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Review

Beneficial Effects of Nutraceuticals, Especially Polyphenols on Canine Health

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Abstract: The use of nutraceuticals, mainly phytogenics, is increasingly widespread in animal nutrition, especially in dogs. The materials typically used to provide these very diverse natural compounds come from plants, but lately algae and fungi have also been used. In animal nutrition, these compounds are applied to obtain better results in the production and stability of feed and also as biofunctional substances with benefits for animal health. Polyphenols are natural compounds from the secondary metabolism of plant matter present in animal food (e.g., seeds and nuts, fruits, vegetables, herbs/aromatic plants, spices, cereals, and vegetable oils, among others). Most of the biological effects of these compounds associated with health benefits have been attributed to their antioxidant potential because they can protect cellular elements against oxidative injury, reducing the risk of dysfunctions and diseases associated with oxidative processes. Polyphenols are constituted by multiple families of substances with wide applications in pet therapy and nutrition. In this work, we review the most relevant phytogenic polyphenols, exploring their characteristics, sources, and implications for canine health. Our focus includes the effects on gastrointestinal functions and its microbiota, as well as aspects such as obesity, diabetes, and fat metabolism. Additionally, we examine their impact on cardiovascular, neurological, and immunological systems, along with their potential anti-oncogenic role. Finally, we discuss the overall role of polyphenols in dog diets and their future implications.

Keywords: dogs; pets; pet food; pet health; phytogenics; polyphenols

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1. Introduction

Pets are companion animals that provide us with emotional, therapeutic, and psychological support, which has led us to share our lives intimately with them in homes [1]. This panorama is reflected in a report from the American Pet Products Association in which 70% of American households have pets in 2021 [2], so considering families in the United States of America (USA), Brazil, the European Union (EU), and China have more than 500 million pets, it is estimated that more than half of the world has a pet at home [3]. EU has one of the highest cat and dog ownership rates in the world, with 46% (91 million households), where the cat with approximately 114 million individuals is the most popular, followed by the dog with about 93 million. While in Spain, the number of dogs (27%) and cats (16%) living in our homes has only increased in recent years, with the values between 2018 and 2021 indicating the upward trend of these animals between 6–9 million dogs and between 3–6 million cats, ranking second for dogs (behind Germany) and fourth (behind Germany, France, and Italy) for cats, respectively [4]. It should also be noted that there are more than 10 million dogs in the United Kingdom (UK), of which two and a half million have been acquired by guardians from breeders (32%), a private seller (23%), or rescue/relocation centers (14%) [5]. These data reveal a strong bond between humans. Many pets' owners (guardians) consider their pets to be family members [6], sharing their homes fully with them and celebrating pet birthdays in a process called 'humanization' [7]. This trend has led to increased spending on pet care [6]. In this sense, the pet food industry, with the approval of the guardians, has considered the selection of ingredients for human consumption for the production of pet food as they are considered more appetizing and safer [8]. However, this consideration is not legislated in any animal feeding regulations [9].

Epidemiological relationships between food components and the current high incidence of allergies, gastrointestinal diseases, and oral health issues, among various other health problems, have been described [10]. Likewise, the incidence of health problems related to being overweight and obese is increasing in cats and dogs, as is the case with their guardians [11]. In many cases, musculoskeletal, cancer, diabetes, respiratory, and skin disorders result in a reduction in the life expectancy of these animals [9]. The possible causes or practices that cause these problems in dogs are mainly the following: (i) not following the recommended nutritional guidelines correctly (excessive caloric intake or insufficient/deficit), (ii) insufficient physical exercise, (iii) bad eating habits acquired from their guardians (for example, excessive food treats), and (iv) a guardian confusion due to the existence of a wide and varied pet food offer [12–14]. Consequently, guardians have a main responsibility for the health of their pets, especially through the commitment of maintaining their well-being and health through the choice of food products for monitoring or consuming a nutritionally balanced diet [10,15].

Currently, cat and dog guardians are very interested in knowing the nutritional content of foods (quantity and quality), especially those nutrients with adverse effects on health (unhealthy lipid profile, excess sugars, antinutrients, among others) [16,17]. Likewise, guardians look for foods similar to those existing in the human food market because they tend to anthropomorphize their pets and perceive such foods improve the health, quality of life, longevity, and well-being of their pets [1]. The composition of foods is easily modified by changes in the ingredients used in their preparation, by the presence of bioactive compounds naturally, or by their addition to the food. In fact, food reformulation allows both the use of traditional ingredients and those specifically designed to provide healthy properties [18].

According to the European Association of Nutraceuticals, these compounds differ from pharmaceutical products (drugs) by not being chemical compounds formulated for health goals. The phrases "*dietary supplements*" and "*functional foods*" are used interchangeably as synonyms for nutraceuticals, although in some cases the differences are evident. Dietary supplements contain substances derived from food, which are commonly arranged in the form of capsules, powders, liquids, or tablets. Nutraceuticals are compounds derived from food that help in the prevention of diseases and health disorders or disorders diseases and health alterations or disorders [19].

Lately, numerous new nutraceuticals have been proposed, creating a large and varied list of ingredients and sometimes surprising. This list includes polyphenols, both flavonoid and non-flavonoid types, organic acids (vitamin C), tocopherols (vitamin E), carotenoids (provitamin A), and mono- and polyunsaturated fatty acids (MUFA and PUFA, among others), along with prebiotic and probiotic products [20].

In general, nutraceuticals of plant origin (phytogenics) tend to be better accepted by consumers than others, which has considerably increased the incorporation of phytogenics into the diets of dogs and cats by companies, thereby complementing the offer of conventional products [9,21–23]. This has been a consequence of demand by guardians looking for ingredients that can provide additional health benefits beyond basic nutrition, simulating the trend of functional foods in humans [24].

In 2020, the global market for functional foods (including organic foods) for pets reached a value of USD 1,955 million, estimated to reach USD 4676 million by 2030, forecasting a growth of 9% in this period. The dog segment in this market corresponded to 69% during 2019, representing approximately 50% of the global market for functional foods for pets during 2020, which is expected to continue during the forecast period [25]. By contrast, EU guardians spent more than EUR 29.1 billion on pet food supplies during 2022. This sales within the EU market largely stemmed from increased awareness of ingredients, personalized food products, organic and grain-free foods, among others [4]. Generally, veterinary experts agree with the use of functional foods, as long as their recommendation is supported by scientific data that support the safety and effectiveness of these novel products [9].

This review details the potential of polyphenols and polyphenol-rich foods in addressing various canine health issues. We focus on their impact on gastrointestinal function, microbiota, obesity, diabetes, fat metabolism, and cardiovascular, neurological, and immunological systems. We also explore their potential anti-oncogenic role. While plant-based foods are increasingly important in canine diets, this review primarily focuses on polyphenols in common dog foods, excluding a detailed analysis of herbs and their preparations. We present the main classes of polyphenols and their content in dog food and briefly touch upon other plant-based functional ingredients like phytosterols and essential oils. Throughout, we offer insights into the role of polyphenols in dog diets and discuss their future implications.

2. Functional Ingredients in Pet Food

Functional foods contain a variety of ingredients. In addition to classic nutraceuticals like vitamins, minerals, and healthy fats, new substances have been identified. These new ingredients, alone or combined, are often promoted as miracle foods or ingredients. In the pet food sector, we can classify these compounds as the following:

(1) Polyphenols. Polyphenols contain subfamilies such as simple phenols, including hydroxycinnamic acids, hydroxybenzoic acids and their derived alcohols, flavonoids (flavones, isoflavones, flavanols, flavanones, flavonols, anthocyanins, pro-anthocyanidins, catechins, and tannins); also, stilbenes, coumarins, lignans, betalains (betacyanins and betaxanthins), anthraquinones, and curcuminoids. Tables 1 and 2 show the basic chemical structures and some examples, along with their common functionalities described of non-flavonoid and flavonoid types of phenolic compounds, respectively [25–28].

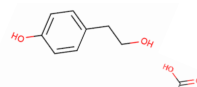
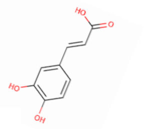
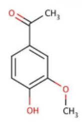
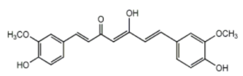
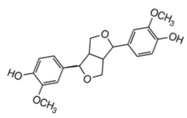
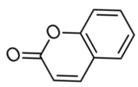
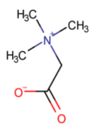
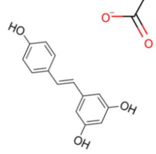
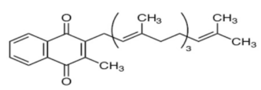
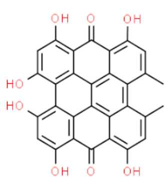
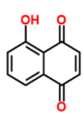
(2) Glucosinolates. From an evolutionary perspective, these compounds are found in two distinct plant families: Brassicaceae, Capparaceae, and Caricaceae, as well as in the Putranjivaceae family. These substances contain nitrogen and/or sulfur in their chemical structure and are known as β-thioglucoside-N-hydroxysulfates. Over 120 different glucosinolate compounds have been discovered, which can be categorized into three types: aliphatic glucosinolates (derived from methionine, valine, leucine, or isoleucine), indole glucosinolates (derived from tryptophan), and aromatic glucosinolates (derived from phenylalanine or tyrosine). Sinigrin, raphanin, brassicin, and its gluco-derivatives are habitual components. Their hydrolysis products, mainly isothiocyanates, have been studied due to their role as anti-oncogenic substances [29,30].

(3) Terpenoids or isoprenoids. These organic compounds are derived from the 5-C compound isoprene, with modified structures through the addition or deletion of methyl groups and/or oxygen atoms. Terpenoids are classified according to their number of isoprene units, including mono-, sesqui-, di-, tri-, tetra-, and polyterpenoids, among others. The most traditional use in food dogs are carotenes (α- and β-carotene, lycopene), although several xanthophylls with excellent characteristics have been considered. Another group of isoprenoids with interesting applications are essential oils (EOs), which are composed of mono-, di-, and sesquiterpenes, in addition to several phenolic compounds. Aspects such as their enormous diversity and their great ethnopharmacological history are making them increasingly used as functional ingredients. Also, triterpene saponins such as squalene and others have shown interesting future applications as hypocholesterolemic and anti-inflammatory agents [31].

(4) Alkaloids. Constituted by a broad family of compounds, organic compounds contain at least one nitrogen atom in their structure. Mainly used pharmacologically for their psycho- and neuro-physiological properties, lately they are being revisited with extensive studies (capsaicin, piperine, piperidine, hypericin, etc.) on their func-

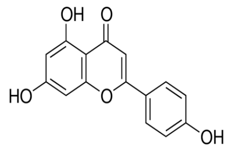
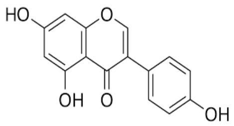
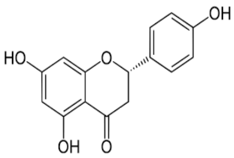
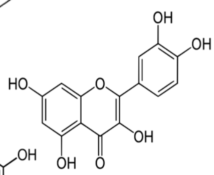
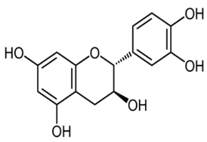
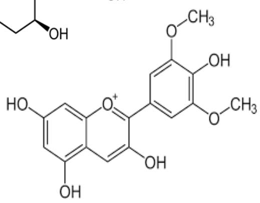
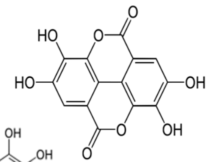
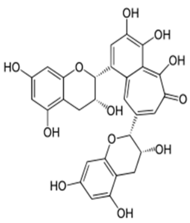
tional properties [32,33]. This is also the case of anthraquinones (a class of phenolic compounds, classified as alkaloids in some cases), with examples such as emodin, barbaloin, rhein, chrysophanol, and rufigallol that are currently studied for their antimicrobial properties, among other functions [34–36]. All these compounds are provided by plants, constituting a huge and diverse store of functional ingredients with enormous application prospects in animal nutrition and also in pet food [27].

Table 1. Chemical structures, classification, examples, and potential benefits of non-flavonoid type phenolic compounds (chemical structures as examples were indicated in red, correlatively).

Chemical Name/Subclass	Example of Compounds	Potential Benefits
Simple phenols	Arbutin, tyrosol	Antiseptic, diuretic, anti-tumoral
Hydroxycinnamic acids *Free forms* *Esters* *Alcohols, Aldehydes & Glycosides*	Ferulic, caffeic, cinnamic Chlorogenic, rosmarinic, cynarin, cichoric, caftaric acids Coniferyl, caffeoyl, feruloyl, vanillin, eugenol	Antioxidant, chemoprotector, immunomodulatory, neuroprotector, dyspepsia, hypercholesterolaemia
Acetophenones	Apocynin, androsin, piceol, picein	Anti-asthmatic, anti-inflammatory, neuroprotective, sedative
Salicylates	Salicin, salicortin, populin	Analgesic, febrifuges, sciatica, myalgia
Curcuminoids	Curcumin, dimethoxy- and bisdemethoxy-curcumin, and breakdown metabolites	Anti-inflammatory, anti-tumoral, cardioprotective, wound healing, anti-arthritis, antioxidant, anti-depressive
Lignans & Neolignans	Pinoresinol, masoprocol, silybin, schizandrin, podophyllotoxin, enterodiol	Hypoglycemic, chemoprotector, antioxidant, keratosis, anti-fungal, anti-inflammatory, anti-tumoral, phytoestrogen precursors
Coumarins & Furanocoumarins	Coumarin, aesculetin, xanthotoxin, umbelliferone, psoralen, angelican, bergapten, khellin	Photosensitizer, anti-vitiligo, psoriasis, tinea hypopigmentation, spasmolytic, bronchodilator, asthma, anti-hypertensive, renal calculi, hay fever, rhinitis
Betalains *Betacyanins* *Betaxanthins*	Betanin, (iso-, pro-, neo-) Vulga-xanthin (mira-, portula-, indica-)	Antioxidant, antimicrobial, anti-tumoral
Stilbenes	Resveratrol, pinosylvin, piceatannol, piceid, pallidol, viniferin, pterostylbene	Anti-inflammatory, neuroprotective, anti-tumoral, cardioprotective, anti-aging, antioxidant, anti-fungal, hypoglycemic
Quinones *Naphthoquinones,* *Naphthodiantrones,* *Anthraquinones & Kavalactones*	Ubiquinol (Q10), menaquinone (vit K), plastoquinone, phylloquinone Juglone, lapachol, plumbagone, shikonin, hypericin, sennosides, carmine, fagopyrin, emodins, rhein, kavain, yangonin, methysticin	Anti-tumoral, anti-leukemic, antimicrobial, anti-parasitic, anti-fungal, anti-viral, anti-inflammatory, cardioprotective, laxative, hypnotic, sedative, anesthetic

Table 2. Chemical structures, classification, examples and potential benefits of flavonoid type phenolic compounds (chemical structures as examples were indicated in red, correlatively).

	Chemical Name/Subclass	Example of Compounds	Potential Benefits
	*Flavones*	Apigenin, luteolin, baicalein	
	*Isoflavones*	Genistein, diadzein, biochanin	
	*Flavanones*	Naringenin, eriodictyol, hesperetin, liquiritin	Antioxidant, anti-tumoral, anti-microbial, anti-viral, anti-atheromatous, anti-hypertensive, anti-inflammatory, hepatoprotective, endothelial protection, cardioprotective, neuroprotective, chemoprotective, immunoprotective, estrogen-mediated responses, anti-ageing
	*Flavonols*	Quercetin, kaempferol, myricetin, isorhamnetin	
	*Flavanols*	Catechin, epicatechin	
	Flavan-3-ol (OPC) [1]	Epicatechin-3-gallate, epigallocatechin-3-gallate	
	*Anthocyanidins*	Malvidin, cyanidin, delphinidin, europinidin, pelargonidin, peonidin, rosinidin, aurantinidin	
 	*Tannins* *Gallo- & Ellagitannins* *Condensed tannins (Proanthocyanidins)*	Galloyl derivatives, ellagic acid, punicalagin, rugosin-D, oenthein-B, sanguiin, geraniin, agrimoniin, puncialin, corilagin Procyanidins (OPC), propelargonidins, prodelphinidins, profisetinidins, proteracacinidins, theaflavins	Anti-tumoral, anti-inflammatory, antioxidant, antidiarrhoeic, anti-haemorrhagic, antimicrobial, hypolipidaemic, astringent, sclerosis, cardioprotective, endothelial function, platelet function, anti-hypertensive, anti-atherosclerotic, oral health

[1] OPC: oligomeric procyanidins.

Polyphenols: Food Sources

Polyphenolic compounds, ubiquitous in foods of plant origin, are an important contribution to the human and animal diet [37]. In pet foods, polyphenols are used to obtain improvements in the stability of the products and also as functional components with an impact on the health of animals, with wide applications in pet therapy and nutrition [23]. Polyphenols are natural compounds from the secondary metabolism of plants that incorporate a large quantity and variety of compounds [38–40]. The family of polyphenols includes those chemically defined substances that have a basic structure of an aromatic benzene ring with one or more hydroxyl groups and can vary from a simple phenolic molecule to that of a complex high molecular weight polymer [41]. Based on the number of phenol rings and the essential structural elements in the side chain, polyphenols can be subdivided into two groups: flavonoids and non-flavonoids (hydroxycinnamic- and hydroxybenzoic acids, stilbenes, coumarins, lignans, betalains (betacyanins and betaxanthins), anthraquinones, and curcuminoids) (Table 1). Flavonoids have a structure of two aromatic rings (A and B rings) linked through three carbon atoms that often form an oxygenated heterocycle (C ring). Listing the carbon atoms in rings C and A from 2 to 8 and those in ring B from 2′ to 6′. This structure allows variations in the C ring, with the main sub-structures or subfamilies of dietary flavonoids being the following: flavanols, flavonols, flavones, flavanones, isoflavones, anthocyanidins, catechins, and tannins [42] (Table 2). The absorption, processing, and biological effects of flavonoids are influenced by the overall quantity of hydroxyl groups and the arrangement of functional groups surrounding their core structure [43].

Fruits, vegetables, and plant-based products are the main dietary sources of flavonoids [44]. Table 3 shows polyphenol subclasses, including food sources. Worldwide, some of the most important foods due to their consumption in large quantities and their polyphenol content are green and black tea (rich in catechins, theaflavins, and proanthocyanidins), fruits, or berries, with bluish/purple ones being the richer in polyphenols (black chokeberry, black elderberry, cranberry, and black currant). Other fruits with intense colors, such as plum, cherry, and blackberry, are followed by fruits of lesser color, such as strawberry, raspberry, and grape, ending with pome fruits (apple, nectarine, pear, etc.). As for the vegetable sources richest in polyphenols (particularly in tyrosol), they are black and green olives, followed by artichoke heads and red and green chicory (all rich in chlorogenic acid), onion (red or yellow), shallot, and spinach (rich in flavonols). Foods with a lower content include broccoli, asparagus, endive, lettuce, endive, and carrot [45,46].

Table 3. Main subclasses of polyphenols and related sources.

Polyphenol Subclasses	Food/Plant Sources
Non-Flavonoid Types	
Simple phenols and phenolic acids	Coffee, olive, cabbage, apples, cherries, grapes, wine, artichoke, hawthorn, tomatoes, pears, ginger, basil, thyme, oregano, aloe, echinacea, strawberries, orange, pineapple, sunflower, blueberries, oats, rice, peanuts, MAPs
Acetophenones	Almonds, cherries, honeysuckle, jasmine, strawberries
Salicylates	Willow tree, *Gaultheria* fruits, poplar leaves
Curcuminoids	Turmeric roots
Lignans and neolignans	Linseeds, sesame seeds, chives, nuts, roots, leaves, *Brasicaceae*, spices, whole grains, strawberries
Coumarins and furanocoumarins	Tonka beans, cinnamon, figs, celery, parsley, West Indian satinwood, citrus fruits
Betalains (betacyanins and betaxanthins)	*Caryophyllales* order (cacti, carnations, amaranths, ice plants, beets)
Stilbenes	Almond, cocoa seeds, grape seeds, grape skin, red wine, peanuts, blueberries, raspberries
Quinones, naphthoquinones, naphthodiantrones, anthraquinones, and kavalactones	Black walnut, St John's wort, rhubarb, buckthorn, knotgrass, kava plant
Flavonoid types	
Flavones	Celery, red pepper, lemon, onion, oregano, rosemary, parsley, MAPs, flowers of *Trollius* sp.
Isoflavones	Peas, soybean, lentils, red kidney beans
Flavanones	Grapefruit, oranges, tangerines, peppermint, lemons, limes, olives, MAPs
Flavonols	Vitis grape berry skins, onions, leeks, broccoli, black tea, lettuce, apples, green tea, wine, dill leaves
Flavanols	Tea, grapes, red wine, apples, blackberries, apricots, cocoa seeds
Anthocyanins	Blackberries, cherries, strawberries, raspberries, chokeberries, tomatoes, grapes, green coffee, red cabbage, potatoes
Tannins, and Gallo- and Ellagitannins	Bean seeds, persimmons, green coffee, mango, pomegranates, strawberries, walnuts, almonds
Condensed tannins (proanthocyanidins)	Breakax (*Schinopsis*) wood, mimosa, spruce and pine barks, grape seeds, tropical woods

Medicinal and aromatic plants (MAPs) and spices are also rich sources of polyphenols, such as cloves rich in eugenol or star anise rich in anethole. As for MAPs, mint contains considerable amounts of flavanones, such as eriocitrin (a rutinoside derived from eriodyctiol), within the *Lamiaceae* family (mint, sage, rosemary, peppermint, and thyme), that have high amounts of hydroxycinnamic acids, such as rosmarinic acid. A particular example is pinocembrin flavanone (from Mexican oregano, lemon verbena-related). Seeds and nuts are also among the foods richest in polyphenols (linseed rich in lignan secaisolariciresinol, chestnuts and walnuts rich in ellagitannins, hazelnuts, pecans, and almonds rich in proanthocyanidins, and finally soy flour and roasted soybeans rich in isoflavones). Other foods with lower amounts of polyphenols than MAPs are cereals such as wheat and rice, rich in ferulic acid and resorcinols; vegetable oils, such as extra virgin olive oil; rich in tyrosol and derivatives and rapeseed oil containing 4-vinylsyringol; and also algae [47,48].

Dietary flavonoids exist in two forms: as free molecules (aglycones) and as sugar-bound forms (glycosides). In the intestine, these compounds undergo enzymatic hydrolysis, allowing for their absorption. Once absorbed, they are modified into their glucuronide or sulfate forms by phase II enzymes, primarily in the liver and epithelial cells [49]. The hydroxyl groups of flavonoids undergo glucuronidation, methylation, and sulfation, which enter the blood circulation and are excreted through the kidney and bile [50] (Figure 1). The variety of dietary polyphenols and the intricate nature of the gut microbiota indicate that further research is necessary to gain a complete understanding of how gut microbial enzymes metabolize polyphenols [51].

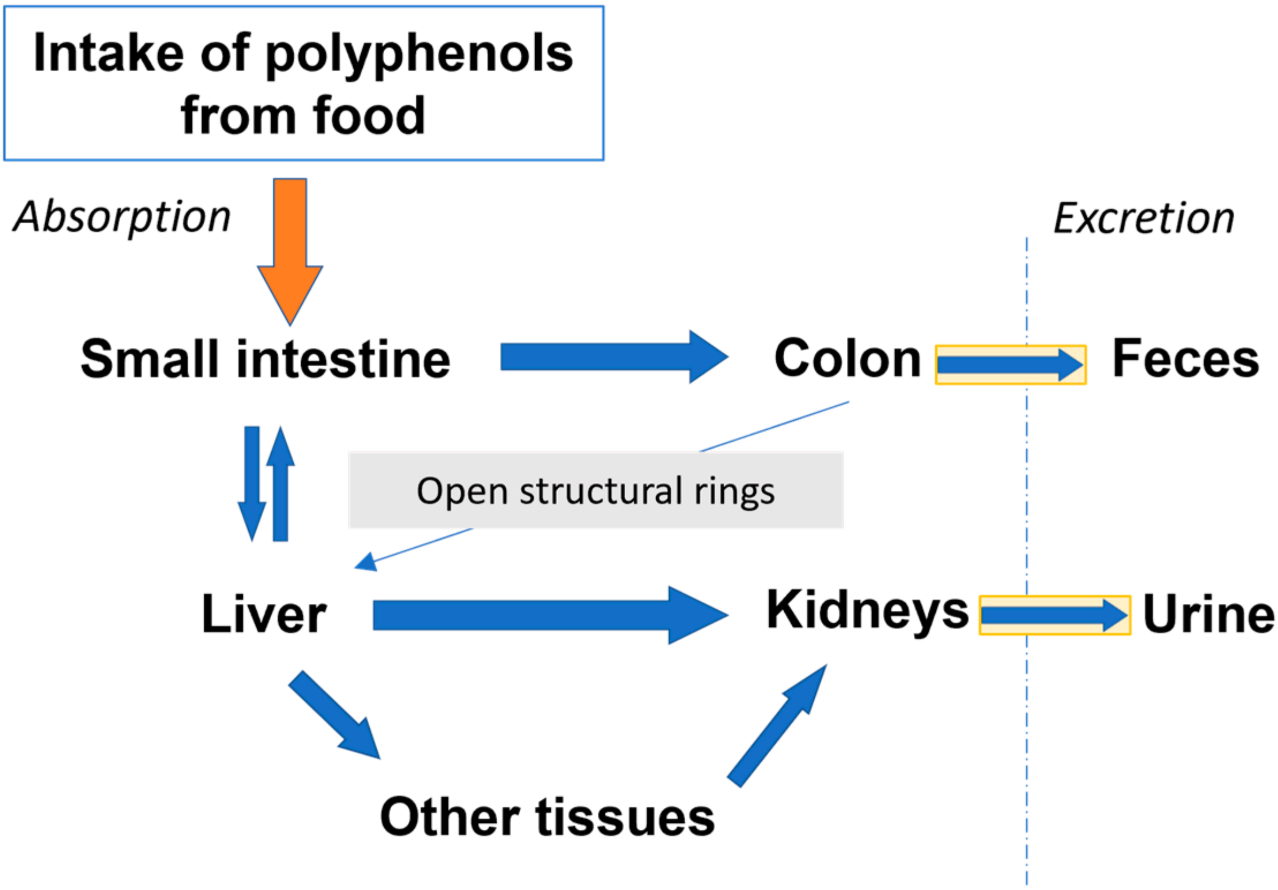


Figure 1. Main organs involved in the metabolism of polyphenols.

3. Effects of Polyphenols in Canine Health

In recent years, there has been a significant interest in the characterization of the possible health benefits associated with the intake of polyphenols in the diet of dogs. These compounds have properties to act as antioxidants, scavenging free radicals that cause cellular and tissue damage [52]. Therefore, the inclusion in the diet of foods rich in polyphenols could favor the beneficial effects against chronic diseases and dysfunctions in companion animals [53]. Table 4 shows the most representative examples of the beneficial effects of polyphenols on the different dysfunctions and diseases in dogs.

Table 4. Some representative examples on beneficial effects of polyphenols in dogs.

Treatment Group	Source	Dosage/Duration	Effects	References
Gastrointestinal effects:				
Beagle (*n* = 20)	Gallic acid	0.02–0.08%/45 d	↓ B/F ratio, P; ↑ A-O, A-I; alleviate I, OS; ↑ SCFAs; regulate serum LM (↓T, FD) and CM in feces; ↓ DR	[54]
Dogs (*n* = 24)	Grape polyphenols	1 or 3 mg/kg LW/28 d	E, Eu, F, Ph, SS, FP	[55]
Breed dogs (*n* = 6)	Pomegranate peel extract.	50 mg/kg BW/30 d	↑ SCFAs; enhance GH (↓ G, C, GP, GS-t)	[56]
Dogs (*n* = 30)	Green tea	0.48–1.92% g/kg/18 weeks	↑ F; ↓ B, Fu,	[57]
Mongrel dogs (*n* = 20)	Seabuckthorn seed oil	5 mL twice d till complete healing	↑ WG, RDP, Hb, PCV, TEC	[58]
American staffordshire terrier (*n* = 30)	Bromelain Quercetin of grape Lentinula edodes	13.5–10 mg/g/28 d. Dosage 1 mg every 10 kg BW	↑ FS, ↓ FC, FCo, FN-M, FI/S; improve GH, PPC	[59]
Beagle puppies (*n* = 19)	Gallic acid	500 mg/kg/weeks	↑FAE, FSc, SCFAs, GP, LF; ↓MDA, ↓PB, ↓ES, ↓CSS1; AA (↓DR: ↓SCo, ↓HSP-70); alleviate OS, I and improve GH	[60]
Obesity effects:				
Beagle (*n* = 20)	Gallic acid	0.08%/45 d	Regulate serum LM (↓ T, ↓ FD) and ↓ B/F ratio; ↓ P; no negative effect on BC; PO	[54]
Dogs (*n* = 30)	Green tea	0.48–0.96–1.92% g/kg/18 weeks	↓ WG, ↓ I; anti-obesity properties	[57]
Labrador Retrievers spayed/neutered (*n* = 14)	Soy isoflavones	25% more than their maintenance energy requirement/12 month	Reducing body fat accumulation	[61]
Labrador Retrievers (Obeses) (*n* = 30)	Soy germ meal	579 mg/kg/6 month	↑ BF; prevent LBM; promote: LW, MH (↓ BC, ↓ T, ↓ IS, ↓ L, ↓ PIGC); reduce CI (↓ CY, ↓ CH)	[62]
Diabetes and insulin sensitivity effects:				
Rottweiler (*n* = 45)	Rosemary leaves Basil leaves	0.025–0.05%/8 weeks	↓ SG; inhibite activity EA; ↑ IS, G, C, SD; ↓ Co, MD, LD; positive Pβ; ↑ CNMT	[63]

Table 4. *Cont.*

Treatment Group	Source	Dosage/Duration	Effects	References
Beagle insulin-resistant (*n* = 10)	Green tea	80 mg/kg per d/12 weeks	↑ ISI 60%, ↓ T 50%; improve I, LM; altered expression genes involved GC and LH	[64]
Dogs induced myocardial infarction (*n* = 6)	Curcuminoids	250 mg/180 d	↓ OS, ↑ GSH/GSSG; improved IS sensitivity; reduce cardiovascular complications	[65]
Fat metabolism effects:				
Beagle (*n* = 8)	Phytosterols	1300 mg/15 d	↓ LDL, ↑ HDL; hypolipemiant hypolipemiant drugs (LM: T and BC)	[66]
Dogs (*n* = 7)	Grape seed/skin	threshold doses (individually or in combination)/8 d	Inhibit platelet aggregation	[67]
Cardiovascular effects:				
Dogs induced myocardial infarction	Quercetin	50 mg/kg/15 d	Cardioprotective; enhance CFLVM, CYC; ↓ FHR, ↓ CDS; prevent formation ITS	[68]
Dogs induced myocardial infarction	Nanozime FeCurTA	10 mg/kg i.v./30 d	↓ IFS, ↑ LVEF, ↓ LV-ESV, ↓ LGE, ↓ T1 mapping, ↓ ECV, ↑ GLS, ↑ IVS, ↑ Ki67; preserve CF; inhibite CIY	[69]
Neurological effects:				
Senior Beagle (*n* = 40)	Tomato pomace	106 mg/g/30 d	Plasma ↓ 4-EPS; ↑ fecal microbiota: *Blautia*, *Parabacteroides*, *Odoribacter*; improve anxiety-linked metabolite	[70]
Senior Beagle (*n* = 24)	Polyphenol extracts (grape and blueberry)	240–480 ppm/75 d	Improve WM and cognitive performance	[71]
Immunological system effects:				
Beagle (*n* = 20)	Gallic acid	0.08%/45 d	↓ SA in Fece; enhance immunity	[54]
Dogs (*n* = 74)	*Echinacea angust.* *Curcuma longa* *Vaccinium myrtillus* *Silybum marianum*	EA 0.1 mg/kg BD/60 d CL 6.6 mg/kg BD/60 d VM 0.2 mg/kg BD/60 d SM 1.5 mg/kg BD/60 d	IMA, A-I, A-O, ↓ PIC, LPA	[72]
Puppies (*n* = 45)	Resveratrol	10 mg/Kg BW/7 d	↓ OS; improve TLC and NC	[73]
Cancer effects:				
Canine osteosarcoma epithelial cells	Myricetin	100 µM, dose-dependent	↓ Osteosarcoma progression, cell division, DNA replication ↑ DNA fragmentation, ROS, mitochondrial damage, apoptosis induction Regulate several MAPK factors (AKT, ERK1/2, JNK, PI3k)	[74]

Table 4. *Cont.*

Treatment Group	Source	Dosage/Duration	Effects	References
92 adult Scottish Terriers with cell carcinoma and83 Scottish Terriers healthy	Supplemented diets with extra vegetables: yellow-vegs, green-vegs, and cruciferae-vegs	Extra vegs: Only once; Once a week; Three times a week.	Inverse relationship between vegs intake and cell carcinoma progression Green-vegs > yellow-vegs > Crucif-vegs > vitamin suplements	[75]
Respiratory effects:				
Dogs (*n* = 41)	Echinacea purpurea	1 g/10 kg/8 weeks	↓ Symptoms and improvement in 92% after 4 weeks	[76]
Liver effects:				
Dogs (*n* = 74)	*Sylibum marianum*	SM 1.5 mg/kg BD/60 d	↓ ALT, ↑ PXA	[72]
Dogs (*n* = 12)	Orange bioflavonoids *Sylibum marianum*	one tablet/15 kg/8 weeks	↓ ALT, ↓ AST, ↓ ALP, ↓ GGT, ↓ BL; hepatoprotective activity	[77]
American staffordshire terrier (*n* = 15)	Orange bioflavonoids *Sylibum marianum* S-acetyl-glutathione	one tablet/15 kg/35 d	Enhanced LBP; ↑ GP	[78]
Dental effects:				
Dogs (*n* = 38)	Gallic acid	0.8% mouth spray/42 d	↓ GI, ↓ PI, ↓ CI; altered oral microbiota	[79]
Joint effects:				
Dogs w/arthrosis (*n* = 20)	Supplement with different herbs	0.5 mL/kg LW/90 d	Improving joints and reducing pains in dogs with advanced osteoarthritis	[80]

↑: increase, ↓: reduction. 4-EPS: 4-ethylphenyl sulphate. AA: antidiarrheal activity. A-I: anti-inflammatory. ALP: alkaline phosphatases. ALT: alanine transaminases. A-O: anti-oxidative. AST: alanine aminotransferases. B: Bacteroidetes. BC: blood cholesterol. BF: body fat. BIL: bilirubin. BW: body weight. C: catalase. CDS: conductivity disorders. CF: cardiac function. CFLVM: contractile function of left ventricular myocardium. CH: chemokines. CI: calculus index. CI: chronic inflammation. CIY: cardiac injury. CM: carbohydrate metabolism. CNMT: clinico-nutritional management. CSS1: clostridium. CY: cytokines. CYC: coronary circulation. DR: diarrhea rate. E: Escherichia. EA: enzyme amylase. ECV: extracellular volume. ES: Escherichia–Shigella. Eu: Eubacterium. F: Firmicutes. FAE: fecal acetate. FC: fecal calprotectin. FCo: fecal cortisol. FD: fat digestibility. FHR: frequency of heart rate. FI/S: fecal indole/skatole (harmful bacterial metabolites). FN-M: fecal N-methylhistamine. FP: fecal propionate. FS: fecal SCFA. FSc: fecal score. Fu: Fusobacterium. G: glutathione. GGT: gamma–glutamyl transferase. GH: gut/gastrointestinal health. GI: gingival index. GLS: global longitudinal strain. GP: glutathione peroxidase. GS-t: glutathione S-transferase. Hb: hemoglobin. HDL: high-density lipoprotein. HSP: heat shock proteins. I: inflammation. IFS: infarct size. IMA: immunomodulatory activity. IS: Insulin. ISI: insulin sensitivity index. ITS: intravascular thrombus. IVS: interventricular septum. L: leptin. LBM: lean body mass. LBP: liver blood parameters. LD: lactate dehydrogenase. LDL: low-density lipoprotein. LF: Lactobacillus fecal. LGE: late gadolinium enhancement. LH: lipid homeostasis. LM: lipid metabolism. LPA: liver protectant activities. LVEF: Left ventricular ejection fractions. LV-ESV: left ventricular-end systolic volume. LW: loss weight. MDA: malondialdehyde. MH: metabolic health. NC: neutrophil count. OS: oxidative stress. P: Parasutterella. PB: proteobacteria. ES: PCV: packed cell volume. Ph: Phascolarctobacterium. PI: plaque index. PIG: postprandial interstitial glucose. PO: prevents obesity. PPC: psycho-physical conditions. PXA: paraxonose activity. Pβ: pancreatic β-cell function. RDP: restoration of digestive processes. PIC: pro-inflammatory cytokines. SA: succinic acid. SCFAs: short-chain fatty acids. SD: superoxide dismutase. SG: serum glucose. SS: salivary serotonin. T: triglyceride. TEC: total erythrocyte count. TLC: total leukocyte count. WG: weight gain. WM: working memory.

3.1. Antioxidant Activity of Polyphenols

Cellular antioxidant capacity is an important factor related to animal health [81]. As part of the global antioxidant defense system, antioxidant metabolites and antioxidative enzymes played a key role, which protect cells from oxidative damage from free radicals and xenobiotics [82]. In recent years, plant polyphenols have become a popular focus for the development of new functional foods, presenting a variety of biological actions, including antioxidant, anti-inflammatory, and anticancer effects [83]. In general, the damage caused by the oxidative stress due to the accumulation of reactive oxygen species (ROS) has a negative impact on many organs and tissues that could cause or mediate the progression of a number of diseases and dysfunctions [84]. Different reports show that oxidative stress contributed to the spread of various canine infections such as leishmaniasis [85], babesiosis, and ehrlichiosis [86–88]. Most of the biological effects of these compounds have been attributed to their antioxidant potential, due to the fact that they can protect cell constituents against oxidative damage, decreasing the risk of oxidative diseases [89].

However, while recent work reports that dietary polyphenols can relieve stress in dogs, providing a basis for the development of new functional pet foods aimed at stress management [90], some studies assess malpractice in the design of diets with these functional ingredients. A good example is the "*antioxidant paradox*", in which adverse effects occur when the balance of the redox system is compromised in favor of an excessively reduced state due to the presence of too many antioxidants, causing reducing stress [91]. In this respect, and according to other authors [92], we believe that the frontier between eustress situations (activators of functional cell anti-stress response) and distress (ROS overaccumulator step and cell dysfunctions) is delicately regulated by the cellular redox network, and therefore, the balances between oxidative and anti-oxidative compounds and enzymes are easily altered when exogenous antioxidants without control are incorporated into dog diets.

3.2. Gastrointestinal Effect of Polyphenols

The digestive system of dogs is home to a diverse microbiota that plays a crucial role in regulating metabolism and immune function, helping to prevent the development of gastrointestinal disorders. Various studies have indicated that the gut microbiome is dynamic, primarily consisting of similar bacterial populations formed by anaerobic genera. Metagenomic analyses have shown that the nutritional composition of a dog's diet can influence the bacterial populations and metabolites present in their intestines. There are strong connections between dietary elements and the intestinal microbiomes, with gastrointestinal diseases often linked to dysbiosis of the gut microbiota and metabolic disorders [93]. A healthy gut microbiome is essential for regulating the immune system, aiding in the defense against intestinal pathogens, and supplying the host with vital vitamins and nutrients [94].

Recent studies have highlighted the importance of diagnostic methods and treatments aimed at enhancing a balanced intestinal microbiota through dietary changes [95]. Research has demonstrated that the gut microbiota in dogs can ferment a variety of plant fibers and convert polyphenol conjugates and oligomers into more accessible forms. Additionally, the inclusion of polyphenols in their diet may affect the composition and functionality of microbial populations within the gut microbiota [23,24]. As a result, adding polyphenols to the diet has been suggested as a potential treatment for acute diarrhea in dogs, owing to the antioxidant, anti-inflammatory, and microbiome-modulating effects of polyphenols and their catabolites [96]. Interestingly, the gut microbiomes of dogs and humans exhibit very similar genetic characteristics and dietary responses, largely due to the long history of domestication that dogs have undergone throughout their evolution. So, research on canine intestinal microbiota could also be applied to humans [97]. Interestingly, the oral administration of an extract rich in polyphenols in obese mice modified the composition of the intestinal microbiome. The authors concluded that pomegranate extract rich in polyphenols has a prebiotic effect capable of modulating intestinal microbiota in favor of bifidobacteria. Furthermore, they suggested that this extract could have other positive health impacts associated with the prevention of obesity and cardiovascular diseases [98]. As in similar human studies, the authors suggested that more information was required about the "new" prebiotics generated during the digestion of polyphenols and their potential beneficial effects [99,100].

In an interesting study, the potential risk of long-term (45 days) consumption (0%, 0.02%, 0.04%, and 0.08%) of a polyphenolic compound (gallic acid) on the gastrointestinal tract of healthy dogs has recently been evaluated by analyzing the fecal microbiota and metabolomics. The authors suggested that dietary supplementation with 0.08% gallic acid mainly affected carbohydrate metabolism by downregulating fecal succinic acid (a simple phenol). Therefore, gallic acid supplementation improved the metabolic activity of the gut by modulating the gut microbiota, thereby promoting gut health by improving antioxidant capacity and reducing the rate of inflammation (relieving oxidative stress) and diarrhea. Overall, this study confirmed the beneficial effects of long-term consumption of polyphenols on lipid metabolism and gut health [54].

Regarding gastrointestinal health and gut microbiota, diets enriched with grape proanthocyanidins for 28 days have been shown to significantly increase the abundance of certain populations of fecal microbiota (*Escherichia*, *Eubacterium*, *Fusobacterium*, and *Phascolarctobacterium*) and short-chain fatty acids (fecal propionate) in healthy adult dogs [55]. Polyphenol supplementation from pomegranate peel extract (50 mg/kg body weight) increased fecal concentrations of total short-chain fatty acids and fermentative metabolites, as well as improved antioxidant status in healthy dogs [56]. Also, green tea polyphenol supplementation altered the structure of the gut microbiota in adult dogs (30 males) after 18 weeks [57].

In veterinary medicine, gastric ulcers and erosions are commonly recognized issues, particularly in small animals, often resulting from prolonged use of steroids and non-steroidal anti-inflammatory drugs (corticosteroids), even at therapeutic levels in dogs [101]. The goal of veterinary treatment is to reduce or block gastric acid production while maintaining the health of the gastric mucosa. Common medications used for this purpose include famotidine, lansoprazole, misoprostol, and sucralfate. A study's findings indicated that hematological parameters showed significant improvement by the end of the research, while serum biochemical parameters remained within normal physiological ranges throughout the duration of the study. Concluding that sea buckthorn oil (rich in carotenoids, phytosterols, tocopherols, and polyphenols) [102] was the best therapeutic agent for dogs compared to the oral drugs famotidine, lansoprazole, misoprostol, and sucralfate [58].

According to a recent study in kennel dogs, a mixture of three natural substances (quercetin, bromelain—an enzyme extract derived from the stems of pineapples—and *Lentinula edodes*) with high antioxidant capacity results in a significant improvement in intestinal health, reducing the inflammatory state and improving the composition of the intestinal microbiota with anti-inflammatory and immunomodulatory effects [59]. In a different study, the addition of 0.05% gallic acid to the diet was found to lower fecal scores and demonstrated antidiarrheal effects against diarrhea induced by environmental stress in puppies. Furthermore, this supplementation led to an increase in fecal acetate and total short-chain fatty acids (SCFAs), enhanced glutathione peroxidase activity, and reduced malondialdehyde levels, although it did not impact serum total antioxidant capacity or superoxide dismutase activities. Additionally, there was an increase in the relative abundance of fecal Lactobacillus spp., while levels of Escherichia, Shigella, and Clostridium decreased. Finally, metabolomic analyses of fecal and serum samples indicated that gallic acid significantly corrected the disruptions in amino acid, lipid, carbohydrate, and nucleotide metabolism caused by stress. In summary, the dietary inclusion of 0.05% gallic acid helps to reduce oxidative stress and inflammation in stressed puppies by promoting positive changes in gut microbiota and metabolites, which may enhance both gut and overall health in these animals [60].

In some cases, some authors have proposed the use of polyphenols for their potential in the treatment of intestinal inflammation. For example, canine acute diarrhea, especially during acute diarrheic episodes [103], and also as an adjunct therapy, reducing the intestinal injury in parvovirus enteritis-infected puppies [73]. In general, more clinical studies in dogs are needed, especially to know the effect of polyphenols on the microbiota and the impact of its byproducts (aglycones and glycosides) on other physiological functions of the animal.

3.3. Effects of Polyphenols on Obesity

Obesity is the most common nutritional disorder in domestic dogs [104,105]. Recently, the use of bioactive components has been considered as a new approach in the prevention and management of this disease. Some polyphenols have properties that modulate the physiological and molecular pathways involved in energy metabolism. Some studies highlight the importance of both the action of individual polyphenols and polyphenolic mixtures in the prevention of obesity. The possible beneficial effects of polyphenols depend on the amount ingested and their bioavailability, which is a handicap in the polyphenols/metabolism studies. Considering in vitro and in vivo *studies*, these compounds could act on weight loss involving aspects such as activation of fatty acid β-oxidation processes, induction of satiety, stimulation of energy expenditure, promotion of adipocyte apoptosis, and increasing lipolysis; also through inhibition of adipocyte differentiation [106].

Gallic acid is a natural hydroxybenzoic acid with many health benefits. In an interesting study, the addition of gallic acid in the diet of dogs has been carried out to evaluate its effects, concluding that the addition of 0.08% gallic acid for 45 days regulates the metabolism of lipids in the blood by reducing serum triglycerides, succinic acid level, fat digestibility, and the *Bacteroidetes*/*Firmicutes* ratio. Also, the relative abundance of *Parasutterella* was decreased and increased short-chain fatty acid-producing bacteria, along with the accumulation of fecal acetate and total short-chain fatty acid content. Furthermore, long-term consumption of this simple phenol added to the diet (0.02–0.08%) had no negative effects on canine body condition, indicating that in dogs, gallic acid has anti-obesity, antioxidant, and anti-inflammatory capacities [54].

In a study using a cell model system resembling human abnormal adipose tissue, the role of hydroxytyrosol (a catechol-derived polyphenol) on the expression of genes related to inflammation was evaluated. The findings showed that hydroxytyrosol influenced the expression of genes in adipocytes, leading to a reduction in oxidative stress and the inhibition of NF-κB. This process interfered with the recruitment of macrophages and downregulated the signaling pathways linked to obesity-related conditions. It was concluded that hydroxytyrosol has beneficial effects on obesity-related diseases by paralyzing the recruitment of macrophages and improving chronic inflammation of adipose tissue, suggesting that more studies are necessary to reproduce these results both in animals and in clinical trials [107]. Obesity is a known cause of chronic inflammation in dogs [108]. Dogs fed diets with 25% more calories than required and supplemented with soy isoflavones resulted in less weight than those who did not receive the extra isoflavones [61]. In another study by the same author, overweight dogs consuming soy isoflavones were more likely to achieve weight loss goals than untreated dogs [62]. A recent study on overweight/obese Labrador Retrievers found that an isoflavone-rich weight-loss diet led to greater fat loss while preserving lean body mass [109]. The diet also improved metabolic health by reducing cholesterol, triglycerides, insulin, and leptin levels and maintaining lower post-meal blood sugar. Additionally, it decreased several markers of inflammation, supporting its potential to promote healthy weight loss and reduce chronic inflammation in overweight and obese dogs.

Green tea is rich in flavonoids, particularly in associated catechin derivatives, with anti-inflammatory and anti-obesity properties. The intake of green tea polyphenols has a positive impact on weight status, inflammation, and gut microbiota populations in dogs [57]. Green tea polyphenols attenuate the impacts of a high-fat diet for 12 weeks, reducing weight gain and inflammation through down-regulation of mRNA expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) associated with liver inflammation and liver fat content in Beagle dogs (16 healthy males) [110].

3.4. Effect on Diabetes and Insulin Sensitivity

Diabetes mellitus (DM) is becoming more common in dogs, typically presenting as type 1 DM. This spontaneous form of type 1 DM in dogs is characterized by significant gastrointestinal dysbiosis and altered levels of unconjugated bile acids in feces, resembling the patterns seen in type 2 DM in humans [111]. Insulin sensitivity in dogs refers to insulin's ability to lower blood glucose levels by promoting peripheral glucose uptake and decreasing glycogen breakdown, which helps maintain normal blood sugar levels. Insulin resistance is often misunderstood but is generally associated with changes in metabolic function, even in otherwise healthy dogs [112]. When it comes to treating DM with medication, it can impact the gastrointestinal microbiome, highlighting the need for personalized treatment approaches to effectively manage related metabolic disorders. Given the macronutrient composition and its relationship with the gut microbiome, it makes sense to utilize nutrition in the management of canine DM. Researchers have explored new plant-based compounds that may have insulin-enhancing and glycemic effects. For instance, the use of saturated fatty acids can influence insulin sensitivity differently, with insulin resistance noted in dogs that have been made obese. Conversely, no insulin sensitivity was observed in dogs that were fed a diet consisting of 65% corn oil [113].

There are several plant-based foods that have been studied as potential therapies for both healthy and diabetic dogs, including the following examples:

(a) Annatto condiment is a food coloring carotenoid-rich from the achiote seeds (*Bixa orellana*). Annatto extracts reduced the postprandial rise in blood glucose level and increased insulin level in female dogs treated for one hour, improving insulin affinity at blood red cell and mononuclear leukocyte receptors [114].

(b) Rosemary (*Rosmarinus officinalis*) and basil (*Ocimum basilicum*). Supplementation with rosemary and basil (polyphenol-rich leaf powder) in Rottweiler dogs with DM applying different diets (G1, basal diet (BD); G2, BD + commercial palatant; G3, BD + 0.05% rosemary; G4, BD + 0.05% basil; G5, BD + rosemary and basil each at 0.025%) reduced fasting glucose levels. The hypoglycemic effect observed was linked to increased insulin secretion in groups G1 and G3. Basil (G4) was found to inhibit the enzyme amylase, raise insulin levels, and lower cortisol levels. Additionally, the combination of basil and rosemary (G5) led to significant increases in the levels of glutathione, superoxide dismutase, and catalase, while reducing malondialdehyde and lactate dehydrogenase levels. The polyphenols present in the leaves of basil and rosemary also played a role in enhancing the hypoglycemic effect, positively influencing the function of pancreatic β-cells. The authors concluded that dietary supplementation with rosemary and/or basil (either 0.05% powder alone or 0.025% in combination) shows potential as a nutritional strategy for preventing and managing diabetes mellitus in puppies aged 4 to 8 months [63].

(c) Green tea extract. Polyphenols from green tea enhanced the insulin sensitivity index in 60% of dogs that were obese and insulin-resistant. The findings from this study suggest that dietary amounts of green tea extract not only improved insulin sensitivity and lipid profiles but also modified the expression of genes related to the regulation of glucose and lipid balance [64].

(d) The consumption of curcuminoids (250 mg) by a group of six diabetic dogs over a period of 180 days led to a significant reduction in oxidative stress, resulting in an increased ratio of glutathione to oxidized glutathione, while cytokine levels remained unchanged. Proteomic analysis indicated that the intake of curcuminoids modified the expression of proteins such as alpha-2-HS-glycoprotein, transthyretin, and apolipoproteins A-I and A-IV, implying that curcuminoids may enhance insulin sensitivity and lower the risk of cardiovascular issues. Additionally, no adverse effects on clinical symptoms, kidney function, or liver markers were observed [65].

3.5. Effect on Fat Metabolism

Hyperlipidemia refers to elevated levels of triglycerides, cholesterol, or both in the serum and/or plasma [115]. Treatment typically includes a combination of low-fat supportive diets and omega-3 fatty acid supplements, among other approaches [116]. Herbal extracts have been used in human medicine to lower circulating cholesterol levels. To broaden the use of these therapies in veterinary practice, several researchers have investigated the potential of phytosterols in dogs as a means to manage hypercholesterolemia. They found that administering 1300 mg of phytosterols orally, divided between two regular meals, effectively lowered LDL cholesterol and improved the HDL/LDL ratio in healthy dogs without dyslipidemia with no adverse effects noted. This suggests that phytosterols could be considered as part of a treatment plan for dogs with hypercholesterolemia [66]. Additionally, phytogenic compounds like the lignans enterodiol and enterolactone, as well as the isoflavone equol, are produced in mammals through the microbial metabolism of plant-based foods [117], induced anti-inflammatory, antioxidant, and free radical-scavenging activity to the host [118]. Likewise, phytosterols found in plant oils can play an important role in reducing elevated plasma triglyceride and cholesterol levels in hyperlipidemic dogs [66].

3.6. Effect on Cardiovascular Diseases

In cardiovascular diseases, the consumption of phytogenics has beneficial effects [119]. The evaluation of the effects of seed/skin grape extracts on platelet aggregation in dogs was studied by several authors, indicating that the combination of these grape extracts rich in polyphenols inhibited platelet aggregation in healthy dogs and could reduce excessive cholesterol levels associated with canine cardiovascular diseases [67]. High blood pressure is another cardiovascular disease in dogs. The different beneficial effects of unsaturated fats of plant origin as effective dietary interventions have been noted studying several cardiovascular markers in these animals. Additionally, research has been conducted on the impact of certain phytogenic compounds on platelet aggregation, which is a recognized risk factor for thrombotic events in canine cardiovascular diseases. Specifically, the administration of the flavonoid quercetin to dogs with induced myocardial infarction showed that quercetin possesses cardioprotective properties, helping to preserve cardiac function and inhibit the formation of blood clots. Canines with dilated cardiomyopathy and congestive heart failure generally have a significant increase in the production of ROS species, resulting in increased oxidative stress and diminished levels of natural antioxidants. As a result, incorporating exogenous antioxidants through phytogenic sources could help lower both ROS levels and oxidative stress, ultimately reducing the risk of cardiovascular disease. In another example, supplementation with dry extracts of grape, blueberry, and blackberry seeds containing relevant levels of resveratrol, α-tocopherol, lutein, and β-carotene showed the ability to reduce oxidative stress generated by physical activity associated with non-induced cardiovascular diseases in dogs [20].

In healthy sled dogs, the administration of polyphenols from blueberries has been shown to attenuate oxidative damage after exercise, elevating antioxidant status [120]. Quercetin, administered (50 mg/kg) to dogs experiencing an experimental myocardial infarction, has also been reported to limit damage to coronary tissues and arteries and prevent the formation of blood clots, thus demonstrating that this flavonoid is cardioprotective by helping to maintain cardiac function and circulation [68]. Two studies involving dogs with coronary stenosis found that purple grape juice, which is high in flavonoids such as quercetin, kaempferol, and myricetin (administered at 10 mL/kg of body weight), exhibited antithrombotic properties [121,122]. In a separate trial, healthy dogs given grape seed extracts, including the skin, at doses of 5 and 20 mg/kg of body weight also demonstrated an antiplatelet effect similar to that of grape juice. Additionally, resveratrol and other antioxidants from a formulation containing extracts of blueberries, strawberries, blackberries, and grape seeds significantly decreased oxidative stress induced by exercise in dogs [123].

Dogs with congestive heart failure and dilated cardiomyopathy have increased ROS production and oxidative stress, along with lower endogenous antioxidant levels [124], although causality for these heart conditions has not been established. The cellular antioxidant systems typically counterbalance the heightened production of ROS that occurs during periods of increased oxygen metabolism [125]. Some researchers propose that a relative lack of endogenous antioxidant activity could influence cardiovascular diseases in dogs [126]. Consequently, incorporating exogenous antioxidants from phytogenic sources into their diet may help lower ROS levels and, in turn, reduce oxidative stress, thereby alleviating or minimizing the effects associated with various cardiovascular conditions in dogs [120,126]. However, although the studies carried out so far point to a viable possibility of reducing cardiovascular diseases through phytogenic uses, more clinically meaningful data are needed for further validation [20].

Severe systemic inflammation that occurs after a myocardial infarction (MI) is a significant contributor to patient mortality. The inflammation caused by MI can lead to the generation of free radicals, which subsequently exacerbate inflammation in heart lesions, creating a cycle of inflammation and free radical production that can result in heart failure and death. A study involving a beagle dog model of MI tested a complex known as Fe-CurTA, which consists of Fe^{3+}, curcumin, and tannic acid. The findings indicated that hearts treated with Fe-CurTA had a smaller infarct size and improved cardiac function. Additionally, this complex demonstrated strong free radical scavenging and anti-inflammatory effects by decreasing immune cell infiltration, encouraging macrophages to adopt an M2-like phenotype, and inhibiting the release of inflammatory cytokines. Overall, the study showed that administering the Fe-CurTA complex after MI injury in a preclinical beagle model effectively protected cardiac function and reduced heart damage [69].

3.7. Effects on Neurological Diseases

In recent years, there have been many studies on nutritional management to reduce or relieve stress in dogs, focusing on effectiveness against oxidation, anxiety, and/or maintaining intestinal health. Generally, the consumption of foods rich in polyphenols seems to shift/modulate metabolites towards a more beneficial profile for the gut-brain axis and for kidney health [70].

Canine cognitive dysfunction (CCD) is similar to human dementia, as both conditions may exhibit comparable neuropathological features, including brain atrophy, ventricular enlargement, reduced blood flow, lower levels of brain-derived neurotrophic factor, and the buildup of β-amyloid plaques [127–129]. Clinically, CCD manifests as impairments in various cognitive areas, such as learning and memory (the ability to perceive, store, and recall information), executive function (the capacity to plan and execute cognitive tasks), attention (the ability to concentrate on relevant stimuli), and visuospatial skills (the ability to recognize and integrate spatial and visual information). These cognitive deficits can lead to behavioral changes, which are characteristic of CCD, including confusion or disorientation, anxiety, disturbances in the sleep/wake cycle, and reduced interaction with their guardians [128]. Research indicates that 74% of dogs over seven years old exhibit at least one potential sign of CCD [130]; however, there are no established diagnostic criteria for the condition, leaving the true prevalence of CCD in older dogs uncertain.

Increased oxidative stress and inflammatory markers have been observed in the brains of dogs with CCD compared to those of healthy dogs [131]. This has led to the hypothesis that nutrients with antioxidant and anti-inflammatory properties may play a significant role in preventing this condition. In a study, twenty-nine Beagle dogs aged over nine years were randomly divided into three dietary groups: a low-antioxidant diet, a moderate-antioxidant diet (containing 173 ppm vitamin E, less than 32 ppm vitamin C, 42 ppm L-carnitine, and less than 20 ppm lipoic acid), and a high-antioxidant diet (containing 799 ppm vitamin E, 114 ppm vitamin C, 294 ppm L-carnitine, and 135 ppm lipoic acid). After 90 days, dogs on the moderate or high-antioxidant diets made significantly fewer errors on learning tasks compared to those on the low-antioxidant diet, particularly when the tasks were more challenging [132].

In another study, a higher proportion of healthy and elderly Beagle dogs (8–14.5 years old) showed an improvement in their working memory after receiving a polyphenol-rich supplement composed by mixed grape and cranberry extracts for 75 days, compared to those receiving no supplement at all. Thus, the results revealed that the intake of this polyphenol-rich ingredient can improve the cognitive performance of senior beagle dogs [71].

In a different study, researchers took a nutrition-focused approach to investigate how fish oil and a mixture of natural fruits and vegetables high in polyphenols affect anxiety-related biomarkers in dogs. The results showed a reduction in plasma levels of metabolites linked to anxiety disorders, specifically 4-ethylphenyl sulfate. This suggests that diets enriched with polyphenols and omega-3 fatty acids may influence the gut microbiota, leading to an improvement in anxiety levels [70]. These findings support the potential use of this new natural food supplement to improve the gastrointestinal health and also affect the psycho-physical conditions of dogs [59].

3.8. Effects on the Immunological System

The immune system plays a crucial role in defending and healing the body, serving as a key indicator of overall health by preventing and combating diseases. In mammals, this system is not fully developed during the first year of life, making young animals more vulnerable to infections. To address this vulnerability, mammals have adapted to provide passive immunity, such as the transfer of maternal antibodies through the placenta and via colostrum or milk during nursing. However, this protective effect diminishes over time. The immune system continues to mature in the early years of life and can be affected by nutrition. Nutrients can have beneficial impacts both directly, by being absorbed and recognized by cells, and indirectly, through the interactions between the gut microbiota and the immune system [133–135]. There is no single biomarker that can accurately represent immune status, its functionality, or its connection to nutrition; thus, various parameters are assessed to examine different facets of the immune system [136]. However, there is evidence that some functional ingredients (vitamin E, β-carotene) can positively influence the immune health of pets [137].

There is evidence suggesting that polyphenolic compounds can serve as functional ingredients in dog diets to enhance immune system health [54]. Specifically, antioxidant components play a crucial role in preventing oxidative damage, which subsequently bolsters both the immune system and the gut microbiome [138]. Studies indicate a strong link between gut health and immune response in pets [139]. Consequently, changes to intestinal cells caused by an unbalanced diet, antibiotics, medications, or other factors may lead to various dysfunctions in these animals [140].

Antioxidants are compounds that can enhance immune function by activating the body's own antioxidant defenses and maintaining a balanced oxidative state within cells by neutralizing free radicals and halting the lipid peroxidation process. For instance, lignans are commonly prescribed for treating Cushing's disease in dogs [141]. In another study, the incorporation of herbal extracts—such as *Echinacea angustifolia* (0.10 mg/kg body weight as echinacoside for 14 dogs), *Vaccinium myrtillus* (0.20 mg/kg body weight as anthocyanidin for 13 dogs), *Curcuma longa* (6.60 mg/kg body weight as curcumin for 18 dogs with arthrosis), and *Silybum marianum* (1.5 mg/kg body weight as silibin for 8 dogs with liver issues)—demonstrated that these herbs can modulate immune responses. Specifically, after 60 days of consumption, there was a downregulation of inflammatory gene expression in the circulating white blood cells of the dogs. These observations were associated with the presence of different natural compounds such as echinacoside and related immunomodulatory activity; anthocyanidin and related anti-inflammatory and antioxidant activities; curcumin downregulating the main pro-inflammatory cytokines; and sylibin and their antioxidant and liver protectant activities [72].

Aging is a multifaceted process that adversely affects the immune system's development and functionality, leading to increased vulnerability to infections, cancer, and autoimmune disorders [142]. One approach to addressing the rise in illness and mortality associated with these conditions in older individuals is to find methods to prevent immune deficiencies. As a result, the immune systems of elderly individuals can be enhanced through the use of immunomodulators, such as sea buckthorn, which various researchers have identified as a promising candidate for this purpose [143,144]. Subsequently, another study showed that sea buckthorn can be used as an immunomodulator to strengthen the immune response in senior animals [145]. A study on the inflammatory and immune response of healthy geriatric Beagle dogs tested the combined effects of consuming foods fortified with antioxidants (1000 ppm vitamin E, 275 ppm L-carnitine, 125 ppm lipoic acid, 80 ppm vitamin C, and/or fruits/vegetables (spinach leaves, tomato residue, grape residue, carrots, and citrus pulp, each including 1%). The results showed that enrichment of combined antioxidants + fruits/vegetables increased neutrophil phagocytosis and B-cell populations. However, antioxidant supplementation alone did not prove to be statistically effective [146].

Food allergies in dogs, which are immune-mediated, often manifest with skin and digestive problems [147]. A weakened immune system increases susceptibility to infections, immune-mediated diseases, cancers, and other issues. Studies show that plant-based ingredients rich in carotenoids like β-carotene and lutein can bolster the canine immune system [148–151]. While more research is needed on the effects of polyphenols specifically, there's growing interest in their potential immune benefits. Several studies explore the connection between the immune system, canine infections, and phytotherapy [76,152,153]. Essential oils (EOs), containing polyphenols along with mono- and sesquiterpenoids, offer a unique case. These compounds have various beneficial effects on the immune system and other functions. EOs are used as supplements in dogs to address multiple issues, including stress, hair loss, and various organ dysfunctions. Some stress-relief supplements even combine EOs with melatonin, and topical creams containing EOs can be used to treat dermatitis caused by infections like Leishmaniosis [21,22].

3.9. Effects on Cancer

Cancer is a broad term that encompasses a wide range of diseases capable of impacting any area of the body. A key feature of cancer is the swift production of abnormal cells that proliferate beyond their normal boundaries, allowing them to invade nearby tissues and metastasize [154]. In fact, certain cancers may be inherently immunosuppressive in dogs [139]. Oncogenic processes are extremely common in older dogs, occurring in about one in 3–4 dogs, and are a leading cause of death [155,156]. Currently, the triterpene squalene obtained from shark liver, and also from plants, can regulate the activation of anti-oncogenic response and effectively inhibit the appearance of colon, lung, and skin tumors in mammals [31].

In addition, foods rich in polyphenols have been used for cancer prevention due to their high antioxidant properties [157]. Canine osteosarcoma is a highly aggressive primary bone tumor that spreads to distant areas and is linked to a significant mortality rate, representing 5% of all tumors in dogs. Given its common occurrence and unfavorable long-term outlook, there is a need for alternative treatment options. This study demonstrated that flavonoid myricetin can induce apoptosis in canine osteosarcoma cells [74]. Additionally, treating these cells with lycopene (a carotenoid) or baicalein (a flavone) resulted in reduced cell proliferation and varying levels of apoptosis across different cell lines [158].

Finally, a retrospective case study described the correlation between the development of transitional cell carcinoma (TCC) of the urinary bladder and the consumption of vegetables in the diet in dogs (175 Scottish Terriers), observing an inverse relationship with the consumption of any vegetable (added to commercial feed, in home-prepared diets or in leftovers from human tables, at least three times a week) and the risk of developing TCC. Yellow-orange vegetables and leafy greens specifically were significantly associated with a 61% and 90% decrease in the risk of developing TCC, respectively, which is attributed to their high carotenoid content. On the other hand, dietary fiber, phytosterols, and polyphenols are phytonutrients present in vegetables, which, with their possible anti-cancer activities, could prevent the development of TCC. In this case, the results of the retrospective study provided positive ratings between vegetable consumption and canine cancer prevention, albeit in a narrow cohort [75]. Plant flavonoids that possess antioxidant properties may have the ability to inhibit reactive oxygen species (ROS), thereby preventing oxidative stress and the associated inflammatory responses, mutagenesis, apoptosis, and disruption of the cell cycle. Furthermore, these flavonoids may exhibit phytoestrogenic effects, meaning they can interact with steroid hormone receptors, which play a crucial role in regulating cell proliferation, apoptosis, and the development of cancer [159].

Polyphenols are currently gaining great attention due to their important anti-oncogenic effect against stem cells, being effective in some cases, such as the suppression of breast cancer stem cells, blocking the formation and growth of neoplasms, and suppressing epithelial cell proliferation, migration, invasion, and mesenchymal transition [160–165].

However, key mechanisms that explain the various effects of polyphenolic compounds in preventing/reducing carcinogenesis remain unknown; therefore, further research is needed and also to study the effective doses in each case.

3.10. Other Effects

3.10.1. Respiratory Diseases

A multi-centered veterinary clinical trial demonstrated the effectiveness of a plant-based immune stimulant containing *Echinacea purpurea* in dogs with chronic and seasonal upper respiratory tract infections. After 8 weeks of treatment, 92% of dogs showed significant improvement, with reduced severity and improvement of clinical symptoms like nasal secretions, enlarged lymph nodes, cough, and dyspnea [76].

3.10.2. Liver Diseases

Previous research has shown the hepatoprotective effects of polyphenols in dogs with liver disease. Silymarin, a flavonoid complex, reduced alanine transaminase activity and increased paraxonase activity in dogs with liver disease, also upregulating mitochondrial SOD expression [72]. Another study found that a supplement containing orange bioflavonoid and *Silybum marianum* improved blood glutathione levels and key liver parameters in dogs with cholangitis/cholangiohepatitis [77]. Additionally, a randomized controlled trial demonstrated that S-acetyl-glutathione, silybum, and silybin supplementation increased GPX levels and positively impacted liver blood parameters, even in healthy dogs, without any adverse effects [78].

3.10.3. Dental Diseases

A pilot study investigated the effects of a gallic acid mouth spray on oral health and microbiota in dogs. After 42 days, the spray reduced gingival, plaque, and calculus indices. It also improved the abundance of beneficial oral bacteria and reduced pathogenic species [79].

3.10.4. Joint Diseases

A nutritional supplement containing glucosamine sulfate, krill oil, chondroitin sulfate, krill meal, and various herbal products was studied in dogs with arthrosis. After 90 days, all clinical signs improved significantly compared to the control group. Hematological parameters also showed improvements in bone remodeling and lipid metabolism. Additionally, oxidative stress markers improved, and inflammatory markers shifted favorably. The supplement was well-tolerated with no adverse effects [80].

4. Conclusions and Future Perspectives

Polyphenols are natural compounds contained in foods of plant origin with a multitude of biological effects attributed to their great antioxidant power, protecting against the risk of diseases associated with oxidative stress, in addition to other functionalities described. These actions allow the inclusion in the diet of foods rich in polyphenols due to their beneficial and protective effects against the diseases that can have a significant impact on dog health.

In this study, a wide list of phytogenics, especially polyphenols, and their classification and source according to their chemical structure and their possible beneficial effects have been presented. The most interesting cases in dogs results were analyzed, discussing the effects of the action of polyphenols on the different aspects of canine health.

The use of phytogenics, particularly polyphenols, in pet food comes with several challenges that need to be addressed. These include: (i) determining the correct dosage while considering safety, with guidance from recognized organizations like EFSA and FDA being crucial; (ii) ensuring the stability of ingredients during industrial processing methods such as extrusion and sterilization, as well as considering whether the food is wet or dry; (iii) conducting significant in vitro and in vivo scientific research to establish the functional profile of these preparations; (iv) utilizing innovative nanoencapsulation techniques to enhance both functionality and stability; (v) prioritizing natural ingredients over synthetic ones, despite potential cost disadvantages, such as choosing natural extracts high in phenolics instead of their synthetic counterparts; and (vi) providing clear and informative labeling on pet food products to effectively communicate the beneficial properties of phytogenics to consumers. Looking to the future, we can consider the application of standardized natural extracts rich in polyphenols and with different profiles within the wide variety of phenolic compounds as prospects to be achieved. These extracts, some of which are already on the market, can be used as fortifiers for feed and dietary supplements to deal with various dysfunctions of our pets as phytotherapeutics. In addition, the use of natural extracts rich in antioxidants (polyphenols and others) in pet food should be imposed as a common practice in a few years, replacing synthetic antioxidants that are unhealthy.

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