_{50}$). Controls consisted of untreated infected (virus titer), treated noninfected (extract control), and untreated noninfected (cell control) cells. Antiviral activities could be calculated as the difference of virus titer between treated infected and untreated infected control cultures [31].

During *in ovo* tests, different concentrations of the plant extracts were injected into allantoic cavity of 7-day-old embryonated chicken eggs, in order to find the MNTC. If the extracts were not toxic for the eggs, the chickens would be born alive and healthy after 2 wks of incubation. For the test of antiviral activity of the extracts, a virus strain (*e.g.*, NDV) was inoculated to infection-free 9-day-old embryonated chicken eggs. After 4 days, the allantoic fluid was harvested, and hemagglutination (HA) test was applied to confirm the virus. Next, the plant extracts were mixed with different concentrations of the virus, and the mixture was inoculated after incubation to allantoic cavity of viable 7- to

10-day-old embryonated eggs. Uninoculated eggs and eggs with virus suspension without plant extract served as controls. The allantoic fluid was harvested 5 days after inoculation and analyzed for virus titer by a standard HA test. Antiviral activity of the plant extracts was measured by the reduction assay of viral titer and explained by inhibition percentage [32, 33].

As an example, for *in vivo* studies, the evaluation of the antiviral effectiveness of various doses of *Aloe vera* (L.) Burm.f. (Xanthorrhoeaceae) and *Glycyrrhiza glabra* L. (Leguminosae) extracts on the course of experimental PPMV-1 infection in pigeons is described [34]. The experiment was performed on pigeons divided into 5 groups, including 1 control group and 4 experimental groups, which were orally administered aloe vera or licorice extracts at 300 or 500 mg/kg BW for 7 days after experimental inoculation with PPMV-1. On day 4, 7, and 14 after inoculation, cloacal swabs and samples of organs were collected from 4 birds in each group. The samples were analyzed to determine the copy number of PPMV-1 RNA by TaqMan qPCR. The results indicated that both extracts inhibited PPMV-1 replication by decreasing viral RNA copy numbers in the examined organs (brain, kidney, and liver) compared to the control group [34].

The following sections present the information regarding virus families and their crucial members against which plant species were noted to exert antiviral activity, as evidenced in the literature.

Herpesviridae

Table 1S, Supporting Information, lists 20 plant species exhibiting antiviral effects against BoHV-1, 1 against BoHV-2, 2 against BoHV-5, 8 against EHSV, and 10 against SuHV-1. Moreover, **Table 1S**, Supporting Information, presents 3 plant species that exerted antiviral activity against ILTV and 2 plant species against the fish herpes virus, OMV.

Herpesviridae is a large family of DNA viruses that cause infections and certain diseases of animals, as well as humans [35]. Overall, more than 130 herpesviruses are known [36], some of them noted in mammals, birds, fish, reptiles, amphibians, and molluscs [37].

One representative of this family is BoHV-1, subfamily *Alphaherpesvirinae*, known to cause several diseases in cattle worldwide, including rhinotracheitis, vaginitis, balanoposthitis, abortion, conjunctivitis, and enteritis. Although these symptoms are primarily nonlife-threatening, it is an economically critical disease because the infection causes a drop in production and affects trade restrictions. Like other herpesviruses, BoHV-1 causes a lifelong latent infection and sporadic shedding of the virus. Some European countries have successfully eradicated the disease by applying a strict culling policy.

Antiviral activities against BoHV-1 could be observed in several Brazilian medicinal plants, such as *Banisteriopsis variabilis* B. Gates (Malpigiaceae), *Byrsonima intermedia* A. Juss. (Malpigiaceae), *Campomanesia xanthocarpa* (Mart.) O. Berg (Myrtaceae), *Cissus erosa* Rich. (Vitaceae), *Erythroxylum deciduum* A. St.-Hil. (Erythroxylaceae), *Lacistema hasslerianum* Chodat (Lacistemataceae), *Ocotea pulchella* (Nees & Mart.) Mez (Lauraceae), and *Xylopia aromatica* (Lam.) Mart. (Annonaceae) [31]. In addition, *Bumelia sertorum* Mart. (Sapotaceae), *Coffea arabica* L. (Rubiaceae), *Endopleura uchi* (Huber) Cuatrec. (Humiriaceae), *Leandra purpurascens* (DC.) Cogn. (Melastomataceae), *Psidium cattleianum* Afzel. ex Sabine (Myrtaceae), and *Uncaria tomentosa* (Willd. ex Schult.) DC. (Rubiaceae) exhibited antiviral activity on BoHV-1 as well as SuHV-1 [38].

The activity of the leaf extract of *Azadirachta indica* A. Juss. (Meliaceae) against BoHV-1 is attributed to the polysaccharide arabinogalactan [39]. Hot aqueous extracts of *Acacia nilotica* (L.) Delile leaves exhibited a 3 times stronger antiviral effect against BoHV-1 than the pods [40].

BoHV-5, the bovine encephalitis herpesvirus, causes meningoencephalitis and respiratory disease in cattle and sheep. Hexane and ethyl acetate extracts of *Plocamium brasiliense* (Greville) M. Howe & W. R. Taylor (Plocamiaceae), a marine alga, inhibited virus attachment in MDBK cells [41].

Antiviral activity of the *Lippia graveolens* Kunth, Mexican oregano (Verbenaceae) essential oil and its main compound carvacrol was observed to be active against BoHV-2 [42]. The essential oil of *L. graveolens* provides the advantage to be effective against both RNA and DNA viruses. Besides herpesviruses, BVDV (*Flaviviridae*), a RNA virus, was also inhibited in the same study [42].

Paramyxoviridae

Citations of 30 plant species with activity against NDV were noted in the literature (**Table 1S**, Supporting Information). Recent investigations were performed on extracts of the brown leaves of *Allium cepa* L. (Amaryllidaceae) and the bulbs of *Allium sativum* L. (Amaryllidaceae) [43], ethanol/water extract of flowers of *Achillea millefolium* L. (Asteraceae) [32], and aqueous extract of *G. glabra* L. (Leguminosae) powder, all of which inhibited NDV in embryonated eggs [44].

As listed by the World Organisation for Animal Health (OIE), Newcastle disease is a disease of major significance in poultry and other birds. It is caused by specified viruses of the avian paramyxovirus type 1 of the family *Paramyxoviridae* [45]. The disease is characterized by respiratory or neural signs, partial or complete cessation of egg production or misshapen eggs, greenish watery diarrhea, and edema of the tissues around the eyes and the neck.

Fucoidan is a sulfated polysaccharide present in the cell wall matrix of the brown algae *Cladosiphon okamuranus* Tokida (Chordariaceae). It exhibited antiviral activity against NDV in the Vero cell line with low toxicity, and this inhibition was observed particularly in the early stages of infection [46].

Orthomyxoviridae

Well-known representatives of the family *Orthomyxoviridae* are the 4 genera of influenza viruses A–D. These viruses cause influenza in vertebrates, including birds, humans, and other mammals.

The literature revealed 30 plant species that exhibited activity against several types of influenza viruses (**Table 1S**, Supporting Information), mostly the ones causing avian influenza and swine flu.

Highly pathogenic avian influenza virus of the H5- and H7-types, as well as swine origin influenza (H1N1), were all inactivated in cell culture assays by the commercially available preparation of *Echinacea purpurea* (Echinaforce = EF) at different concentrations. Detailed studies with the H5N1 strain indicated that direct contact between EF and virus was required, before infection, to obtain maximum inhibition of virus replication. Hemagglutina-

tion assays revealed that the extract inhibited the receptor binding activity of the virus, suggesting that the extract interferes with the viral entry into cells. Upon sequential passage studies, no EF-resistant variants emerged during treatment in the cell culture with the H5N1 virus, in contrast to Tamiflu, which produced resistant viruses upon passaging. Furthermore, the Tamiflu-resistant virus was just as susceptible to EF as the wild type virus [47].

The review of Arora et al. [48] presented a list of medicinal plants used in Ayurveda and traditional Chinese medicine with antiviral effects against influenza, which could be useful in the management of H1N1 flu, the pandemic arising from swine flu.

Glycyrrhizin, a triterpene saponine of licorice root (*G. glabra* L.), was comprehensively investigated for its antiviral properties. It has been noted to interfere with replication or cytopathogenic effect induction in several viruses, including respiratory viruses and influenza viruses [49]. Michaelis et al. [50] studied the effect of glycyrrhizin on highly pathogenic H5N1 influenza A viruses in lung epithelial cells, which induce avian influenza but are considered potential influenza pandemic progenitors [51, 52]. Glycyrrhizin concentrations from 25 to 50 µg/mL substantially inhibited H5N1-induced expression of the pro-inflammatory molecules CXCL 10, IL-6, CCL2, and CCL5. However, for interference of H5N1 replication and H5N1-induced apoptosis, concentrations of 100 µg/mL or higher were necessary. The mechanism by which glycyrrhizin interferes with H5N1 replication and H5N1-induced pro-inflammatory gene expression includes inhibition of H5N1-induced formation of reactive oxygen species, thereby reducing the activation of NFκB, JNK, and p38 redox-sensitive signaling events that are known to be relevant for influenza A virus replication. Therefore, glycyrrhizin may complement the arsenal of potential drugs for the treatment of H5N1 disease [50].

Pterocarpans and flavanones isolated from *Sophora flavescens* Aiton (Leguminosae) were noted to inhibit neuraminidase, an enzyme crucial in the proliferation of the influenza virus [53].

Parvoviridae

Two plant species with antiviral activity against PPV were included in this review. PPV causes reproductive failure of swine characterized by embryonic and fetal infection and death, often without any outward maternal clinical signs. The virus is ubiquitous among swines worldwide and is enzootic in most herds that have been tested. Diagnostic surveys have indicated that PPV is the major infectious cause of embryonic and fetal death. The essential oil as well as aqueous extracts of *Mentha spicata* L. (Lamiaceae) [54] and *Isatis tinctoria* L. (Brassicaceae) [55] exhibited activity against PPV *in vitro*. Moreover, *I. tictonia* L. was active against GPV [56].

Poxviridae

Humans, vertebrates, and arthropods serve as natural hosts of *Poxviridae*. The virion is exceptionally large and carries its genome in a single, linear, double-stranded segment of DNA.

The literature reported antiviral activity of 16 plant species primarily against FWPV, 2 plant species against GTPV, and 1 plant species against BPXV (**Table 1S**, Supporting Information). Notably, methanolic extracts of different Sudanese medicinal plants were observed to exhibit antiviral activity against FWPV [57] as well as aqueous decoctions and acetone extracts of galls of *Guiera senegalensis* J. F. Gmel. (Combretaceae) *in vitro, in ovo*, and *in vivo* [58–60]. Treatments with an ethanolic extract of the root bark from *Synadenium glaucescens* Pax (Euphorbiaceae) demonstrated significantly higher mean embryo weight in an *in ovo* assay against FWPV compared with other extracts of the same plant [61].

Nimaviridae

WSSV of the family *Nimaviridae* is responsible for causing white spot syndrome in a wide range of crustacean hosts [62]. White spot syndrome is a viral infection of penaeid shrimp and causes severe economic losses to aquaculture. The disease is highly contagious and lethal, killing shrimps quickly [63]. Until date, there are no commercially available drugs to control the virus. This serious problem has been the focus of several recent investigations on medicinal plants with antiviral activity against WSSV, leading to 51 publications in CAB database. This review lists 12 plant species with activity against WSSV in **Table 1S**, Supporting Information, that were investigated in a study of 2007 [63] and described in 9 publications from 2014 to 2019 [64–72].

Reoviridae

Infection with avian orthoreovirus, also known as ARV, causes mainly arthritis and tenosynovitis in poultry. Aqueous extracts of 8 plant species [31, 73, 74] exhibited antiviral activity against ARV *in vitro*. BRV are the most common cause of neonatal diarrhea in calves. Clinical disease in calves older than 1 mo is rare. However, periodic asymptomatic re-infection and shedding occurs in older cows and calves. Theaflavins of *C. sinensis* (L.) Kuntze (Theaceae) were noted to be active against this virus [75].

Coronaviridae

Avian IBV is a coronavirus that infects chickens, causing infectious bronchitis. It is a highly infectious avian pathogen that affects the respiratory tract, gut, kidneys, and reproductive system of chickens. The aqueous extract of *A. sativum* L. (Amaryllidaceae) [76], the ethanolic (80%) extract of *Sambucus nigra* L. (Adoxaceae) [77], polysaccharides of *Astragalus species* [78], and the essential oil of *Rosmarinus officinalis* L. (Lamiaceae) [79] were determined to be active against IBV *in vitro*. Furthermore, theaflavins of *C. sinensis* (L.) Kuntze (Theaceae) exhibited activity against BCV [75].

Other viruses

The antiviral activity of plant extracts against viruses of insects was not the primary focus of this review. Therefore, only a few examples were presented in this review highlighting the possibilities to fight against viruses causing diseases in bees. Five plant species were noted to be active against AcNPV (*Baculoviridae*), namely *Aconitum nasutum* Fisch. ex Rchb. (Ranunculaceae), *Hypericum androsaemum* L. (Hypericaceae), *Laurus nobilis* L. (Lauraceae), *Rhododendron caucasicum* Pall. (Ericaceae), and *Urtica dioica* L. (Urticaceae) [80]. Furthermore, the antiviral potential of *L. nobilis* leaf ethanolic extract on forager honeybees naturally infected with BQCV (*Dicistroviridae*) [81] should not go unmentioned.

Antivirals display a variety of mechanisms of action, and while some block a specific enzyme or a particular stage in the viral replication cycle, others like zanamivir and oseltamivir have the ability to inhibit prokaryotic neuraminidase. More recent research has

revealed antiviral activity of the following plant species during *in vitro* enzyme assay: *Geranium sanguineum* L. (Geraniaceae), *Eucalyptus globulus* Labill. (Myrtaceae), *Ginkgo biloba* L. (Ginkgoaceae), *Echinacea angustifolia* DC. (Asteraceae), and *Zingiber officinale* Roscoe (Zingiberaceae) [82]. Nevertheless, it is imperative to persevere with exploring and developing new antiviral compounds because viruses are continually evolving into new antiviral-resistant strains by virtue of their high mutation rate [1].

This review demonstrates that there exists an overwhelming number of plant species with the potential to fight against various highly pathogenic animal viruses, and these plant species need to be analyzed for their potential prophylactic and therapeutic applications. Notably, some plant species are promising candidates for developing new antiviral remedies that are required urgently.

Supporting Information

Table 1S is a compilation of plant species exhibiting antiviral activity against animal viruses causing notifiable diseases (virus marked in bold) or diseases with high infection rate leading to high mortality or large economic losses; plant family; virus species; reference; kind of extracts, fractions or compound(s) investigated; plant part investigated, and design of trial.

Contributors' Statement

Data collection: T. Marschik, K. Zitterl-Eglseer; design of the study: K. Zitterl-Eglseer, T. Marschik; analysis and interpretation of the data: T. Marschik, K. Zitterl-Eglseer; drafting the manuscript: T. Marschik, K. Zitterl-Eglseer; critical revision of the manuscript: K. Zitterl-Eglseer.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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