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# The use of cannabinoids in animals and therapeutic implications for veterinary medicine: a review

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**ABSTRACT:** Cannabinoids/medical marijuana and their possible therapeutic use have received increased attention in human medicine during the last years. This increased attention is also an issue for veterinarians because particularly companion animal owners now show an increased interest in the use of these compounds in veterinary medicine. This review sets out to comprehensively summarise well known facts concerning properties of cannabinoids, their mechanisms of action, role of cannabinoid receptors and their classification. It outlines the main pharmacological effects of cannabinoids in laboratory rodents and it also discusses examples of possible beneficial use in other animal species (ferrets, cats, dogs, monkeys) that have been reported in the scientific literature. Finally, the article deals with the prospective use of cannabinoids in veterinary medicine. We have not intended to review the topic of cannabinoids in an exhaustive manner; rather, our aim was to provide both the scientific community and clinical veterinarians with a brief, concise and understandable overview of the use of cannabinoids in veterinary medicine.

**Keywords:** cannabinoids; medical marijuana; laboratory animals; companion animals; veterinary medicine

## Abbreviations

**AEA** = anandamide (N-arachidonylethanolamine, CB<sub>1,2</sub> receptor agonist), **2-AG** = 2-arachidonoylglycerol (CB<sub>1</sub> receptor agonist), **2-AGE** = 2-arachidonyl glyceryl ether (noladin ether, CB<sub>1</sub> receptor agonist), **AM 251** = N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide (synthetic CB<sub>1</sub> receptor antagonist/inverse agonist), **CB<sub>1</sub>** = cannabinoid receptor type 1, **CB<sub>2</sub>** = cannabinoid receptor type 2, **CP-55,940** = (-)-cis-3-[2-Hydroxy-4-(1,1-dimethylheptyl)phenyl]-trans-4-(3-hydroxypropyl)cyclohexanol (mixed CB<sub>1,2</sub> receptor agonist), **FAAH** = fatty acid amide hydrolase, **GABA** = gamma-amino butyric acid, **GPR18** = G-protein coupled receptor 18, **GPR55** = G protein-coupled receptor 55, **GPR119** = G protein-coupled receptor 119, **HU-210** = (6aR)-trans-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol (synthetic mixed CB<sub>1,2</sub> receptor agonist), **HU-308** = [(1R,2R,5R)-2-[2,6-dimethoxy-4-(2-methyloctan-2-yl)phenyl]-7,7-dimethyl-4-bicyclo[3.1.1]hept-3-enyl] methanol (highly selective CB<sub>2</sub> receptor agonist), **IgE** = immunoglobulin E, **MGL** = monoacylglycerol lipase, **NADA** = N-arachidonoyl dopamine (CB<sub>1</sub> receptor agonist), **PEA** = palmitoylethanolamide, **SR144528** = N-[(1S)-endo-1,3,3-trimethylbicyclo[2.2.1]heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-[(4-methylphenyl)methyl]-1H-pyrazole-3-carboxamide (CB<sub>2</sub> receptor antagonist/inverse agonist), **THC** = delta-9-tetrahydrocannabinol (mixed CB<sub>1,2</sub> receptor agonist), **TRPV1** = transient receptor potential cation channel subfamily V member 1, **WIN 55,212-2** = (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (synthetic CB<sub>1,2</sub> receptor agonist)

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### 1. Introduction

Cannabinoids have been used in traditional medicine for thousands of years. There are reports going back to ancient China (Unschuld 1986; Zuardi 2006), medieval Persia (Gorji and Ghadiri 2002) or in Europe to the 19<sup>th</sup> century (following the Napoleonic invasion of Egypt) (Kalant 2001). It is important to emphasise that the use of cannabinoids in ancient or medieval cultures was not only because of the psychoactive effects of these substances; treatment was largely aimed at various somatic disorders including headache, fever, bacterial infections, diarrhoea, rheumatic pain or malaria (Kalant et al. 2001; Gorji and Ghadiri 2002; Zuardi 2006). Despite this fact, the use of cannabinoids is still illegal in many countries due to their psychoactive effects and addictive potential. Attempts by pharmaceutical companies in the sixth decade of the twentieth century to produce cannabinoids with pharmacological effects and without psychotropic activity were not successful (Fisar 2009; Pertwee 2009), although cannabinoids with very weak or no psychotropic activity are known (e.g. cannabidiol, cannabigerol, cannabichromene) (Izzo et al. 2009; Hayakawa et al. 2010).

Although cannabinoids have been attracting attention for many years, the last four decades have brought completely new and scientifically well-founded insights into their therapeutic potential. Since 1975 more than 100 controlled clinical trials with cannabinoids (or whole-plant preparations) for several indications have been carried out and the results of these studies have led to the approval of cannabis-based medicine in various countries (Grotenhermen and Muller-Vahl 2012). Consequently, there is increasing interest, particularly in companion animal owners, regarding the possible use of cannabinoids in veterinary medicine.

In order to cover this broad theme in a concise manner the text will first be focused on the classification of cannabinoids and cannabinoid receptors.

Attention will then be turned to the therapeutic potential of cannabinoids with regard to veterinary medicine.

### 2. The endocannabinoid system and classification of cannabinoids

The endocannabinoid system consists of several subtypes of cannabinoid receptors (the best characterised are subtypes CB<sub>1</sub> and CB<sub>2</sub>), endocannabinoids (endogenous substances that bind to the receptors) and enzymes involved in endocannabinoid biosynthesis through phospholipases or degradation: post-synaptically by FAAH (fatty acid amide hydrolase) and pre-synaptically by MGL (monoacylglycerol lipase) (Pertwee 2005; Muccioli 2010; Battista et al. 2012). This system represents a ubiquitous lipid signalling system (that appeared early in evolution), which plays important regulatory roles throughout the body in all vertebrates (De Fonseca et al. 2005). Below, we will focus on the cannabinoid receptors and their ligands (cannabinoids) because of their principal therapeutic significance.

Cannabinoids are chemical substances which act primarily on specific cannabinoid receptors and are basically divided into three groups; beside endogenous cannabinoids (endocannabinoids) also herbal cannabinoids (phytocannabinoids) and synthetic cannabinoids have been described (Fisar 2009).

Endocannabinoids are endogenously formed from membrane phospholipids in response to increases in intracellular calcium; they are immediately released and act as ligands of cannabinoid receptors (Miller and Devi 2011). The first endogenous ligand, *N*-arachidonylethanolamine, was identified in 1992 from porcine brain (Devane et al. 1992). It was named anandamide (AEA) based on the Sanskrit word 'ananda' which means 'internal bliss'. Other endogenous cannabinoids include 2-arachidonoylglycerol (2-AG), 2-arachidonylglyceryl ether (2-AGE, noladin ether) (Hanus et al.

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2001), O-arachidonylethanolamine (virhodamine) (Porter et al. 2002) and N-arachidonoyldopamine (NADA) (Bisogno et al. 2000; Gaffuri et al. 2012; Mechoulam et al. 2014). Within the nervous system endocannabinoids are released from post-synaptic neurons (retrograde neurotransmission) and they bind to presynaptic CB<sub>1</sub> receptors (see below) which results particularly in inhibition of GABA or glutamate release (Heifets and Castillo 2009). In neuron-astrocyte signalling cannabinoids released from post-synaptic neurons stimulate astrocytic CB<sub>1</sub> receptors, thereby triggering glutamatergic gliotransmission (Castillo et al. 2012).

Phytocannabinoids are chemicals produced especially by female plants of *Cannabis sativa* and are present in the resin of the herb. It has been found that these plants contain over 100 phytocannabinoids (Hill et al. 2012). The most studied cannabinoids from *Cannabis sativa* include e.g. delta-9-tetrahydrocannabinol (THC), cannabidiol, tetrahydrocannabivarin, tetrahydrocannabiorcol, cannabichromene and cannabigerol (Maione et al. 2013). THC was first isolated in 1964 (Gaoni and Mechoulam 1964) and the majority of the herbal cannabinoids soon after.

Synthetic cannabinoids are manufactured compounds which bind to cannabinoid receptors (with either agonistic or antagonistic activity) and many of them were originally synthesised for research purposes in University scientific departments or pharmaceutical companies. The most frequently reported series are represented by JWH (John W. Huffman, Clemson University), CP (Pfizer), HU (Hebrew University), AM (Alexandros Makriyannis, Northeastern University), WIN (Sterling Winthrop) and RCS (Research Chemical Supply) (Presley et al. 2013). Both phytocannabinoids and synthetic cannabinoids mimic the effects of endocannabinoids (Grotenhermen 2006).

Two cannabinoid receptors were initially recognised, CB<sub>1</sub> and CB<sub>2</sub>. Both these subtypes belong to the large family of receptors that are coupled to G proteins (Svizenska et al. 2008). Cannabinoid CB<sub>1</sub> receptors are among the most plentiful and widely distributed receptors coupled to G proteins in the brain (Grotenhermen 2006). The CB<sub>1</sub> receptor was cloned in 1990 (Matsuda et al. 1990) and CB<sub>2</sub> in 1993 (Munro et al. 1993). CB<sub>1</sub> receptors are present primarily in the central nervous system in regions of the brain that are responsible for pain modulation (certain parts of the spinal cord, periaqueduct-

al grey), movement (basal ganglia, cerebellum) or memory processing (hippocampus, cerebral cortex) (Grotenhermen 2006). To a lesser extent, they can also be found in some peripheral tissues such as pituitary gland, immune cells, reproductive tissues, gastrointestinal tissues, sympathetic ganglia, heart, lung, urinary bladder and adrenal gland (Pertwee 1997).

CB<sub>2</sub> receptors are particularly expressed in the periphery, in the highest density on immune cells, especially B-cells and natural killer cells (Pertwee 1997) and also in tonsils or spleen (Galiegue et al. 1995); nevertheless, their presence has also been described in the CNS (Van Sickle et al. 2005). The frequently discussed psychotropic effects of cannabinoids are mediated only by the activation of CB<sub>1</sub> receptors and not of CB<sub>2</sub> receptors (Grotenhermen and Muller-Vahl 2012).

Endocannabinoids have also been shown to act on TRPV1 receptors (transient receptor potential cation channels subfamily V member 1, also known as the “capsaicin receptor” and “vanilloid receptor” 1) (Ross 2003). The existence of other G-protein cannabinoid receptors has also been suggested. These proposed receptors (also called putative or non-classical cannabinoid receptors) include GPR18, GPR55 and GPR119 that have structural similarity to CB<sub>1</sub> and CB<sub>2</sub> (Alexander et al. 2013; Zubrzycki et al. 2014).

### 3. The use of cannabinoids in animals

It has been shown that the mechanism of action of cannabinoids is very complex. The activation of cannabinoid CB<sub>1</sub> receptors results in retrograde inhibition of the neuronal release of acetylcholine, dopamine, GABA, histamine, serotonin, glutamate, cholecystokinin, D-aspartate, glycine and noradrenaline (Grotenhermen and Muller-Vahl 2012). CB<sub>2</sub> receptors localised mainly in cells associated with the immune system are involved in the control of inflammatory processes. Their activation results in, among other effects, inhibition of pro-inflammatory cytokine production and increased release of anti-inflammatory cytokines (Zubrzycki et al. 2014). In addition, some cannabinoids were shown to act not only at cannabinoid receptors but also at vanilloid or serotonin 5-HT<sub>3</sub> receptors (Contassot et al. 2004; Grotenhermen and Muller-Vahl 2012). This complexity of interactions explains both the

large number of physiological effects of cannabinoids and the pharmacological influences of cannabinoid preparations (Grotenhermen and Muller-Vahl 2012).

There are a huge number of reports on the possible beneficial effects of cannabinoids in human medicine. Their therapeutic potential has been demonstrated in the treatment of many disorders including pain, inflammation, cancer, asthma, glaucoma, spinal cord injury, epilepsy, hypertension, myocardial infarction, arrhythmia, rheumatoid arthritis, diabetes, multiple sclerosis, Parkinson's disease, Alzheimer's disease, depression or feeding-related disorders, and many others (e.g. Porcella et al. 2001; Robson 2001; Rog et al. 2005; Blake et al. 2006; Pacher et al. 2006; Russo 2008; Scheen and Paquot 2009; Karst et al. 2010; Lynch and Campbell 2011; Caffarel et al. 2012; Grotenhermen and Muller-Vahl 2012; Hill et al. 2012; Maione et al. 2013; Lynch et al. 2014; Serpell et al. 2014; Lynch and Ware 2015).

Information concerning the effects of cannabinoid on animals can be found on the experimental level and were obtained during the pre-clinical testing of individual substances in mice, rats and guinea pigs (i.e. laboratory rodents). Beneficial effects of cannabinoids in these animals have been reported e.g. for disorders of the cardiovascular system, cancer treatment, pain treatment, disorders of the respiratory system or metabolic disorders, and suggest the usefulness of further research in this direction. Examples are summarised in Table 1.

For many further examples see the following reviews: Croxford (2003), Guzman (2003), Croxford and Yamamura (2005), Mendizabal and Adler-Graschinsky (2007), Sarfaraz et al. (2008), Nagarkatti et al. (2009), Steffens and Pacher (2012), Velasco et al. (2012), Han et al. (2013), Massi (2013), Stanley et al. (2013), Kucerova et al. (2014), Pertwee (2014), Kluger et al. (2015).

Compared to reports from laboratory rodents, there are a much smaller number of published papers dealing with pre-clinical testing of cannabinoids in other species (rabbits, ferrets, cats, dogs), and an even smaller number of reliable sources are available to date concerning the clinical use of cannabinoids in veterinary medicine for both companion and large animals. Indeed, the majority of articles concerns actually marijuana poisoning and its treatment rather than therapeutic applications (Girling and Fraser 2011; Meola et al. 2012; Fitzgerald et al. 2013).

It is therefore interesting that Mechoulam (2005) reported the use of cannabinoid acids (which are

precursors of the neutral cannabinoids, such as THC and cannabidiol) for veterinary purposes in Czechoslovakia already in the 1950s because of their antibiotic properties. The use of cannabinoids as antibiotic drugs, however, was not further investigated, although it has been shown that cannabinoids exert antibacterial activity (Appendino et al. 2008; Izzo et al. 2009).

The most frequently reported use of cannabinoids in companion animals (on a pre-clinical basis) is in association with the topical treatment of glaucoma. Pate et al. (1998) administered AEA, its R-alpha-isopropyl analogue, and the non-classical cannabinoid CP-55,940 into the eyes of normotensive rabbits. These substances were dissolved in an aqueous 10–20% 2-hydroxypropyl-beta-cyclodextrin solution (containing 3% polyvinyl alcohol). The doses were 25.0 µg for CP-55,940 and 62.5 µg for AEA and R-alpha-isopropyl anandamide. The low solubility of the cannabinoids in water was modified with cyclodextrins. It was shown that CP-55,940 had considerable ocular hypotensive effects, R-alpha-isopropyl anandamide exerted these effects to a smaller extent and AEA caused a typical bi-phasic initial hypertension and subsequent decrease in intraocular pressure (Pate et al. 1998). Song and Slowey (2000) administered the substance WIN 55212-2 (CB<sub>1,2</sub> receptor agonist) topically into the eyes of healthy rabbits at doses of 4, 20 and 100 µg. WIN 55212-2 at a dose of 100 mg significantly reduced intraocular pressure at 1, 2, and 3 h after application. The effects of the substance peaked between 1 and 2 h after administration and intraocular pressure returned to control levels at 4 h after application. The effects of WIN 55212-2 on intraocular pressure were dose-dependent. Twenty mg of the substance produced a smaller effect than 100 mg and 4 mg of the drug elicited non-significant lowering effects (Song and Slowey 2000). Fischer et al. (2013) tested the effects of topical administration of an ophthalmic solution containing THC (2%) on aqueous humour flow rate and intraocular pressure in 21 clinically normal dogs. Topical administration of THC ophthalmic solution led to a moderate reduction in mean intraocular pressure in these animals. Chien et al. (2003) used cannabinoids in both normotensive and glaucomatous monkeys (*Macaca cynomolgus*). WIN 55212-2 (CB<sub>1,2</sub> receptor agonist) dissolved in 45% 2-hydroxypropyl-β-cyclodextrin was administered at concentrations of 0.07%, 0.2%, and 0.5%

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Table 1. Examples of cannabinoid use in rodent models

Cardiovascular disorders	Slavic et al. (2013) – blockade of CB <sub>1</sub> receptor with rimonabant (CB <sub>1</sub> receptor antagonist/inverse agonist) improved cardiac functions after myocardial infarction and reduced cardiac remodelling
	Di Filippo et al. (2004) – administration of WIN 55,212-2 (synthetic CB <sub>1,2</sub> receptor agonist) significantly decreased the extent of infarct size in the area at risk in a model of mouse myocardial ischaemia/reperfusion
	Batkai et al. (2004) – endocannabinoids tonically suppressed cardiac contractility in hypertension in rats
	Mukhopadhyay et al. (2007) – treatment with rimonabant significantly improved cardiac dysfunction and protected against doxorubicin-induced cardiotoxicity in mice
Cancer	Steffens et al. (2005) – oral administration of THC (CB <sub>1,2</sub> receptor agonist) inhibited atherosclerosis in mice
	Grimaldi et al. (2006) – metabolically stable anandamide analogue, 2-methyl-2V-F-anandamide (CB <sub>1</sub> receptor agonist) significantly reduced the number and dimension of metastatic nodes in mice
	Guzman (2003) – <i>in vivo</i> experiments revealed that cannabinoid treatment of mice slowed down the growth of various tumour xenografts, including lung carcinomas, gliomas, thyroid epitheliomas, skin carcinomas and lymphomas
Pain	Luongo et al. (2013) – chronic treatment with palmitoylethanolamide (endogenous cannabinoid-like compound in the central nervous system) significantly reduced mechanical allodynia and thermal hyperalgesia
	Pascual et al. (2005) – WIN 55,212-2 (synthetic CB <sub>1,2</sub> receptor agonist) reduced neuropathic nociception induced by paclitaxel in rats
	Hanus et al. (1999) – HU-308 (highly selective CB <sub>2</sub> receptor agonist) elicited anti-inflammatory and peripheral analgesic activity
	Xiong et al. (2012) – administration of cannabidiol (indirect antagonist of CB <sub>1</sub> and CB <sub>2</sub> receptor agonists) significantly suppressed chronic inflammatory and neuropathic pain in rodents
Asthma	Jan et al. (2003) – THC and cannabiniol exhibited potential therapeutic utility in the treatment of allergic airway disease by inhibiting the expression of critical T cell cytokines and the associated inflammatory response in an animal model of mice sensitised with ovalbumin
	Giannini et al. (2008) – CP-55,940 (CB <sub>1,2</sub> receptor agonist) showed positive effects on antigen-induced asthma-like reaction in sensitised guinea pigs and conversely, both SR144528 (CB <sub>2</sub> receptor antagonist/inverse agonist) and AM 251 (CB <sub>1</sub> receptor antagonist/inverse agonist) reverted these protective effects
Vomiting	Darmani et al. (2001a) – THC and CP-55,940 (synthetic agonist at CB <sub>1</sub> and CB <sub>2</sub> receptors) prevented emesis produced by SR 141716A (CB <sub>1</sub> receptor antagonist/inverse agonist) in the least shrew ( <i>Cryptotis parva</i> )
	Darmani (2001b) – THC reduced the percentage of animals vomiting and the frequency of vomits provoked by cisplatin in the same animal species
	Parker et al. (2004) – THC and cannabidiol (indirect antagonist of CB <sub>1</sub> and CB <sub>2</sub> receptor agonists) reduced lithium-induced vomiting in the house musk shrew ( <i>Suncus murinus</i> )
Diabetes	El-Remessy et al. (2006) – cannabidiol (indirect antagonist of CB <sub>1</sub> and CB <sub>2</sub> receptor agonists) reduced neurotoxicity, inflammation, and blood-retinal barrier breakdown in streptozotocin-induced diabetic rats
	Weiss et al. (2006) – cannabidiol significantly reduced the incidence of diabetes in young non-obese diabetes-prone female mice
	Weiss et al. (2008) – cannabidiol ameliorated the manifestations of diabetes in non-obese diabetes-prone female which were either in a latent diabetes stage or with initial symptoms of the disease
Retinitis pigmentosa	Lax et al. (2014) – HU-210 (CB <sub>1,2</sub> receptor agonist) preserved cone and rod structure and function, thus showing neuroprotective effects on retinal degeneration in a rat model for autosomal dominant retinitis pigmentosa
Food intake, body weight	Hildebrandt et al. (2003) – AM 251 (CB <sub>1</sub> receptor antagonist/inverse agonist) reduced inguinal subcutaneous, retroperitoneal and mesenteric adipose tissue mass in Western diet-induced obese mice. Anorectic effects of AM 251 were also reported by e.g. Slais et al. (2003), Chambers et al. (2006) and Tallett et al. (2007)

Five normal monkeys received 50 µl (2 × 25 µl) of WIN 55212-2 to the right eye, and an equal volume of the vehicle to the left eye. In glaucomatous monkeys, 50 µl of WIN 55212-2 was administered to the glaucomatous eye only. Moreover, a multiple-dose study was carried out in 8 monkeys with unilateral glaucoma. WIN 55212-2 (0.5%) was administered to the glaucomatous eye twice daily at 9:30 AM and 3:30 PM for five consecutive days. It was shown that in the five normal monkeys unilateral application of the substance significantly decreased intraocular pressure for up to 4, 5, and 6 h following administration of the 0.07%, 0.2%, and 0.5% concentrations, respectively. The maximum changes in intraocular pressure were found at 3 h after drug application. In the eight glaucomatous monkeys the administration of WIN 55212-2 also resulted in a significant decrease in intraocular pressure (Chien et al. 2003).

Other potential and promising indications for cannabinoid use in veterinary medicine include inflammation and pain treatment as well as possible applications in dermatology and oncology. With respect to inflammation and pain, Re et al. (2007) authored a review in which they focused on the role of an endogenous fatty acid amide analogue of the endocannabinoid AEA – termed palmitoylethanolamide (PEA) – in tissue protection. PEA does not bind to CB<sub>1</sub> and CB<sub>2</sub> receptors but has affinity for the cannabinoid-like G-coupled receptors GPR55 and GPR119. It acts as a modulator of glia and mast cells (Keppel Hesselink 2012), and has been shown to enhance AEA activity through a so-called “entourage effect” (Mechoulam et al. 1998). Re et al. (2007) concluded that the use of natural compounds such as PEA influences endogenous protective mechanisms and can represent an advantageous and beneficial novel therapeutic approach in veterinary medicine. Regarding dermatology, Scarpella et al. (2001) administered the substance PLR 120 (an analogue of PEA) to 15 cats with eosinophilic granulomas or eosinophilic plaques. Clinical improvements of signs and lesions were evident in 10 out of 15 cats, suggesting that PLR-120 could be a useful drug for the treatment of these disorders (Scarpella et al. 2001). Similarly, Cerrato et al. (2010) isolated mast cells from the skin biopsies of 18 dogs, incubated these cells with IgE-rich serum and challenged them with anti-canine IgE. Subsequently, histamine, prostaglandin D<sub>2</sub> and tumour necrosis factor-alpha release was measured in the presence and absence of increasing concentrations of palmitoylethanolamide.

The authors found that histamine, prostaglandin D<sub>2</sub> and tumour necrosis factor-alpha release induced by canine anti-IgE were significantly inhibited in the presence of PEA. Thus, it can be concluded that PEA has therapeutic potential in the treatment of dermatological disorders involving mast cell hyperactivity (Cerrato et al. 2010). Moreover, Cerrato et al. (2012) evaluated the effects of PEA on the cutaneous allergic inflammatory reaction induced by different immunological and non-immunological stimuli in six spontaneously *Ascaris*-hypersensitive Beagle dogs. These dogs were challenged by intradermal injections of *Ascaris suum* extract, substance P and anti-canine IgE, before and after PEA application (orally at doses of 3, 10 and 30 mg/kg). The results have shown that PEA was effective in reducing immediate skin reaction in these dogs with skin allergy (Cerrato et al. 2012). With respect to oncology, Figueiredo et al. (2013) found that the synthetic cannabinoid agonist WIN-55,212-2 was effective as a potential inhibitor of angiogenesis in a canine osteosarcoma cell line. Although further *in vivo* research is certainly required, the results thus far indicate that the use of cannabinoid receptor agonists as potential adjuvants to chemotherapeutics in the treatment of canine cancers could be a promising therapeutic strategy. Looney (2010) reported the use of cannabinoids for palliative care in animals suffering from oncological disease to stimulate eating habits. Finally, McCarthy and Borison (1981) reported antiemetic activity of nabilone (synthetic CB<sub>1,2</sub> agonist) in cats after cisplatin (anti-cancer drug) treatment and similarly Van Sickle et al. (2003) reported that THC (0.05–1 mg/kg *i.p.*) reduced the emetic effects of cisplatin in ferrets.

#### 4. Prospective veterinary use of cannabinoids

As can be seen from the above instances, cannabinoids have a myriad of pharmacological effects and the beneficial impact of different cannabinoids has been proven and documented many times in various laboratory/companion animals. It has been shown that the same cannabinoid drug can elicit divergent responses in humans and animals. For example, Jones (2002) reported increased heart rate and slightly increased supine blood pressure after THC administration in humans, whereas the cardiovascular effects in animals were different, with bradycardia and hypotension (Jones 2002). Thus, a definite advantage of the use of cannabinoids in

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animals is that the research and pre-clinical testing was carried out on various animal species and these categories can now represent target species in the case of veterinary use. In other words, the risk of divergent responses to the same drug, which has been described for humans and animals, is much lower.

It should also be taken into account that the majority of cannabinoids possess psychotropic properties which may change the behaviour of animals (e.g. locomotion) and that these substances have addictive potential (Fattore et al. 2008; Landa et al. 2014a; Landa et al. 2014b). On the other hand, other drug classes with even stronger effects on the CNS and addictive properties have been used therapeutically in both humans and veterinary medicine for centuries (e.g. opioids) because their benefit outweighs the risks.

Cannabis-based medical products were introduced to human medicine in the last years in many countries (among others Austria, Canada, Czech Republic, Finland, Germany, Israel, Italy). Preparations approved for use in human medicine include Cesamet, Dronabinol, Sativex, Bedrocan, Bedrobinol, Bediol, Bedica or Bedrolite. For dogs and cats, the veterinarian-recommended, ready-made hemp based supplement Canna-Pet is presently available (containing non-psychoactive cannabidiol). PEA can at present be used to restore skin reactivity in animals in a veterinary medication sold under the trade name Redonyl (LoVerme et al. 2005). It is therefore not surprising that owners of animals are also exhibiting increasing interest in the possible use of cannabinoids/medical marijuana in veterinary medicine as can be seen by the number of internet forums concerned with this issue (e.g. dvm360 magazine, Cannabis Financial Network or Medical Daily). In the Journal of the American Veterinary Medical Association, Nolen (2013) reported anecdotal evidence from pet owners describing beneficial effects of marijuana use in dogs, cats and horses and, moreover, also the opinions of professionals who believe in the potential usefulness of cannabis use in veterinary medicine. The reluctant attitude of veterinarians towards the use of cannabinoids/medical marijuana in animals could be associated with the risk that owners will make attempts to treat their animals using cannabis-based products, which can lead to intoxication. In the article by Nolen (2013), Dr. Dawn Boothe (Clinical Pharmacology Laboratory at Auburn University College of Veterinary Medicine) concluded that

veterinarians should be part of the debate about the use of cannabinoids/medical marijuana, e.g. by means of a controlled clinical trial dealing with the use of marijuana to treat cancer pain in animals.

## 5. Conclusions

The isolation of THC in 1964 represented a breakthrough in research progress concerning cannabinoids. The discovery of the cannabinoid receptors and their endogenous ligands, definition of the endocannabinoid system and description of other cannabinoid substances elicited increased interest in this research and in the possible therapeutic potential in animal models. The results from this basic research finally led to the addition of cannabinoids/medical marijuana to the spectrum of therapeutic possibilities for various disorders in humans. The therapeutic effects of cannabinoids/medical marijuana on companion animals are now the subject of discussion in numerous internet forums and such debate could result in attempts at treatment using cannabinoids without the necessary safety precautions. Thus, the prospective use of cannabinoids for veterinary purposes needs to be taken seriously; this could decrease the risk of attempts at unauthorised and non-professional treatment by animal owners. Legislative regulations may differ in various countries and the use of cannabinoids/medical marijuana must be in accordance with the respective rules.

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