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Efficacy of plant-derived compound compared to ectoparasiticides: A literature review

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1. Introduction

Antiparasitic agents constitute a prominent sector within the pharmaceutical industry, with profound implications for both human and animal health. On the one hand, parasitic infestations, whether endo- or ectoparasitic, can serve as reservoirs for many transmitted vector-borne diseases, which are currently significant contributors to human infection. Recognising that the animal is a vital link in transmitting these diseases, acting as an intermediary between parasites and humans is imperative. On the other hand, controlling the infection of the animals is primordial for ensuring their health and well-being. Therefore, utilising antiparasitic agents is essential for ensuring animal health preservation and the human-animal relationship's safety.

In addition, as society increasingly prioritises eco-friendly and bio-products, concerns have arisen regarding the safety of molecules against parasites that may be detrimental and threaten humans, animals, and environmental wellbeing. Most molecules against ectoparasites at the present day have been used for decades, and the creation of new drugs is a long process. Furthermore, technological and scientific advancements have succeeded in discovering new modes of action and targeting specific insect receptors. Nevertheless, one might wonder whether potential drawbacks from the latest innovations could help mitigate potential risks associated with antiparasitic drugs, such as resistance, residues and adverse effects in animals or humans. In this context, the emergence of botanical insecticides has captured the attention of farmers worldwide, offering a response to the socioeconomic challenges posed by traditional anti-ectoparasiticides.

While botanical insecticides have demonstrated outstanding potential in livestock animals, it is also crucial to explore how these alternative plant-derived products can benefit companion animals and if they could help this shift toward a more natural and eco-friendly approach for the well-being of pets and their owners.

2. Objectives of the study

In the thesis, my aim was to collect the most important methods of control and treatment of external parasites, including new alternative methods based on the use of plant-derived active substances. Given the complexity of the subject, I focused my work on diseases caused by ectoparasites in companion animals. I have listed the ectoparasites that most commonly cause or transmit diseases in companion animals. Then, I collected the main synthetic anti-parasitic agents used today against these parasites, detailing their mechanisms of action. I then addressed the side effects and disadvantages of synthetic agents, including the growing problem of resistance. I have collected knowledge about the plant-derived active substances used today in relation to their external anti-parasitic properties. I have summarized the literature on the use of these agents as external parasiticides in companion animals. Finally, I compared the frequency of their use and their efficacy compared to conventional agents and commented on their future use.

3. Methods

After defining the objectives of my study, the selection of the databases was carried out. The sources used as databases were PubMed, CAB Direct, Web of Science and Google Scholar. The resources from the web pages of European Scientific Counsel Companion Animal Parasites (ESCCAP), Companion Animal Parasite Council, and MSD Veterinary Manuel were sources of information mainly used to describe the ectoparasites and the synthetic drugs. I read two books; the first book, titled "Les Soins des Animaux par les Plantes" [1], is written by a French veterinarian and a French pharmacologist for the part of plant-derived compounds; the second that I used was for the ectoparasite and is titled "Veterinary Clinical Parasitology". For the selection of articles from the database, the period was between 2013 and 2023, and there were no criteria based on geographical localisation. In the advanced search of each database, the primary keywords employed were "Ectoparasites" or the specific species, "Ticks", "Fleas", "Mites" and "Lice". When seeking articles related to active substances, their effects and modes of action, I used the family name in the query with the field tag "ALL=". In the section dedicated to plant-derived products, my search was generated using the terms "Plant-derived product" ("Essential oils" OR "Volatile oils") followed by the arthropod species. It is important to note that many search results were focused on livestock animals. To narrow down the search results and find articles specifically related to pets, synonyms for "dogs" and "cat" or the specific arthropod species were added to the search to make sure to retrieve articles that are more closely related to these animals.

In all cases, the following criteria were considered for the sources used: in the case of journals, only peer-reviewed publications with impact factors were considered. For books, peer-reviewed works were also used. The selection criterion focuses on studies with a large number of cases.

4. Literature Review

4.I. Ectoparasites of dogs and cats

Ectoparasites, alternatively referred to as external parasites, can be subdivided into distinct categories. Some parasites, such as lice, keds, and mites, are established permanently on the skin's surface, whereas others have specific stages in their life cycle during which they rely on their host, as seen with ticks and flies [2]. Fleas, ticks, and flies are easily noticed and commonly treated as external parasites. Moreover, lice and mites have a significant effect on the well-being and health of the animal. Being infected with these parasites can lead to various harmful effects, including tissue damage to blood loss from feeding, increased hypersensitivity reactions after exposure to their substance, additional infections, and, most importantly, the transmission of diseases (Table 1) [3].

Table 1: The most prevalent vector-borne diseases and their arthropod.

Arthropod parasite	**Species [4]**	**Related challenge/ disease/infestation**	**Pathogenic agent transmitted [3]**
Fleas	*Ctenocephalides canis* *Ctenocephalides felis*	Vector (dipylidiosis, bartenellosis) Flea infestation Flea allergy dermatitis Flea spotted fever Pelicosis	*Dipylidium caninum*, *Bartonella henselae* , *Bartonella vinsonii*, *Rickettsia felis*
Mosquitoes	*Aedes* spp. *Culex* spp. *Anopheles* spp.	Vector (dirofilariosis) Heartworm disease Subcutaneous filariosis Mosquitoes' infestation	*Dirofilaria immitis*, *Dirofilaria repens,*

Table 1: The most prevalent vector-borne diseases and their arthropod.

Arthropod parasite	Species [4]	Related challenge/ disease/infestation	Pathogenic agent transmitted [3]
Flies	***Phlebotomus* spp.** *Stomoxys* spp. *Haematobia* spp.	Vector (ocular filariodiosis, leishmaniosis), phlebotome infestation (Sandfly), Canine leishmaniosis Myiasis, Fly infestation	***Thelazia spp*.** ***Leishmania infantum* (Sand fly)**
Ticks	*Rhipicephalus sanguineus* *Ixodes* spp. *Dermacentor* spp.	Vector (piroplasmosis, babesiosis; hepatozoonosis, ehlichiosis, anaplasmosis, borreliosis, rickttsiosis, tick-borne encephalitis,)	*Babesia canis, Babesia gibsoni, Theileria annae, Cercopithifilaria spp., Hepatozoon spp., Ehrlichia canis, Ehrlichia spp., Anaplasma phagocytophilum, Anaplasma platys, Rickettsia spp., Borrelia burgdorferi s.l., Flaviviruses*
Lice (Chewing and sucking lice)	*Trichodectes canis* *Linognathus setosus* *Heterodoxus spiniger*	Louse infestation Phtiriosis	*Dipylidium caninum*
Mites	*Demodex canis/cati*	Canine/Feline demodicosis Localised/ Generalized From squamous demodicosis to severe pustular demodicosis	
	Sarcoptes scabiei canis	Initially erythema with papules, followed by crust and alopecia. Intense pruritus, leading to self-inflicted traumatic lesions.	Human household infestation
	Otodectes cynotis	Ear mange – otocariosis	None described
	Notoedreas cati	Notoedrig mange	None described
	Cheyletiella yasguri and *Cheyletiella blakei*	Cheyletiellosis	None described
	Netrombicula (trombicula) *autumnalis, Straelensia cynotis*	Trimbiculosis	None described

Ectoparasites, by inducing skin diseases and triggering immune responses, are regarded as pathogens that can lead to secondary bacterial or viral infection. Consequently, effective management against ectoparasites plays a crucial role in reducing the overuse of antibiotics and antiviral medication [5]. The general approach for dogs and cats recommended by the Companion Animal Parasite Council is the prophylactic prevention rather than the therapeutic treatment [6]. Several prophylactic application methods exist, such as dusting powders, baths, aerosol sprays and impregnated insecticidal collars, followed by increased popularity for spot-on in the 1990s. Those products presented as spot-on collars or tablets have a longer duration of action and thus extended protection over the year [7].

4.I.A Ectoparasites – Acarian (ticks, mites)

Ticks are relatively large parasites and can be found across the world. Their distribution varies depending on the climate, spanning from arid to humid regions. Ticks are a significant concern to both veterinary and human medicine since they have been shown to carry and transmit several diseases according to species and geographical location [8]. One of Europe's most common tick genus is *Ixodes*, which can be found in a wide range of environments, including forests, urban areas, and suburban regions. Recently, there has been an expansion in the distribution of *Dermacentor reticulatus*. Additionally, *Rhipicephalus sanguineus*, also known as the brown dog tick, poses challenges in terms of elimination and is primarily in dogs. Its presence is notable even in temperate climates [9]. Those species present in Europe are summarised in the following table (Table 2)according to the causative agent they can transmit and the severity of the vector-borne disease [3, 8]:

Table 2 adapted from [3, 8]: The above tick-borne parasites are marked in different colours according to their taxonomy, with viruses in blue, bacteria in red, protozoa in green, and nematodes in purple.

Disease	Vector	Causative agent	Severity/ frequency
European Tick-borne encephalitis	*Ixodes ricinus, Ixodes persulcatus*	*TBE virus Flavivirus*	Severe in human Sporadic in dog Not commonly reported
Borreliosis/tick-borne recurrent fever		*Borrelia spp.*	
Q-fever or coxiellosis	*Rhicephalus* spp., *Dermacentor* spp.	*Coxiella burnetii*	Subclinical
Lyme borreliosis	*Ixodes* spp.	*Borrelia burgdorferi*	Subclinical
Mediterranean spotted fever	*Rhicephalus sanguineus*	*Rickettsia conorii*	Moderate - severe
Ehrlichiosis		*Ehrlichia canis*	
Filariosis		*Acanthocheilonema dracunculoides, A. reconditum, Cercopithifilaria spp.*	
Tick-borne lymphadenopathy	*Dermatocentor* spp.	*Rickettsia slovaca, Rickettsia raoultii, Rickettsia rioja*	
Tularemia	*Various genera (Ixodes* spp., *Dermacenter* spp., *Rhipicephalus sanguineus)*	*Francisella. tularensis*	Subclinical, occasionally moderate to severe in young cat
(Piroplasmosis) Babesioses	*Dermacentor reticulatus*	*Babesia canis*	Moderate – severe
	Rhipicephalus sanguineus	*Babesia vogeli*	Mild – moderate
	Dermacentor spp. *Haemphysalis* spp.	*Babesia gibsoni and Babesia gibsoni-like*	Moderate – severe
Cytauxzoonosis	*Dermacentor* spp., *Rhipicephalus sanguineus, Ixodes ricinus*	*Cytauxzoon felis, Cytauxzoon manul*	Moderate – severe
Anaplasmosis	*Ixodes ricinus*	*Anaplasma phagocytophilum*	Mild and subclinical Common
Anaplasmosis	*Rhicephalus sanguineus*	*Anaplasma platys*	Commonly asymptomatic

Ticks are strictly blood-feeders, meaning their survival relies on taking a blood meal from their host, but they are also categorised as temporary ectoparasites. The prophylactic strategy to combat ticks is designed according to several factors, such as the seasonality and the ongoing prevalence of the tick population. The protection should be adequate for the entire period during which the tick is active (Table 3) [3]. Furthermore, the current prevention against ticks does not only rely on chemical usage but also on other strategies, for example, avoiding areas where the tick population is increasing or the use of repellent. It is preconised to remove immediately any tick attached to the human or domestic individuals taking care of not crushing, twisting or jerking the head since it increases the host exposure to a possible pathogenic agent [7].

Table 3: The most prevalent tick species in dogs and cats

Arthropod species	Activity	Challenge	Control
Ixodes Ricinus	From March to October [10]	Year-round activity in oceanic climate Questing behavior Climbing capacity Ubiquitous Versatile [11]	Fast acting pyrethroid or pyrethrin spray for heavy infection. Dinotefuran, pyriproxyfen and permethrin combination [12]
Dermacentor reticulatus	Throughout the year, including winter [13]	Highly reproduction rate Rapid development Cold resistance Overwintering Aquatic survival [11]	Repellent with fipronil and permethrin combination. [14] Fluralaner spot-on or orally [15] Afoxolaner orally [16]
Rhipicephalus sanguineus	Temperate line – March to August Tropical line – June to November [17]	Found in cracks and crevices in houses, garages, and dog kennels. [17] Pyrethroid resistance [18]	Cyfluthrin, permethrin, or other pyrethroids spray for environmental infestation. Fluralaner spot-on or orally [15] Afoxolaner orally [16]

Table 4: The most prevalent mite species in dogs and cats

Mites species [6]	Host	Challenges [19]
<u>Demodectic</u>:		
Demodex canis	Dogs	Normal commensals Increased population is associated with intercurrent disease or immunity
Demodex cati	Cats	Causes rarely disease
<u>Sarcoptic</u>:		
Sarcoptes scabiei var. canis	Dogs, foxes, (rarely cats)	Intense pruritus, can lead to self-inflicted traumatic lesions Zoonosis
<u>Notoedric</u>:		
Notoedres cati	Cats	Zoonosis
<u>Otodectic</u>:		
Otodectes cynotis	Dogs, cats, and ferrets	Common in young
<u>Fur</u>:		
Cheyletiella blakei	Cats, dogs	Zoonosis
Cheyletiella yasguri	Dogs,	Common in young More prevalent in short-haired breed Zoonosis
<u>Harvest</u>:		
Neotrombicula (trombicula) autumnalis		Larvae can transmit *Orientia tsutsugamushi[20]*
Straelensia cyanotis	Dogs, cats	Very painful infection

Mites (Table 4) are usually at most 1 mm in length. According to the species, they can have predilection sites [21]. *Demodex species* account nowadays for 140 species, and this genus is host specific. They have been identified from various animals [22]. Canine demodicosis is highly prevalent and usually results from concomitant immune disease. *Demodex* is the commensal inhabitant of hair follicles and is present in healthy dogs. Moreover, there are different forms according to the extent of the infestation. Usually, localized demodicosis does not require treatment, but the generalized form requires the usage of isoxazoline- and macrocyclic lactone-containing products [23]. Moreover, a recent study concerning the diagnosis and treatment of demodicosis confirmed that the usage of isoxazolines as treatment was impressive and suggested that resistance development is low due to their selective inhibition [24]. *Sarcoptes scabiei*, or the itch mite, is a host-specific genus and is found in a broad range of hosts. The taxonomy of the genus is referred to according to the host on which it is found, for example, *Sarcoptes scabiei* var *canis*, *Sarcoptes scabiei* var *suis*, *Sarcoptes scabiei* var *hominis* [21]. These parasite species are extremely pruritic while disrupting the skin barrier of the host. They are able to burrow themselves deep into the epidermis and depose their egg and faeces in these tunnels, causing intense itching. Clinical symptoms are usually alopecia, hyperkeratosis, and dermal thickening of the ear margins, lateral elbow, and lateral hock location [25]. The feline mange mite, *Notoedres cati*, occurs worldwide in cats and other *Felidae* [21]. The pathognomonic signs are confined to the head of an individual and cause lichenification, but they may spread to other regions of the body. Cats with severe infestation may be treated with antibiotics for secondary bacterial infection. The main treatment relies on ivermectin when the lesion is serious. The veterinarian should preconise selamectin or fipronil compound-based products for prevention [26]. The Ear mite, namely *Otodectes cynotis*, has a specific location on the host, which is the ear canal. Infestation commonly causes otitis externa and is described as the main causative agent of this disease [27]. The animal can suffer from severe pruritus if there is bacterial decomposition at the same time. Moreover, a heavy infestation can develop outside the ear, while the main clinical symptoms correspond to head shaking accompanied by copious black, waxy cerumen [21]. Current studies advise the usage of a combination and demonstrate the effectiveness of the selamectin plus sarolaner. Indeed, results showed a high level of miticidal activity on day 30 as well as a high level of flea control on day 60 and day 90. Moreover, these combined compounds have a broad spectrum and also target gastrointestinal nematodes (Table 5) [28].

Table 5 adapted from [27]: the current treatment of *Otodectes cynotis* in dogs and cats

SUBSTANCE	DOGS	CATS
IVERMECTIN		
MILBEMYCIN	/	Labeled product
IMIDACLOPRID/MOXIDECTIN		
SELAMECTIN	Labeled product	/
PYRETHRINS	Effective	
IVERMECTIN	Variable dosage, not label approved	
DORAMECTIN	/	not label approved
FIPRONIL	/	not label approved
AFOXALANER, FLURALANER, AND SAROLANER	Label dose	

Cheyletiella species, commonly named walking dandruff, occur worldwide and are considered fur mites, not skin dwellers. These species can live up to 10 days in the environment without its host. Many infected animals do not show clinical signs of infestation, but young animals may demonstrate crusting, skin scurf and pruritus [21]. *Cheyletiella blakei* is highly contagious, and the current treatment includes topical application of selamectin, fipronil, and lime sulfur dips; the other possible therapy is oral ivermectin for several weeks [29]. The Companion Animal Parasite Council remind the correct usage and administration of permethrin-based product in cats, and should only be used in case it is specifically approved for cats [30]. Trombiculid mites, also called chigger, harvest mites or scrub itch mites, can parasitise a wide variety of animals and mammals. In Europe, the most encountered is the *Neotrombicula autumnalis*. However, only the larval stage is parasitic and fed on the host for a few days before displacement. They left behind their stylostome, which is very irritating to [21]. Lesions can become very pruritic, and severe hypersensitivity can develop. However, they are only active during a specific period throughout Europe, between July and October [19]. Finally, the last species cited is the *Straelensia cynotis*. The species was reported in France, Spain and Portugal and described in 2000 [19]. It also belongs to the family of Trombiculidae and is responsible for severe follicular dermatitis and maculae that develop into erythematous papules. A single administration of the combined amitraz and metaflumizone appeared to be followed by the regression of clinical signs [31].

4.I.B Ectoparasite – insects (fleas, lice)

Table 6 adapted from [19]: The most prevalent flea species in dogs and cats source

Flea species	Host	Challenge
***Ctenocephalides felis felis* (cat flea)**	Cats, dogs, ferret and various small-sized wild mammals	Low level of infestation may result in mild pruritus. Large flea population induces severe pruritus, alopecia and anemia. Flea-atopic dermatitis.
Pulex irritans and Pulex simulans	Dogs and cats (humans, pigs)	Heavy infestation produces intense irritation and pruritus. Vector of *Yersinia pestis*, and *Rickettsia typhi, Rickettsia felis*

Fleas (Table 6) belong to a unique group of insects and are the most common infestation before the tick [4]. They are one of the most famous causatives of vector-borne diseases, the bubonic plague bacillus. Since fleas are well adapted to indoor environments, they can be the source of infestation of human households. Untreated dogs and cats can be the bridge between humans and the insect. Dogs can either serve as a deliberate or an incidental part of the natural transmission cycle of pathogens carried by fleas [32]. Currently, there are a total of 15 species that can be found in wild and domesticated Canidae. Research in cats has demonstrated that *Ctenocephalides felis* has been the most encountered in France, followed by *Spilopsyllus cuniculi* and *Ctenocephalides canis* [33]. Flea-control programs aim to prevent the infestation of the animals and their environment. Every household member should undergo an annual treatment. In case of a confirmed infestation in the household, the ESCCAP preconises administering a product that is effective against all flea life stages [34]. Flea infestations pose a veritable challenge nowadays and are characterised by a broad spectrum of clinical manifestations depending upon several factors, such as the frequency of exposure, the duration of the infestation, the presence of a secondary infection or coexisting skin diseases, and the degree of hypersensitivity exhibited by the affected host. The development of an immunological reaction to flea saliva serves as a pivotal precursor to the onset of flea atopic dermatitis, or FAD. Animals suffering from FAD usually develop pruritus, alopecia, papules and erythematous macules with crusts predominantly manifesting in the dorsal lumbar and tail region. Effective therapeutic intervention consists of two approaches. Firstly, it is necessary to eliminate the present infestation of adult fleas with approved ectoparasiticides, the selection of which depends on the severity of the infestation.

Importantly, it is imperative to acknowledge that all pets living in the household should also undergo the treatment. Secondly, to address the immature stages of fleas in the environment, a comprehensive strategy involving the eradication of flea eggs, larval and pupal stages is crucial. Various designated environmental applications, such as sprays or foggers, are employed to accomplish this control [3].

Table 7 adapted from [35]: The most prevalent lice species in dogs and cats

Lice species	**Host**	**Challenge**
Linognathus setosus	Dogs	Pruritus and dermatitis Severe infestation can lead to anemia.
Trichodectes canis	Dogs and other canids	Pruritus and poor hair condition. Intermediate host for *Dipylidium caninum*.
Felicola subrostratus	Cats	Pruritus is variable, but when present self-excoriation can lead to trauma, alopecia and crust formation.

Lice (Table 7) are wingless animals and dorsoventrally flattened insects, exhibiting a size range from about 1 to 8 mm. The infestation in domestic animals by lice, often termed pediculosis, is most frequently encountered during winter. They are highly host-specific, and the entire life cycle is completed on the host. Lice are taxonomically divided into two groups based on how they feed: anopluran, or sucking lice, and mallophagan or chewing lice. Nowadays, these ectoparasites do not pose any public health considerations [35]. The current studies confirmed the rapidly reducing existing infestation and the prevention of reinfestation for up to 8 weeks by using the spot-on formulation containing fipronil [36]. Concerning infestation *Trichodectes canis* infestation, the parasite is host-specific and thus does not represent a risk of transmission to other species. However, confirmed infestation dogs must be treated due to their negative impact on dog health and welfare. In a study assessing the efficacy of afoxolaner, researchers demonstrated that this well-known broad-spectrum active substance also has 100% efficacy against *Trichodectes canis [37]*.

4.II. Synthetic Anti-parasitic Drugs used Against Ectoparasites and Their Limitations

4.II.A Overview of Commonly Used Drugs

The discovery of insecticides and crop protection research has helped develop many ectoparasiticides. It has led companies to develop quarter offices dedicated to it, and most of the active ingredients are linked to crop protection. There are two distinct classifications of anti-parasitic drugs: endo- and ectoparasiticides. These drugs have been utilised for more than 20 years to maintain the healthy status of animals. The classification has become unclear with the discovery of endectocides, which are active against both endo- and ectoparasites. The availability of products against ectoparasites in veterinary medicine is considerable and represents the second-largest segment of the global animal health market [38]. Moreover, ectoparasites are currently the most prevalent infection encountered in companion animals [4]. The purchasing trend for anti-ectoparasite drugs targeting ticks and fleas for dogs in the USA has demonstrated an adherence toward long-acting protection product [39]. Veterinarians in the United States, the United Kingdom and France typically recommend a year-round protocol of 12 months for flea protection and 9-11 months for tick protection. Thus, owners exhibit a stronger preference for extended-duration flea and tick protection such as fluralaner and typically purchase a 1-3 month-long protection. Across all three countries, the majority of cat owners express greater adherence to dosing schedules when using extended-duration fluralaner products compared to those requiring monthly administration for flea and tick control [40].

Newer compounds have replaced the oldest active substances, such as organophosphate and carbamates. In the present day, the available ectoparasiticides are pyrethrin and synthetic pyrethroids, macrocyclic lactone, formamidines, pyrazoles, neonicotinoids, spinosyns, semicarbazones, isoxazolines, and the insect growth regulator such as the hormone analogue S-methoprene and the benzoylphenyl urea lufenuron. The latest and newest class of insecticidal and acaricidal molecules are the isoxazolines group that was introduced in the market at the end of 2014 and is considered highly effective and one of the most promising ectoparasiticides [38] [41]. While many commercial products typically consist of just a single active component, it is not unusual for manufacturers to blend two or more of them to achieve heightened effectiveness or a broader spectrum of ectoparasite. The utilisation of brand names can contribute to increased ambiguity. It is imperative to carefully read the label to ascertain the ingredient, any age or species restrictions and usage instructions. Thus, the following table is a presentation of the different chemical groups currently used in dogs and cats with their mode of action and spectrum (Table 8) [2].

Table 8 adapted from the ESCCAP, MSD Manual Veterinary, CAPC, and [7, 42]

Chemical family	**Mode of action**	**Actives substance example**	**Species**	**Spectrum**
Organophosphates (OP)	Irreversible inhibition of the acetylcholinesterase	Dimpylate	Dog, cat	Ticks and fleas
Carbamates	Reversible inhibition of the acetylcholinesterase	Propoxur	Cat	
Formamides	Interference with the octopaminergic system of arthropod, inducing the detachment/inhibition of attachment and feeding	Amitraz	Dog	Lice, mites and ticks
Pyrethroids (Synthetic derivate of natural pyrethrin) [43]	Disruption of the Na+ and K+ ion transports, resulting in spontaneous depolarization, an increased secretion of neurotransmitters, and a neuromuscular blockage to induce reversible paralysis	Permethrin Deltamethrin Flumethrin	Dog, cat	Insects and ticks
Phenylpyrazoles	GABA mediated Cl^- channel antagonist	Fipronil Pyriprole	Dog, cat	Flea, lice, mites, and ticks
Neonicotinoids	Agonist of insect nicotinic acetylcholine receptors	Imidacloprid Nitenpyram Dinotefuran	Dog, cat	Fleas and other insects
Macrocyclic lactone	Binding of the glutamate-mediated Cl^- channel in the arthropod nervous system, causes an increased influx of Cl- ions into the nerve cell inhibiting its activity and resulting in the paralysis of the parasite	Selamectin Moxidectin Milbemycin oxime	Dog, cat	Endectocides (Nematodes and ectoparasites)

Table 8 adapted from the ESCCAP, MSD Manual Veterinary, CAPC, and [7, 42] (continued):

Chemical family	Mode of action	Actives substance example	Species	Spectrum
Spinosyns	Agonist of insect nicotinic acetylcholine receptors at a unique site, leading to paralysis and death	Spinosad (mixture of Spinosyn A and B)	Dog, cat	Fleas and other arthropods
		Spinetoram	Cat	
Oxadiazines	Once ingested and metabolized by insects, blocks insect voltage-gated Na^+ ion channels	Indoxacarb	Dog, cat	Eggs, larvae, and adult flea
Isoxazolines	GABA/glutamate-gated Cl^- channel	Afoxolaner, Fluralaner, Lotilaner, Sarolaner	Dog, cat	Fleas, ticks and mites
Insect growth regulators	Juvenile hormone mimics that limits development of flea in the environment	Methoprene	Dog, cat	Fleas
		Pyriproxyfen		

4.II.B Advantages and Benefits of Ectoparasiticides

Effective management and control of diseases in companion animals is essential for their overall well-being. The current focus of anti-ectoparasite treatment research is on identifying advanced and convenient treatment options while considering the potential risks of resistance associated with their use [38]. The predominant approach for managing ectoparasites involves periodic or consistent administration of external antiparasitic medications, accounting for 75% of all antiparasitic drugs used in dogs. [42]. The following paragraph encloses the different formulations (Table 9) used in companion animals, their importance for each chemical group of anti-ectoparasitic drugs, as well as their disadvantages.

Table 9 adapted from the website « Index des Médicaments autorisés en France » [44]

Compound	Combination	Formulation	Target	Species
Dimpylate	/	Collar	Flea treatment and prevention	Cat
		Collar	Flea, tick treatment and prevention	Dog
Propoxur	/	Skin spray	Flea treatment and prevention	Cat
Amitraz	/	Skin spray	Demodicosis treatment	Dog
Compound	**Combination**	**Formulation**	**Target**	**Species**
Permethrin	/	Skin spray	Flea, tick treatment and prevention	Dog
	Imidacloprid	Spot-on	Flea, tick treatment and prevention Mosquito repellency/antifeeding effect	Dog
	Fipronil	Spot-on		Dog
	Pyriproxyfen	Cutaneous solution	Flea treatment and prevention Tick prevention	Dog
	Neomycin, nystatin, triamcinolone	Ear ointment	*Otitis externa* - against mixed infection (bacterial, fungal, parasitic)	Dog, cat
Deltamethrin	/	Collar	Flea, tick, and mosquitos prevention	Dog
Flumethrin	Imidacloprid	Collar	Flea, and tick treatment and prevention	Dog, cat
Fipronil	Methoprene	Spot-on	Flea, and tick treatment and prevention Biting lice treatment	Dog, cat
	/	Spot-on	Flea, and tick treatment and prevention Biting lice treatment	Dog, cat
Pyriprole	/	Spot-on	Flea, and tick treatment and prevention	Dog
Imidacloprid	/	Spot-on	Flea treatment and prevention	Cat
			Mite and flea prevention and treatment	Dog
	Moxidectin	Spot-on	Flea, biting lice, ear mite, sarcoptic mange treatment and prevention Treatment of circulating L3/L4 microfilariae, cutaneous dirofilariasis Treatment and prevention of gastrointestinal nematodes	Dog, cat
Nitenpyrame	/	Tablet	Flea treatment	Dog, cat
Dinotefuran	Pyriproxyfen, permethrin	Spot-on	Flea, and tick treatment and prevention Mosquito repellent	Dog
	Pyriproxyfen	Spot-on		Cat

Compound	Combination	Formulation	Target	Species
Selamectin	/	Spot-on	Flea infestation treatment and prevention Prevention of heartworm disease Treatment of ear mite	Dog, cat
			Treatment of adult roundworm, and intestinal hookworm, and biting lice infestation	Cat
			Treatment of biting lice, sarcoptic mange, and adult intestinal roundworms	Dog
	Sarolaner	Spot-on	Flea, tick, mite, gastrointestinal nematodes, and prevention of dirofilariasis	Dog, cat
Moxidectin	Pyrantel, sarolaner	Chewable tablet	Ectoparasite treatment and prevention (flea, tick,), treatment of flea allergy dermatitis	Dog
	/	Injection	Heartworm disease prevention and treatment	Dog
	Fluralaner	Spot-on	Flea, tick, mite, heartworm treatment and prevention	Cat
Milbemycin oxime	Praziquantel	Tablet	Cestodes and nematodes treatment and prevention Prevention of dirofilariasis	Dog, cat
	Lotilaner	Tablet	Flea and tick treatment and prevention Gastrointestinal nematode treatment, dirofilariasis prevention, angiostrongyliasis prevention	Dog
	Praziquantel	Tablet	Cestodes and nematode treatment Prevention of dirofilariasis	Dog, cat
	Afoxolaner	Tablet	Flea and tick treatment and prevention, dirofilariasis prevention, gastrointestinal nematodes treatment, demodicosis and sarcoptic mange treatment Angiostrongyliasis and thelaziosis prevention	Dog
Spinosyns, spinetoram	No medication found in France			
Indoxacarb	/	Spot-on	Flea and tick treatment and prevention	Dog, cat
Afoxolaner	/	Tablet	Flea and tick treatment and prevention, demodicosis and sarcoptic mange treatment	Dog
	Eprinomectine, esafoxolaner, praziquantel	Spot-on	Ectoparasite (flea, tick, ear mite) treatment and prevention Nematodes (gastrointestinal, cardio-pulmonary, and urinary) and gastrointestinal cestodes	Cat

Compound	Combination	Formulation	Target	Species
Fluralaner	/	Spot-on, tablet	Flea and tick treatment and prevention, demodicosis and sarcoptic mange treatment	Dog, cat
Lotilaner	/	Tablet	Flea and tick treatment and prevention	Dog, cat
Sarolaner	/	Tablet	Flea and tick treatment and prevention, demodicosis and sarcoptic mange treatment, and ear mite treatment	Dog

Amitraz is explicitly labelled for dogs only and not approved for cats. There is a suggestion to use this active substance to treat canine demodicosis as a leave-on rinse-off formulation. However, it showed great variability efficacy [45]. This active compound is effectively utilised to manage ticks, such as *Ixodes*, *Rhipicephalus* and *Dermacentor* species, and mite infections, like *Demodex* and *Sarcoptic* mange infections. Amitraz can be administrated in formulation, including collars, lotions, and spot-on treatment. It can even be combined with fipronil to treat or prevent flea and tick infestations [42].

Pyrethroids are synthetic derivates of natural pyrethrin and have started to predominate for their high insecticidal activity in agriculture and gardening worldwide. The classification encloses the two following groups. The first, Class I, including allethrin, bifenthrin, permethrin, phenothrin, resmethrin, tefluthrin, and tetramethrin, and the second, Class II, which is composed of cyfluthrin, cyhalothrin, cypermethrin, deltamethrin, fenvalerate, fenpropathrin, flucythrinate, flumethrin, fluvalinate, and tralomethrin. It was demonstrated that the usage of pyrethroid as a pesticide is more specific toward target species than organophosphate and carbamate groups. However, it could indirectly result in neurotoxicity in non-target species such as fish, bees, and birds [46]. Moreover, due to their deficiency in glucuronic conjugation enzymes, cats are less tolerant to pyrethroids, especially to permethrin, while in other mammals, it results in low toxicity [4]. In dogs, pyrethroids formulations are the following: sprays, shampoos, lotions, collars, and spots-on and are used to prevent flea and tick infestation but repel flying insects such as mosquitoes including *Phlebotomus*, *Aedes*, *Culex* species [46]. Regarding spectrum range, the combination of permethrin with fipronil has been evaluated as effective for protecting dogs against *Ixodes ricinus*, a tick species able to transmit many pathogens [14]. The spot-on made from the combination of permethrin and imidacloprid was the most cited by dog owners in 2015 [47]. While it serves as an effective repellent against vectors like ticks, it offers sufficient protection for most dogs by knocking off the arthropod and inducing reversible paralysis.

Regarding tick control, the imidacloprid-permethrin formulation delivers repellent properties and, in contrast to other ectoparasiticides, it also offers tick expulsion, making them more efficient in preventing rapid canine vector-borne disease transmission. In 2022, a study assessed the exposure to pesticides in people and their dogs, using a wristband in the owner and a tag in the pet. The screening could detect the presence of permethrin in the urine and conclude that owners are exposed to pesticides in a home environment [48].

Phenylpyrazoles, comprising fipronil and pyriprole, are used to control acarians, including ticks and mites, but also for insects, such as fleas, lice, phlebotomes, and mosquitoes. Currently, the formulation of this active substance is primarily spot-on, and recently, it has been available as a tablet. Fipronil is the second most commonly used parasiticide in veterinary medicine [49]. The usage of fipronil is extensive, and its application in several domains such as crop protection, urban pest control including cockroaches, ants, termites, and veterinarian application, as well as fish farming controlling rice water weevil infestation [50]. In veterinary medicine, fipronil is applied mainly topically for cats and dogs once a month and shows efficacy against *Ixodes ricinus [51]* and *Trichodectes canis* [52–54]. Moreover, the combination of permethrin plus fipronil demonstrated 100% preventive efficacy when dogs were exposed to leishmaniosis transmitted by *Leishmania infantum* in the high endemic area [55].

Neonicotinoids target insect-specific receptors and have a wide safety margin in mammals [4]. Imidacloprid, in combination most often, is used as a spot-on formula, as well as impregnated collars for dogs and cats and relies on its residual activity in the coat of the animal by being absorbed in the sebaceous glands, and thus remains on the surface of the animal and does not contribute to its environmental toxicity [4, 49]. Currently, imidacloprid is usually combined with flumethrin, permethrin or methoprene to broaden its spectrum activity [4, 42, 56]. Imidacloprid and fipronil, when combined, are efficient against the flea *Ctenocephalides felis felis* and the ticks *Ixodes ricinus*, *Amblyomma americanum* and *Rhipicephalus turanicus* [57]. Additionally, when both substances are combined in collars, they were proven to be both safe and highly effective in preventing *Leishmania infantum* infection transmitted by Lutzomyia sand fly in a large population of dogs in highly endemic regions, such as Brazil, where it can help to minimise the occurrence in human [58]. However, imidacloprid has a harmful impact on aquatic arthropods and terrestrial invertebrates at lower concentrations compared to mammals. Exposure to the active agent is expected when a recently treated dog enters a body of water and appears to be more toxic under the Mediterranean climate than in temperature area [49]. Nitenpyram is a systemic insecticide, like imidacloprid, and is delivered as an oral formulation to carnivores. One particular advantage of nitenpyram-containing products is their short-acting effect on flea infestation. Indeed, this active substance can achieve 100% flea elimination at the time the treatment was administered and maintain this level of effectiveness for 24 hours [59].

Macrocyclic lactones are composed of semisynthetic avermectins and semisynthetic milbemycins groups. Selamectin is derived from avermectin, and moxidectin is derived from milbemycins [2]. Macrocyclic lactones are considered endectocides as they are active against both ecto- and endoparasites. After spot-on application, active substances are absorbed transcutaneously and circulate in the plasma to finally be stored in the fat tissue of the animal [4]. Selamectin is used as a single active substance in products and cited in the ESCCAP guide three times for the control of mites, such as canine nasal mites (*Pneumonyssoides (Pneumonyssus) caninum)* and fur mites (*Cheyletiella species*), and sarcoptic mange mites (*Sarcoptes scabiei*) [3]. Two field studies were conducted in the United States on cats to assess the efficacy and safety of the topical combination of selamectin and sarolaner against flea infestations and ear mite infestations, respectively. In the first study against flea infestation, treatments were given at a specific time (Day 0, 30, and 60), and the efficacy was determined according to the reduction in flea counts, and results were compared to those control group, which received imidacloprid plus moxidectin combination. The flea counts of the selamectin plus sarolaner group were significantly lower and thus better compared to the control group at all treatment time points. The study also concluded on reduced clinical signs of flea allergy dermatitis, and no adverse effects could be noticed during the treatment with selamectin plus sarolaner. In the ear mite study, a single application of selamectin plus sarolaner resulted in a high clearance of mites within 14 days compared to the control group. Overall, the product selamectin plus sarolaner was well-tolerated and highly effective for treating and preventing flea infestation and treating ear mite infestation in cats [28]. Milbemycin oxime may be indicated in dogs with demodicosis as an oral formulation, but its efficacy was found to be reduced in dogs with late-onset infection. Moreover, dogs homozygous for the MDR-1 gene are more sensitive to this active substance, and this suggests administering a lower dose of milbemycin oxime [24]. Furthermore, a study has been done to determine the most effective treatment for sarcoptic mange in dogs, and it could be deduced that milbemycin oxime, when combined with afoxolaner can result in a parasitological cure accompanied by a notable improvement of the clinical symptoms [60]. Moxidectin can usually be combined with imidacloprid for the purpose of extending the spectrum. This combination is effective against certain nematodes plus has an insecticidal and acaricidal effect [4]. It seems crucial to emphasise that various macrocyclic lactones constitute a significant advancement in the management of filarial infection and are strongly recommended for employment in the prophylaxis and treatment of *Dirofilaria immitis* infection. It is advised to consider their usage in regions where the vector is highly prevalent and to administer a topical formulation at 30-day intervals containing a combination of moxidectin and imidacloprid [61]. An investigation has been performed to determine the efficacy of a chewable, oral product comprising moxidectin, sarolaner and pyrantel against flea and tick infestation in dogs. The findings lead to the conclusion that one single administration was not only safe but also effective for the duration of 1 month. Additionally, it was observed that this formulation was majoritarily uptake by dogs willingly and completely consumed, leading to the rapid elimination of fleas [62].

The insecticidal spinosyns represent naturally occurring compounds originating from the microbial source *Saccharopolyspora spinosa* and are categorised within the macrolides. A total of 25 spinosyns, designated from A to Y, have been isolated, but Spinosyns A and D emerged as the principal active constituents. These primary compounds exhibit a high level of insecticidal efficacy and demonstrate selectivity towards crop pests [63]. Spinosyns have played an essential role as a source of active ingredients for the development of novel synthetic insecticides. Spinosad and spinetoram, introduced to the commercial market in the 1990s, are noteworthy ingredients in this regard. Spinosad, a naturally occurring mixture of spinosyns, is administered orally in the form of chewable tablets and is often combined with milbemycin. Its application encompasses the prevention and treatment of flea infestation, effectively targeting adult fleas and larvae [64, 65]. In contrast, spinetoram has been specifically designed to combat existing flea infestation. This active substance delivers a high level of control over fleas within a 48-hour timeframe, particularly against the cat flea (*Ctenocephalides felis*). Commercially, it has been available as a topical spot-on formulation, combining fipronil plus methoprene [66].

Indoxacarb is the only active ingredient belonging to the chemical group oxadiazines used in veterinary medicine [2]. Among the other compounds, indoxacarb is the first insecticide categorised as a selective to the sodium channel blocker and is classified as a proinsecticide, meaning it transforms into an insecticidal metabolite, referred to as N-decarbomethoxylated (DCJW), within insects through a bioactivation process. The key factor contributing to the advantageous selective toxicity of indoxacarb relies on its conversion into DCJW, with the bioactivation process being notably less efficient in mammals compared to insects [67]. Topical spot-on formulation demonstrated remarkable efficacy, surpassing 99.6%, in controlling flea infestation in cats for six weeks following a single application. Moreover, indoxacarb exhibited a double impact by either completely eliminating or significantly diminishing egg production throughout the entire period and reducing the viability of the limited eggs [68]. Additionally, the effective control of leishmaniasis in canines presents an opportunity for a reduction in the prevalence of human leishmaniasis. To this end, investigations have searched into the utilisation of a combined formulation involving indoxacarb and permethrin to determine the duration and the strength of the anti-feeding efficacy, as well as the knock-down effect against *Phlebotomus perniciosus*. The term “anti-feeding effect” refers to the repellent action of the insecticide leading to a reduction in the insect’s blood-feeding behaviour. This investigation yielded findings that substantiate the presence of synergistic activity between indoxacarb and permethrin. When administered in the form of a topical formulation, this combination engenders a repellent effect that exerts a sustained anti-feeding efficacy against sandflies for a duration of up to 4 weeks [69].

Isoxazolines represent the newest group of active ingredients for prevention and treatment in dogs and cats against fleas and ticks. As cited, this group is one of the promising innovations of the 21st century due to its new mode of action. Indeed, their high specificity arises from their mode of action, which involves the GABA-gated acid chloride channels and glutamate-gated chloride channels of ectoparasite [38]. Thus, this chemical family is considered neuroinhibitory ectoparasiticides and induced flaccid paralysis [70]. Until now, these active substances have not only been linked for being the most recent anti-ectoparasitic chemical class but have also emerged in the newest context of commercialisation, which is the form of orally administered chewable tables. Indeed, the majority of isoxazolines are dispensed in the form of chewable tablets [71]. Within modern veterinary practices in Brazil, isoxazolines have acquired the highest utilisation and are the most cited among practitioners, making products containing isoxazolines the prevailing choice for the prophylaxis and treatment of ectoparasites and gastrointestinal nematodes [56]. Fluralaner demonstrates elevated selectivity and potency for arthropod channels in comparison to their mammalian counter [72]. This active ingredient has exhibited significant efficacy, manifesting complete flea eradication within an 8-hour window while concurrently exerting control over egg deposition, larval development, and the overall reproductive processes. Activity within 8 hours for the killing of fleas while controlling the egg laying and larval development and flea reproduction [73]. Moreover, this compound has demonstrated a remarkable 100% efficacy in eliminating ticks within a 12-hour timeframe, thereby reducing the transmission of tick-borne [74]. In these studies, they did not observe or find any adverse-related treatment reaction and were considered to be safe when combined with deltamethrin, milbemycin oxime, and praziquantel [75].

4.II.C Resistance Status of External Antiparasitic Agents

The World Health Organization has served as the global coordinator for the standardisation of pesticide-resistance measurements by providing methodology and test kits to measure resistance. In 1957, WHO defined the term resistance as the occurrence in bacteria, viruses, fungi, and parasites of change over time and no longer respond to medicines, making infections harder to treat and increasing the risk of disease spread, severe illness and death. According to the WHO, resistance occurs on a local level and thus, monitoring and control depends on a local decision [76]. The development of resistance to ectoparasiticides (Table 10) occurs when the selection of a specific trait appears within an ectoparasite population due to exposure to an insecticide. This led to an increase in the percentage of the population that can survive a standard dose of the same insecticide due to the passing of genes to the subsequent generation [77, 78]. The development of resistance among ectoparasites is the consequence of the irrational and long-term use of acaricidal drugs. Four types of resistance in parasitology can be mentioned: the natural resistance or tolerance, which “does not develop as a result of acaricidal usage”; the acquired resistance, which “results from heritable decreases in sensitivity due to drugs”; the cross-resistance, which is “the share of resistance among different acaricides with a similar mode of action”; and finally multiple resistance, which is defined as “a resistance to more than one drug, even though they have different modes of actions” [79]. Additionally, if the mechanism of resistance is consistent within a drug class, it is unlikely that new drugs belonging to the same class will work effectively against ectoparasites. This is because the mutation responsible for the current resistance in that class is likely also to make ectoparasite resistant to any alternative drugs within this class [80]. Moreover, approaches such as the combination of compound has been proven to be successful at delaying resistance instead of using them one after the other. In order to improve the chance of success of such a mixture, the initial level of resistance in the parasite population should be low, and the different insecticides present as components should last for a similar amount of time [7]. Table 10 summarises some of the ectoparasiticides and refers to their resistance in certain ectoparasites.

Table 10: Ectoparasiticides and their current resistance:

Ectoparasite	Compound	Resistance rate
Rhipicephalus sanguineus	Deltamethrin	Highly resistant [77]
	Propoxur	Variable [77]
	Ivermectin	Resistance in Argentina[81], India [82]
	Amitraz	Resistance in Mexico [83]
Ctenocephalides felis felis	Pyrethroid, carbamates and organophosphates	Widespread resistance [77]
	Cypermethrin	Resistant[77]
	Permethrin, deltamethrin	[77]
	Fipronil	[78]
Sarcoptes scabiei	Ivermectin	Tolerant [77]

In the analysis of the *Rhipicephalus microplus* population in Brazil's cattle herds, it was evident that there existed a phenomenon of cross-resistance between ivermectin and moxidectin. However, it is noteworthy that such cross-resistance was observed only in a singular population concerning ivermectin and eprinomectin. Reports indicated the regular utilization of injectable ivermectin, either weekly or monthly, within farm settings. This observation led to the conclusion that the frequent administration of ivermectin may engender the emergence of cross-resistance to moxidectin, which was not observed with eprinomectin [84]. Finally, research done in Mexico proved the common resistance of *Rhipicephalus sanguineus* collected from dogs originating from different locations. The widespread use of both acaricides to manage ectoparasites in dogs will likely result in more serious resistance, potentially leading to significant control failure in the future [83].

4.II.D Limitations on the Use of Systemic Ectoparasiticides

External anti-parasiticide agents represent a category of pharmaceutical with the potential to induce severe side effects in the animal being treated. The administration of these drugs is subject to specific usage conditions outlined in the summary of the product. In the context of France, comprehensive product specifications for each pharmaceutical medication can be accessed through the ANSES website [44]. In the year 2011, the Pest Management Regulatory Agency (PMRA) of Health Canada conducted a survey aimed at assessing adverse effects observed from pest control therapies in dogs and cats. Between the period from 2007 to 2009, the PMRA received reports of 708 companion animal incidents involving spot-on designed for flea and tick control. The findings of the survey revealed that cats primarily exhibited neurologic and/or muscular effects, while dogs predominantly manifested cutaneous reactions. It is noteworthy that the survey also explored factors contributing to the observed side effects. It appeared that the most common factor was the misuse of products, including non-compliance with species-specific guidelines, age, and weight recommendations [85].

Notably, on the Health Canada website, reported incidents in the preceding months have raised concerns. These incidents concerned pyriproxyfen, imidacloprid, and permethrin combination in dogs, which have been associated with dermal adverse effects, primarily pruritus. Furthermore, the administration of flumethrin and imidacloprid combination has been linked to a severe outcome, resulting in the mortality of multiple animals [86]. When employed in strict adherence to the labelled instructions, pyrethroids are generally safe to use. However, it is well-known that cats exhibit a heightened sensitivity to concentrated pyrethrin/pyrethroid compounds, particularly those available in spot-on formulations. Even incidental contact with a dog that has recently been treated with a spot-on containing permethrin can elicit signs of toxicosis in a feline individual [71]. With regard to imidacloprid and its metabolites, it is essential to note that they are rapidly absorbed via the gastrointestinal tract. In dogs, such oral administrations may induce salivation or emesis, while in cats, it can result in oral ulcer or gastritis. However, dermal exposure to these substances does not lead to systemic absorption. Instead, this substance disperses across the skin through translocation, with the product being found in hair follicles. This phenomenon may subsequently give rise to dermal hypersensitivity upon topical administration characterised by erythema, pruritus and alopecia at the application site [71]. In general, the main adverse effects associated with antiparasitic drugs can be primarily categorised into three main groups: cutaneous, digestive or neurologic signs. The average incidence of animals experiencing severe adverse effects is significantly low, with approximately 1 animal in every 250,000. Furthermore, the occurrence of a fatal effect leading to death is even rarer, with an incidence rate of approximately 1 animal in 650,000 (Table 11) [87].

Table 11 adapted from [87]: the most prevalent incidence of death and severe side effects (SE) in dogs and cats according to the active ingredient:

Cat		Dog	
Death	**Severe SE**	**Death**	**Severe SE**
Tetramethrin	Tetramethrin plus piperonyl butoxide	Spinosad	Milbemycin oxime plus spinosad
Lufenurone	Indoxacarbe	Fluralaner	Dinotefuran plus permethrin plus pyriproxifen
Spinosad	Tetramethrin	Dinotefuran	Fluralaner
Dinotefuran	Spinosad	Selamectin	Spinosad
Epirnomectine	Dinotefuran plus pyriproxyfen	Flumethrin	Bioallethrin plus piperonyl butoxide

The environmental impact of chemical and pharmaceutical products used to control ectoparasites is deemed relatively low when compared to the challenges face in the present day. Nevertheless, research on the long-term effect of external antiparasitic drugs is restricted. Furthermore, the National Office of Animal Health (United Kingdom) enforces a strict evaluation process for future introduced veterinary products entering the market [88]. This assessment meticulously assesses both the benefits and the potential risks, encompassing the safety consideration and the environmental impact. To secure a Marketing Authorization, the obligatory inclusion of an environmental risk assessment (ERA) is mandatory, and this evaluation plays a crucial role in determining any precautionary advisories or usage restrictions. In the context of pet parasiticides, the ERA evaluates the extent of environmental exposure and subsequently informs the specific warnings or usage guidelines on the product’s labelling. Once authorised, vigilance by either communities or regulatory authorities is dedicated to the continuous monitoring of product safety, aligning with the holistic " “One Health” approach [89]. Nevertheless, a recent assessment has highlighted the potential risk associated with certain active substances. This review specifically focuses on evaluating the toxic effect of the most commonly used companion animal drugs against parasites in United Kingdom. This assessment revearled that parasiticides may pose a potential environmental hazard at certain concentration. While most of the concerns were centered around imidacloprid and fipronil, it failed to provide conclusive evidence regarding the environmental risks associated with any of the six active substances assessed. There was limited or no evidence available regarding the ecotoxicity of the parasiticides. Notably, it was possible to assess that imidacloprid and fipronil are toxic to various aquatic organisms. This assessment underscores that evaluating ecotoxicity based on a single dose is insufficient given the substantial number of doses sold annually. Consequently, it emphyses the necessity for further studies and the quantification of both the level and pathways through which these substances enter the environment [49].

4.III. The Role of Plant-Derived Active Substances in the Control of Ectoparasites

Within the context of medicinal practice, the usage of plants can be defined as the employment of botanical entities with the aim of ameliorating pathological conditions and illnesses. This comprises the utilisation of intact plant species, encompassing various components such as blossoms, roots and seeds, as well as the extracts derived from these botanical sources, in the remediation of diverse maladies [90]. Plant-derived products may be used for the treatment of diseases in animals and could be mutually beneficial for animal health and the environment by reducing the susceptibility to parasitic resistance and lowering the risk of adverse effects, followed by the decreased residues of synthetic products in the animal and environment. Moreover, the advancement of plant-derived products targeting ectoparasites may present a viable alternative for forthcoming agroecological and holistic farming systems [91]. Over time, there has been a growing demand for pest control products that do not have adverse effects on human health or the environment while ensuring the well-being of animals. As a result, these botanical insecticides have been suggested as potential alternatives.

4.III.A General Characteristics of Plant-Derived Products

Establishing a clear demarcation of the different sources of plant products is imperative. We discern four terms in the literature: phytotherapy, gemmotherapy, aromatherapy and homoeopathy. Notably, aromatherapy and phytotherapy are the most prevalent botanical products investigated concerning their efficacy against veterinary parasites [92]. Phytotherapy can be defined as the practice of treating illness using plants, thus the application of a plant itself for therapeutic purposes. These botanical remedies are particularly suitable when a precise medical diagnosis has been established. These plant products are used intact including fresh or dried or most of the time used after transformation. Aromatherapy and gemmotherapy are thus branches of phytotherapy. Aromatherapy refers to the treatment of medical conditions using essential oils. It is vital to distinguish aromatherapy from phytotherapy, as essential oils represent concentrated reservoirs of active biomolecules derived from plants, effectively serving as potent reservoirs of active compounds [93].

These bioactive compounds exhibit therapeutic properties with distinct chemical characteristics and are classified into primary or secondary metabolites [94]. Primary metabolites are involved in the development and reproduction of plants. On the other hand, when plants are exposed to stressful situations caused by living organisms and non-living factors, they produce secondary metabolites that protect themselves in unfavorable circumstances. These strategies allow them to combat their enemies, including insects that are causing damage to the crop population [90]. Secondary metabolites can be classified into three groups, which are the following: terpenoids, phenolic compounds, and nitrogen compounds. Plant-derived antiparasitic products are usually associated with the presence of secondary metabolites and are components of essential oils [94]. Essential oils (EO) are products of complex composition, constituted from volatile substances and characterized by their mode of preparation. They are obtained either by steam distillation, dried distillation, or hydrodiffusion. EO are extracted from different parts of the plant, for example, roots, wood, bark, fruits, leaves, and flowers. The principal and most cited plant families providing a source of EO are the following: Laminaceae, Myrtaceae, and Lauraceae, as well as Asteraceae, Rutacaea, and Abitaceae [93].

4.III.B Advantages of Essential Oils against Ectoparasites

Essential oils (EO) represent an outstandingly promising category of secondary plant metabolites, particularly in light of the extensive knowledge encompassing over 3,000 EO, from which 300 even find their application in the food industry or perfume production [95]. Furthermore, certain compounds have demonstrated an interesting capacity to enhance the insecticidal effectiveness of synthetic insecticides. Specifically, permethrin and deltamethrin, two pyrethroids, have undergone individual assessment when combined with EO to determine their efficacy in mosquito control. This investigation deduced with conclusive evidence that EO significantly augments the toxicity of permethrin and deltamethrin against mosquitoes [96]. Additionally, considering the abundant plant species from which these oils are extracted, their affordability and availability in regions like Serbia could potentially stimulate the development of the economy and contribute to the biodiversity preservation [97]. Numerous studies have highlighted the importance of plant extracts, essential oils and herbal remedies, particularly in African and Asia countries where they have been used for many years. Research findings consistently affirm that phytochemical compounds and essential oils have favorable outcomes in controlling and eradicating eggs, larvae, and adult ectoparasites and in establishing effective repellence measures [79]. The utilisation of plant-based products appears to exhibit a trend within the veterinary profession. This observation is supported by in a survey conducted in Spain, which revealed that the adoption of such products among veterinarians is relatively limited. Furthermore, the survey findings indicated that female veterinarian are more disposed toward the use of essential or plant-derived products in their practice [98]. Enclosed in the subsequent tables are the leading botanical species frequently referenced in veterinary medicine (Table 12) and a compilation of essential oils formulation targeting certain arthropods. (Table 13):

Table 12: the most cited botanical plant species for Canidae quoted in the veterinary medicine application [5] :

Species	Common name	Targeted parasite
Juglans regia L.	Walnut tree	Adult and larvae tick Mites
Nicotiana tabacum L.	Tabak, tabaco, tobacco	*Rhipicephalus sanguineus*
Citrus ladanifer L.	Rockrose	Fly
Plantageo lanceolata L.	Narrow-leaf plantain, Ribwort plantain	No relevant data
Ruta graveolens L.	Common rue	Tick adults, flea, and mosquitoes
Cistus populifolius L.	Poplar-leaved rock rose, Rockrose	No relevant data

Table 13, adapted from [99]:

Ectoparasites	Essential oils	Quantity	Formulation
Fleas	Geranium	4 drops	Shampoo Topical (neck, chest) mixed in 15 ml of hazelnut or macadamia oils
	Java lemongrass	2 drops	
	True Lavander	8 drops	
Ticks	True lavander	20 drops	Mixed with a solubizing agent (5mL) and 100 ml of juniper hydrolat as spray application
	Rosat geranium	20 drops	
	Lemon eucalyptus	20 drops	
Mites larvae	Lemon grass or geranium	Not specified	Locally

4.III.C Mechanism of Action against Ectoparasites

The acaricidal and insecticidal properties present in essential oils (EO) are primarily attributed to the presence of multiple bioactive compounds, each exerting distinct modes of action on ectoparasites, thereby disrupting various functions of their metabolic, biochemical, physiological and behavioral processes [100, 101]. These compounds are distinguished by a potent odor, which serves to defend the plant. This mechanism enables them to deter herbivores and insects from consuming the plant while also potentially manifesting a direct toxic effect or attracting pollinators and diminishing the risk of disease susceptibility. These bioactive compounds act upon insects through a neurotoxic mode of action through inhalation involving mechanisms such as GABA, octopamine synapses and inhibiting acetylcholinesterase, ultimately functioning as repellent to pests, antifeedants or insect growth regulation [79, 101]. Finally, due to their fat-soluble content, they actively permeate the membrane of the skin, as well as target organs, and thus rapidly absorb upon dermal or oral administration and do not accumulate in the body [79].

The majority of insect repellents containing plant-based compounds consist of volatile terpenoids, which possess the capability to repel and drive away undesirable insects while concurrently exerting an attractive effect on more advantageous insects, including honeybees. The repellent activity of EO can be attributed to specific metabolites, with monoterpene compounds against mosquito species and α-pinene demonstrating efficacy in repelling *Ixodes ricinus* tick. However, the mechanism linked to repellence activity is still unclear. It appeared that molecules interact with the sense of smell by inhibiting the olfactory receptors [101].

4.III.D Efficacy of Plant-Derived Product against Ectoparasites

A literature review has added significantly to the existing body of knowledge regarding the efficacy of essential oils in repelling ticks. Notably, a search query employing the keywords "essential oils", "ticks" and "repellent" demonstrated a pronounced exponential growth trend in research publications within the search database. The main finding of this research is that there was a significant increase in articles about essential oils as tick repellents from 2006 to 2016, indicating a growing interest in this topic among the academic community over the past decade (Table 15).

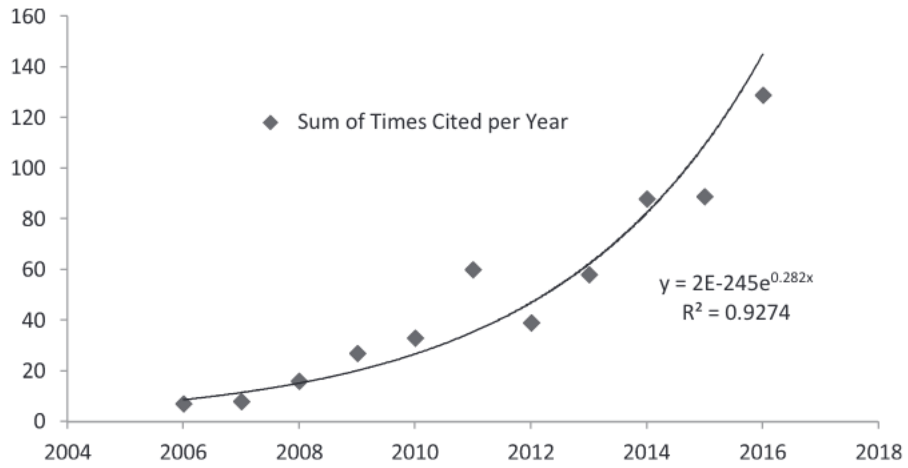

Figure 1 from [102]: the exponential increase of time that “essential oils, “repellent”, and tick as a keyword have been cited in the last decade

The analysis culminated in three core findings: firstly, it was observed that all tested essential oils exhibited effective tick repellence across various tick species; secondly, when evaluating short-term application (within the initial 15 minutes of application), concentration above 1% resulted in 70% repellent effect, while concentration higher than 10% caused complete repellence; thirdly, when extending the application period beyond one hour, it became evident that higher dosages or concentrations were necessitated to achieve the desired level of repellency. In addition to these general findings, the analysis specifically addressed the efficacy of pure compounds and plants in repelling ticks relevant to dogs and cats are outlined in the summarised table below (Table 16) [102].

Table 14 adaptation from [102]: Plants species and compound acting as repellent in ticks for dogs and cats

Tick species	Plant species	Compound
Rhipicephalus sanguineus	*Cleoma hirta* *Gynandropsis gynandra* *Nepeta oleander L.* *Tagetes minuta L.* *Tithonia diversifolia*	β-citronellol
Dermacentor reticulatus	*Citrus bergamia* *Corumbia citriodora* *Cymbopogon winterianus* *Lavandula angustifolia* *Mentha spicata L.* *Mentha x piperita L.* *Ocimum basilicum L.* *Origanum majorana L.* *Syzigium aromaticum* *Thymus serpyllum L.*	
Ixodes Ricinus	*Ammi majus L., Ammi visnaga L., Amyris balsamifera L.* *Artemisia herba-alba Asso, Calendula officinalis L., Conyaz dioscoridis* *Corymbia citriodora* *Cymbopogon winterianus* *Dianthus caryophyllus* *Eucalyptus citriodora* *Goeniculum vulgare* *Hyptis suaveolens* *Lantana camara* *Lavandula angustifolia* *Lawsonia nermis L.* *Matricaria recutita* *Mentha spicata L., Nerium oleander L.* *Ocimum basilicum L.* *Origanum majorana L.* *Pelargonium graveolens* *Ricinus communic L.* *Rosmarinus officinalis* *Tanacetum vulgare L.*	(-)-germacrene D Carvacrol Caryophyllene – 6,7,-oxide, Caryophyllene-6,7-sulfide, β-caryophyllene, Cinnamyl aldehyde, Eucalyptol, Eugenol Geraniol Humulene, humulene-6,7-episulfide, humulene-6,7-oxide, humulene-9,10-episulfide Linalool

Numerous investigations were focused on the responsiveness of *Rhipicephalus* and *Ixodes species* to essential oils. Nevertheless, the majority of these studies have been conducted *in vitro* rather than employing *in vivo* methods, rendering them somewhat limited [103]. The potency of EO in countering tick exhibits variability, an observation emphasised by the divergence in susceptibility among distinct species within the same genus. The application of the *Calceolaria serrata* EO produced dissimilarities in the mortality rates when employed against *Rhipicephalus sanguineus* and *Rhipicephalus microplus*, highlighting distinctions [100]. In 2018, a review explored the potential application of essential oils for managing ectoparasites with veterinary importance. Nevertheless, when focusing on the section dedicated to ticks, the study primarily addressed tick species that affect livestock animals. The study also confirmed the previous remark that most of the research was conducted *in vitro*, thus the need for further *in vivo* trials. It also points to the need for consistent and uniform quality, composition and potency for a herbal product. This means that each batch or formulation must adhere to specific quality standards and meet regulatory requirements to guarantee effectiveness, safety and reliability when using these products [79]. A study investigates the preventive efficacy of a natural oil mixture containing garlic oil, rapeseed oil and rosehip oil against the main tick species, *Ixodes ricinus* and *Rhipicephalus sanguineus*. The mixture was given orally for 3 consecutive days and proved that in infested treated animals, the skin irritation and inflammation caused by tick bites decreased gradually, while alive tick number decreased to a maximum of 99,42% at 6 hours from the 3rds dose and even reached 100% starting from 12 hours. The efficacy of the mixture was proven and resulted in 100% protection against tick infestation with complete safety and no report of adverse effects. Therefore, the application of essential oils mixture is promising against tick infestation in dogs [104]. An additional investigation suggests the potential utility of turmeric essential oil as a tick repellent for dogs. the evidence gained from this study indicated a reduction in the number of tick bites following the spray application of the turmeric EO product. The conducted trial has encountered complexities in effectively distinguishing authentic repellency from expellency, a primordial parameter in the context of the transmission of tick-borne pathogens. Unfortunately, the investigation does not contain information regarding the timing of tick checks by dog owners following each walk [105]. Experiments involving the use of *Tagete minuta* were found to be lethal to all three development stages of *Rhipicephalus sanguineus*. These experiments were conducted in vitro and demonstrated the effectiveness of this herbal remedy in killing unfed ticks before they even attach and proved the reduction of the tick in the dog environment [106]. The combination of monoterpenes thymol and carvacrol and the phenylpropanoid eugenol has been the subject of several studies, which could demonstrate its efficacy against *Rhipicephalus species*. A specific experiment has been conducted to investigate its potency and showed synergistic effects against the two tick species, *Rhipicephalus microplus* and *Rhipicephalus sanguineus* [107].

Regarding flea control, the growing evidence of resistance and the demand for natural products for safety and the environment have led to the research of novel medications containing not yet-used compounds. The objective of the study was to investigate the potential of plant-based food supplements composed of the following plants: thyme (*Thymus vulgaris L.*), rosemary (*Salvia rosmarinus* Spenn.), melissa (*Melissa officinalis L.*), fenugreek (*Trigonella foenum-graecum*), absinthe wormwood (*Artemisia absinthium*), and lemongrass (*Cymbopogon citratus* Stapf). Initially, the mixture was elaborated for repellent activity primarily aimed at combating *Dermanyssus galinae*, the poultry red mite. Subsequently, this product was adapted for use in controlling fleas in pets. The study targeted an environment with a high to very high parasite burden to ensure favourable conditions for the flea life cycle. Two groups of cats were used, namely group A and group B, and were placed in the same geographical region in France. Cats belonging to group A received a neutral diet, while cats in group B were fed with the plant-extract mixture for 150 days. At day 0, meaning at the time of the diet introduction, between 11 and 32 fleas were found. In group A, the population of fleas remained stable, with the development of pruritus in each individual starting from day 60. Concerning group B, the average flea infestation persists in the same way as group B between day 14 and day 60. A statistically significant distinction was observed from day 90 between the two groups, with group A expressing a higher flea prevalence than group B. As a result, the product could reach 77% efficacy, and the level of infestation remained low in group B. However, several limits were described following the results. Firstly, even at a low level of infestation cats remain a potential source of reservoir; secondly, a low load of fleas can be enough for the development of flea-allergy dermatitis according to the individual; thirdly, the size of the cat population evaluated was too small. Furthermore, the study suggested the potential utilisation of the plant-based diet. This dietary option may be suitable in cats with limited exposure to the external environment, such as indoor cats without flea allergies. It may also help reduce the frequent application of more potent drugs. This approach could involve a year-long supplementation using such plant-derived products added regularly to the feed along with an occasional insecticidal treatment [108]. In a recent *in vitro* study, the primary objective was to evaluate the lethal concentration and the toxicity of several essential oils on both mature and immature flea stages. The research employed a method involving bioassays to evaluate the biological activity of these plant-derived substances. The findings indicate that the method used to evaluate the different essential oils was not only practical but also effective in assessing their activity against *Ctenocephalides felis felis.* Moreover, the investigation was able to identify the most effective essential oils in terms of its potential properties among the six tested in the study, which means that the method successfully determined whether the essential oils can exhibit specific functional properties against ectoparasites. Indeed, it appeared that *Ocimum gratissimum* essential oils exhibit the highest efficacy across all flea stages and presented excellent results in the toxicological assay using a eukaryotic model. As a result, the conclusion of this study points toward the promising potential of these findings by suggesting the need for further testing on mammals [109]. Another insvestigaion was conducted to assess the efficacy of three essential oils derived from the following botanical sources: *Cinnamomum cassi* (L.) J. Presl (commonly referred to cassia), *Origanum vulgare* L. (oregano), and *Thymus vulgaris* L. (thyme). Additionally, each plant's chemical constituents were subject to analysis through gas chromatography analysis; the analysis of cinnamaldehyde constitutes 91% of cassie, thyme contains thymol at 44,7% and ocimene at 26,6%, and oregano is primarily composed of carvacrol. The results of the investigation unveiled that cassia and thyme essential oils exhibited a complete adulticide activity at the same concentration of 800 $\mu g.cm^2$, while oregano essential displayed 100% of mortality at lower concentrations (400 $\mu g.cm^2$) compared to cassia and thyme volatile oils. Moreover, it was observed that immature life stages demonstrated higher susceptibility to all three essential oils. However, when comparing the lethal concentration of 50%, it became evident that the pupal and adult stages were the least susceptible to the aforementioned essential oils. In particular, cassia represents the best results for life cycle inhibitions compared to the other two oils. It is essential to acknowledge certain limitations within this investigation. Namely, another reported lower efficacy in terms of ovicidal, larvicidal and adulticidal effectiveness. This discrepancy can be attributed to the utilization of different plant species belonging to the same genus, *Cinnamomum*, underscoring the variability of the essential oils properties across distinct plant species. Furthermore, additional factors contributing to the observed limitation were added in this literature, such as parasite generation, environmental conditions, time of exposure and evaluation technique. It is imperative to recognize that the study demonstrates the pulicidal potential of each essential oil and thus underscores the practical utility of these plant-derived products in environments plagued by an infestation.

When considering the utilisation of plant-derived compounds against mites, the following pertinent insights emerged. An *in-vivo* investigation was assigned to assess the comparative effectiveness of garlic oil (*Allium sativum* L.), marjoram oil (*Origanum majorana* L.), ozonated olive oil and permethrin in the treatment of *Otodectes cynotis* in cats. The efficacies of each essential oil were juxtaposed with that of the synthetic chemical agent, resulting in the formation of four distinct groups of cats. Each cat subject was administered a daily ear drop formulation. The assessment of treatment outcomes was based on microscope evaluation and the regression of clinical symptoms. Remarkably, the group treated with permethrin exhibited complete recovery within 10 days, which complies with the potent efficacy of the synthetic molecule permethrin. Furthermore, the efficacy of ozonated olive oil was manifestly complete in eradicating adult mites by both day 10 and day 30, thereby leading to the conclusion that, among the four treatments, permethrin and ozonated olive oil demonstrated the highest efficacy against adult mites. This evaluation could establish that the application of ozonated olive oil and *Origanum-majorana* L. applied for 10 days as topical treatment can yield comparable efficacy to that of permethrin treatment [110]. In another study, the acaricidal effectiveness of *Azadirachta indica* against *Sarcoptes scabiei var canis* was examined. Notably, it was proven that no significant differences were observed between the hexane extracted from *Azadirachta indica* and the standard control drug, ivermectin, after 14 and 21 days of treatment. This finding provides compelling evidence that *Azadirachta indica* could easily serve as a viable natural alternative to ivermectin in the treatment of canine scabies [111]. Finally, owing to their significant implication in production animals, mites such as *Dermanyssus gallinae, Psoroptes cuniculi* and *Psoreptes ovis* have garnered substantial attention in many *in-vitro* research, reflecting a growing interest in exploring novel natural compounds as potential solutions against ectoparasites [94].

5. Discussion

The variability in parasite lifecycles, the influence of climate changes, and host susceptibility complicate the ability to provide clear recommendations for managing ectoparasite infestation. The major risks of ectoparasites encountered are their adaptation capability, resistance and climate. Climate change poses a major ecological problem accompanied by the spread of certain parasites into new geographical regions. It is well proven in the present day that climatic change and the global travel of people may precipitate these migrations and the spread of vector-borne diseases [38]. Additionally, the convenience of the application route is one of the driving factors of pharmaceutical companies in developing new anti-ectoparasitic drugs, such as chewable tablets, that are easier to administrate to the animal. The second driving factor is the duration of action, and it should cover the specific period of activity at which the parasite is active but also the owner's compliance. The current role of the veterinarian is to bring awareness about the danger of ectoparasites and the link between human and their pets, but also how and when it is vital to administrate this type of drugs [46, 71]. Combining several synthetic compounds can offer effective prevention and, in some cases, even complete eradication of ectoparasites. Conversly, certain combinations have demonstrated therapeutic effects under 24 hours for severe infestation [55, 59, 73].

Moreover, certain active substances of synthetic anti-ectoparasitic drugs are dedicated and highly recommended for the treatment of specific infestations [28]. Targeting a unique receptor within the insect is the primary goal of pharmaceutical development, and the discovery of more highly specific new substances has been successful [67]. Additionally, synthetic active substances have been proven to be highly efficient in specific geographical locations where the insect burden has been extremely high, demonstrating the necessity of their usage in specific occasions [58]

Veterinary medicine concerning anti-parasitic drugs is in constant innovation, but it also incorporates the surveillance of these parasites worldwide. The comprehension of these two parameters plays a significant role in the creation of councils dedicated to the surveillance of resistance and the epidemiology of ectoparasites [3, 6]. However, the resistance development has been linked to other factors than the active substance. The improper dosage and the frequent application of antiparasitic drugs were the principal causes of resistance. In this context, different strategies have been elaborated to delay the resistance development, such as the lack of efficacy report, reduction of the number of treatments, dosing and method of administration, and the development of targeted selective treatment [77]. Thus, a longer duration of action, proper labelling, and communication are the crucial points to acknowledge as a veterinarian practitioner [38, 71].

Nevertheless, on certain occasions, certain individuals, due to the selection of traits and the development of hypersensitivity, can be subject to adverse effects, which are considered essential to report to the authority [7]. The emergence of resistance issues and the growing demand from the public for eco-friendly agricultural and animal production have spurred research into the use of botanical resources. Indeed, the wish for sustainable production without compromising the safety of the animals is crucial [38, 79, 95, 103]. It appeared in this review that plant-derived products are promising and can be effectively used in the environment of companion animals or for treating heavy infestation by using feed supplements. Plant-derived products are considered promising for different points. The first would be their accessibility and the extremendous number of potential plants; the second is their synergistic effect with current synthetic substances; the third is their economic power on a country; and finally, they can definitively participate in the protection of the flora [79, 95–97]. In this review, essential oils have been considered effective and efficient against ticks [79, 102, 104, 105], and by changing the concentration, they can have different targets of the life cycle of parasites [94, 100, 110]. The plant-derived products have also confirmed their usefulness for their implantation as a supplement in formulation, such as environmental spray or feed complement [95, 106, 108]. However, using plant-derived products, such as essential oils in dogs and cats, showed some challenges. The first challenge encountered during this literature review was the variability of the chemical constituent. Indeed, chemical variation can occur due to various pre- and post-harvesting factors, the geographical location of the plant, the plant species, the method of extraction, the condition of harvesting, and the storage conditions, all of which can influence the essential oils chemistry [97, 100, 102]. The second challenge would be their short residual activity explained by their high volatility, meaning that after a topical application of plant-derived product, they can lose their effectiveness after a short time. However, research on technology for slow release has been exploited, for example, microencapsulation, microemulsion and granular formulations. The most significant challenge would be their toxicity when increasing their persistence time since it can lead to increased exposure to beneficial non-targeted organisms, such as pollinators [100]. The variety of insecticidal plant-derived products is extensive and is expected to expand in the future [102]. Numerous studies have been executed *in vitro,* and the need for standardization of the experimental design in mammals is highly required for determining their correct dosages as well as their synergistic and antagonist capacity [79, 100, 112].

In conclusion, the comparative assessment of effectiveness between plant-derived products and conventional ectoparasiticides reveals a certain degree of efficacy in both approaches. Nevertheless, the regulatory pathway for bringing a pharmaceutical compound to the market necessitates a comprehensive evaluation of various factors, encompassing toxicological profiles and potential residual activity, extending beyond the efficacy assessment. Moreover, the financial burden and time-consuming associated with laboratory research into active substances must be acknowledged. In the present day, innovations, such as parasite vaccines, are more in focus in the present day than plant-derived compounds. However, the utilisation of botanical products retains its significance, particularly in the context of livestock production within the sphere of bio-agriculture. Furthermore, the continued exploration of new formulations holds promise for their role in managing environmental parasite infestation and contributing to food supplementation strategies to reduce the use of ectoparasiticides.

6. Abstract in English

The prevention and management of ectoparasite infestations in companion animals represent a critical aspect of preserving their well-being and overall health status. Within the field of veterinary medicine, antiparasitic treatments constitute the second-largest sector of the global segment in the animal health industry, underscoring their indispensable utilization. However, the recent decades have witnessed the emergence of various factors restricting their effective development. Companion animals, such as dogs and cats, may introduce the risk of zoonotic infection. Administrating antiparasitic agents is significant in reducing the potential transmission of these infections to humans. Nonetheless, the appearance of climatic changes may precipitate the increased utilization of anti-ectoparasites, thus increasing the risk of resistance. Additionally, in our current society, the appearance of eco-friendly principles and the demand for botanical products have exerted pressure on the pharmaceutical industry to design medications which are sustainable for animal health without impacting the safety of the environment and humans. This raises the question of whether plant-derived remedies match the efficacy of synthetic ectoparasiticides and offer a possible approach to antiparasitic development drugs.

The objective of this comprehensive literature review is to collect information regarding present-day anti-ectoparasitic drugs and their associated limitations in administration. The review summarizes the most prevalent ectoparasite species in dogs and cats, encompassing ticks, mites, fleas and lice and the effects they can inflict upon the well-being of companion animals. A detailed overview of the synthetic ectoparasiticides follows, accompanied by their mode of action and their formulation of administration. The investigation subsequently gathered recent articles concerning the limitations of synthetic drugs, such as resistance development, adverse effects, and their impact on the environment. Lastly, this study explores the potential utility of plant-derived products in combating ectoparasitic infestations in dogs and cats. To conclude, the review encloses an overview of the most recent research assessing the effectiveness of certain plant-derived products against ectoparasites.

7. Abstract in Hungarian

A társállatok külső paraziták okozta fertőzéseinek megelőzése és kezelése rendkívül fontos jólétük és általános egészségi állapotuk megőrzésének szempontjából. Az állatorvoslás területén belül a parazitaellenes kezelések az állategészségügyi ipar globális szegmensének második legnagyobb szektorát alkotják, ami kiemeli nélkülözhetetlen felhasználásukat. Az elmúlt évtizedekben azonban számos olyan tényező jelent meg, amely korlátozza hatékonyságukat. A társállatok, mint például a kutyák és macskák, zoonózisok kockázatát hordozzák magukban. A parazitaellenes szerek alkalmazása jelentős szerepet játszik e fertőzések állatról emberre történő lehetséges átvitelének csökkentésében. Mindazonáltal az éghajlati változások megjelenése előidézheti a külső parazita ellenes szerek fokozott felhasználását, így növelve a rezisztencia kockázatát. Emellett a jelenlegi társadalmunkban a környezetbarát elvek megjelenése és a növényi termékek iránti kereslet nyomást gyakorol a gyógyszeriparra, hogy olyan gyógyszereket tervezzenek, amelyek segítségével biztosítható az állatok egészsége, anélkül, hogy befolyásolnák a környezet és az emberek biztonságát. Felvetődik a kérdés, hogy a növényi eredetű hatóanyagok rendelkeznek-e a szintetikus külső parazita ellenes szerek hatékonyságával, és képesek-e megoldást kínálni parazitaellenes szerek fejlesztése során.

Ennek az irodalmi áttekintésnek a célja, hogy összegyűjtse a jelenlegi, a külső paraziták elleni gyógyszerekkel és alkalmazásukkal, valamint korlátjaikkal kapcsolatos információkat. Az áttekintés összefoglalja a kutyák és macskák körében leggyakrabban előforduló ektoparazita fajokat, beleértve a kullancsokat, atkákat, bolhákat és tetveket, valamint az általuk a társállatok jólétére gyakorolt hatásokat. Ezután részletesen ismerteti a szintetikus ektoparazita ellenes hatóanyagokat, hatásmódjukkal és alkalmazási formulájukkal együtt. Az összefoglaló ezt követően összegzi a szintetikus szerek korlátaival - például a rezisztencia kialakulásával, a káros hatásokkal és a környezetre gyakorolt hatásukkal - kapcsolatos legújabb cikkeket. Végül a tanulmány felsorolja a növényi eredetű termékek potenciális hasznosságát a kutyák és macskák külső paraziták okozta fertőzései elleni küzdelemben és áttekintést ad az egyes növényi eredetű termékek ektoparaziták elleni hatékonyságát értékelő legújabb kutatásokról.

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Thesis progress report for veterinary students

Name of student: Julie Grosclaude

Neptun code of the student: ND2C5Q

Name and title of the supervisor: Orsolya Farkas PhD, senior research fellow

Department: Pharmacology & Toxicology

Thesis title: Efficacy of plant derived compounds against ectoparasites compared to antiparasitic drugs

Consultation – 1st semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	03	20	Discussion of topic ideas	[signature]
2.	2023	03	27	Literature – agents against ectoparasites	[signature]
3.	2023	04	17	Differences bw animal species	[signature]
4.	2023	05	08	Alternative ectoparasiticide agents	[signature]
5.	2023	05	22	Thesis draft	[signature]

Grade achieved at the end of the first semester: excellent (5)

Consultation – 2nd semester

Timing				Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2023	09	18	changes in thesis draft	[signature]
2.	2023	09	25	Draft review, consultation	[signature]
3.	2023	10	09	Draft review, consult.	[signature]
4.	2023	10	16	Draft review, consult.	[signature]

5.	2023	10	30	Review of final document	[signature]

Grade achieved at the end of the second semester: excellent (5)

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

....
signature of the supervisor

Signature of the student: ....

Signature of the secretary of the department: ....

Date of handing the thesis in.......... ....