



Phenolic Compounds from *Acacia Spp.* Extracts: *In Vitro* Biological Activities and Potential Applications in Companion Animal Health and Nutrition

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Abstract

Acacia spp. are important sources of phenolic compounds, particularly condensed tannins and proanthocyanidins, which have attracted increasing interest due to their diverse biological activities and potential applications in food, pharmaceutical, and animal-health sectors. However, the biological evidence remains fragmented, and the relationship between phenolic compounds, molecular structure, and biological responses is not fully understood. This narrative review aims to summarize studies investigating the biological activities of *Acacia spp.* extracts, providing a comprehensive overview of the biological potential of their phenolic compounds, with particular emphasis on their potential applications in companion animal health and nutrition. Literature searches covering the period from January 2010 to June 2026 were conducted in Web of Science, Scopus, and PubMed using terms related to *Acacia*, phenolic compounds, proanthocyanidins, tannins, antioxidant activity, cytotoxicity, cytoprotection, anti-inflammatory, and antimicrobial effects. *Acacia spp.* represent promising sources of structurally diverse phenolic compounds with potential as functional bioactive ingredients and nutraceutical candidates. Nevertheless, the available evidence is predominantly *in vitro*, and antioxidant, enzyme-inhibitory, antimicrobial, or cellular activities should not be directly interpreted as therapeutic efficacy or cytoprotection *in vivo*. Future research should integrate detailed chemical characterization with studies of gastrointestinal stability, bioaccessibility, metabolism, cellular uptake, pharmacokinetics, dose-response relationships, and *in vivo* safety and efficacy to establish the translational potential of *Acacia*-derived phenolics in food, pharmaceutical, and animal-health applications.

Keywords: Proanthocyanidins; Condensed Tannins; Antioxidant Activity; Antimicrobial Activity; Cytotoxicity; Anti-Inflammatory Activity; Enzyme Inhibition; Functional Ingredients.

Introduction

The *Fabaceae* family is composed of several species of medicinal and arboreal plants that play an important role in human and animal health. Among these species, the genus *Acacia* stands out globally for its functional properties, therapeutic potential, rapid adaptation, and high biomass productivity (Grasel *et al.*, 2019). *Acacia spp.* are plants widely distributed worldwide and exhibit a broad diversity of species. It is important to note that, following taxonomic revisions of the former broad concept of *Acacia* (*Acacia sensu lato*), several species historically reported as *Acacia* have been transferred to the genera *Vachellia* and *Senegalia*. Therefore, throughout this

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review, species are referred to according to the nomenclature used in the original studies, while acknowledging these subsequent taxonomic changes.

The importance of Acacias is recognized for their unique chemical composition and potential applications in the furniture, paper, perfume, pharmaceutical, and other industries. Traditionally, the bark of species such as *Acacia mearnsii* (commonly known as Black Wattle) has aroused great economic and industrial interest due to its high concentration of condensed tannins or proanthocyanidins, which are historically utilized for leather tanning, wood adhesives, and natural coagulants (Missio *et al.*, 2017; Grasel *et al.*, 2019; De Gonçalves Prietsch *et al.*, 2021). However, large-scale silviculture and wood processing generate a substantial amount of forest solid waste, such as bark, leaves and inflorescences, which are commonly discarded in the field (Makino *et al.*, 2011; De Gonçalves Prietsch *et al.*, 2021). Studies have highlighted the presence of bioactive compounds, such as condensed tannins, also known as proanthocyanidins, in different *Acacia* species, which may contribute to their functional properties (Missio *et al.*, 2017; Chen *et al.*, 2018a).

Recent studies have investigated the bioactive properties and cell effects of compounds present in different *Acacia* species: *Acacia auriculiformis*, *Acacia dealbata*, *Acacia mangium*, *Acacia mearnsii*, *Acacia nilotica*, *Acacia seyal*, and *Acacia tortilis*. The accumulation and specific profile of these polyphenolic substances vary considerably among these species, different parts of the plant, flowering maturation stages, extraction solvents, and geographical or climatic conditions (Olajuyigbe & Afolayan, 2011; Revathi *et al.*, 2017; Paula *et al.*, 2022). *Acacia mearnsii* is a widely studied species. Proanthocyanidins isolated from *Acacia mearnsii* bark have demonstrated *in vitro* antioxidant capacity and inhibitory effects on digestive enzymes involved in carbohydrate digestion and absorption (Chen *et al.*, 2018b; Chen *et al.*, 2019). *In vitro* anti-inflammatory properties have also been described in leaf and bark extracts of *Acacia mearnsii* (Xiong *et al.*, 2016; Xiong *et al.*, 2017).

The phenolic compounds with demonstrated antioxidant capacity present in acacia can delay or inhibit lipid oxidation, a process that leads to the formation of free radicals and, consequently, food deterioration. This property is particularly relevant for animal feed preservation, as it may contribute to maintaining product quality and oxidative stability (Zhang *et al.*, 2010). Despite this vast therapeutic and nutritional potential, the direct application of raw *Acacia* polyflavonoids faces technical limitations within biological systems, such as low stability when exposed to light or heat, variable intestinal bioaccessibility, and a highly astringent, bitter taste (Grasel *et al.*, 2019).

Although several reviews have addressed the phytochemical composition, pharmacological properties, and industrial applications of *Acacia* species, information on the biological activities of phenolic compounds derived from *Acacia* remains fragmented. To date, no peer-reviewed studies have directly evaluated the administration or effects of *Acacia spp.* extracts in canine or feline clinical models. However, the molecular mechanisms, enzymatic inhibitions, and antimicrobial properties observed *in vitro* provide a strong biochemical rationale to discuss their potential translation into companion animal health and nutrition. Therefore, this narrative review aims to summarize studies investigating the biological activities of *Acacia spp.* extracts, providing a comprehensive overview of the biological potential of their phenolic compounds, with particular emphasis on their potential applications in companion animal health and nutrition.

Literature Search Strategy

A narrative literature review was conducted to identify studies investigating the antioxidant capacity and biological effects of *Acacia spp.* extracts. Searches were performed in the Web of Science, Scopus, and PubMed databases, covering studies published between January 2010 and June 2026.

Study selection was based on relevance to the scope and objectives of the review rather than on a predefined systematic-review framework. The search strategy combined terms related to *Acacia* species and their bioactive compounds with terms associated with biological activities. The main keywords included: “*Acacia*”, “*Acacia spp.*”, “extract”, “phenolic compounds”, “polyphenols”, “proanthocyanidins”, “tannins”, “antioxidant activity”, “cytotoxicity”, “cytoprotection”, “anti-inflammatory activity”, and “antimicrobial activity”.

Original research articles published in English were considered for inclusion if they investigated extracts obtained from *Acacia spp.* and presented relevant information regarding the chemical composition or biological activities addressed in this review. Studies consisting of review articles, conference abstracts, or book chapters were excluded, as were those that did not investigate *Acacia spp.* extracts or failed to provide information directly relevant to the review's objective. There were no restrictions regarding experimental models, allowing for the consideration of evidence derived from chemical assays, cellular models, and other relevant experimental systems.

The search identified approximately 473 records across the three databases. After removing duplicates, the literature was screened based on titles and abstracts, followed by an assessment of potentially relevant studies. Reference lists of relevant publications were also consulted to identify additional studies within the scope of the review. Based on their relevance to the objectives of this narrative review, 21

original research articles were selected for the qualitative synthesis.

The selected studies were analyzed qualitatively, emphasizing the chemical composition of the extracts, antioxidant activity, antimicrobial effects, enzyme inhibitory activity, anti-inflammatory properties, cytotoxicity, and cytoprotective potential. Data extracted from the selected studies were organized in Microsoft Excel® spreadsheets, including information on authors, year of publication, *Acacia* species, bioactive compounds, and the main biological activities reported.

Discussion

Phytochemical composition and bioactive constituents of *Acacia* spp.

Acacia species are recognized as rich sources of phenolic compounds, particularly condensed tannins, also known as proanthocyanidins, which are considered the main bioactive constituents associated with many of the biological activities attributed to these plants. These compounds are oligomeric or polymeric flavan-3-ols predominantly composed of catechin, epicatechin, fisetinidinol, robinetinidinol, and gallocatechin units. Structurally, these flavan-3-ol monomer units are coupled through C4–C6 or C4–C8 interflavan bonds, forming four major subclasses of proanthocyanidins: prorobinetinidins, profisetinidins, procyanidins, and prodelphinidins (Wei *et al.*, 2010; Makino *et al.*, 2011; Grasel *et al.*, 2019). Analytical and spectrometric characterizations reveal that these polymer chains can exist as monomers up to dodecamers, often exhibiting a wide distribution where the molar ratio of pyrogallol-type B-rings to catechol-type B-rings (P/C ratio) varies significantly among species (Wei *et al.*, 2010; Makino *et al.*, 2011; Grasel *et al.*, 2019). For instance, a high P/C ratio of 3.4 to 5.4 is observed in *Acacia mearnsii* and *Acacia mangium*, demonstrating a strong abundance of pyrogallol structures that influence their chemical reactivity (Makino *et al.*, 2011). These flavonoid-derived compounds are recognized for their ability to scavenge reactive oxygen species and modulate cellular redox balance. Studies employing reversed-phase high-performance liquid chromatography coupled with mass spectrometry (HPLC/MS) have demonstrated that type B proanthocyanidins are among the predominant phenolic compounds present in several *Acacia* spp. (Chen *et al.*, 2018a).

The phytochemical composition of *Acacia* extracts varies considerably according to species, plant tissue, environmental conditions, and extraction procedures. In the bark of *Acacia mangium*, HPLC/MS analyses identified high concentrations of type B proanthocyanidins, particularly catechin- and epicatechin-derived compounds, which have been associated with antioxidant activity and inhibitory effects on carbohydrate-digesting enzymes *in vitro* (Chen

et al., 2019). Similarly, studies on *Acacia mearnsii* have demonstrated that bark extracts are especially rich in condensed tannins, reinforcing the importance of this species as a source of bioactive phenolic compounds (Missio *et al.*, 2017). Quantitatively, the tannin concentration within *Acacia mearnsii* bark can exceed 45% on a dry weight basis, although the exact yield depends heavily on cultivation techniques, soil features, and plant morphology (Olajuyigbe & Afolayan, 2011; Missio *et al.*, 2017; Grasel *et al.*, 2019). Crude industrial aqueous bark extracts typically consist of 70% to 80% condensed tannins, while the remaining 20% to 30% is composed of non-tannin fractions, such as hydrocolloid gums, organic acids, and free sugars (Missio *et al.*, 2017).

The biological properties of *Acacia* extracts are strongly influenced by their phenolic profile. Several studies have reported a positive correlation between total phenolic content and antioxidant capacity, suggesting that phenolic compounds play a central role in free radical scavenging and redox modulation (Zhang *et al.*, 2010). In addition, the analytical characterization of industrial tannin extracts from *Acacia mearnsii* revealed that extraction and fractionation procedures significantly influence the chemical composition of the resulting products. Ethyl acetate fractions were enriched with low-molecular-weight antioxidants and tannins, specifically accumulating shorter oligomeric chains (such as dimers and trimers) that are critical for driving initial, high-velocity radical scavenging and anti-tumour activities (Shen *et al.*, 2010; Missio *et al.*, 2017). Conversely, alcoholic fractions (such as pentanol and propanol) contain purified polyflavonoids and condensed tannins of higher molecular weight and higher degrees of polymerization, whereas the remaining insoluble residues are heavily enriched with polysaccharides, mineral constituents, and an elevated ash content (Missio *et al.*, 2017). Furthermore, the choice of the primary extraction solvent significantly alters the phytochemical distribution, with acetone and methanol extracts demonstrating higher total phenolic and proanthocyanidin concentrations compared to purely aqueous extractions (Olajuyigbe & Afolayan, 2011; Revathi *et al.*, 2017). The remaining fractions were primarily composed of carbohydrates and mineral constituents (Missio *et al.*, 2017).

The high concentration of phenolic compounds in *Acacia* spp. extracts may also be relevant for animal nutrition. Phenolic compounds, particularly condensed tannins and flavonoids, have been investigated as natural alternatives to synthetic additives due to their antioxidant properties (Da Silva Araujo *et al.*, 2025) and their potential to modulate digestive and metabolic processes (Matsumura *et al.*, 2023; Melo *et al.*, 2023). In animal production systems, these compounds may contribute to improving oxidative stability, reducing oxidative stress, and preserving the quality of feed ingredients and finished products (Serra *et al.*, 2021; Camarda *et al.*, 2026; Contò *et al.*, 2026).

Chromatographic fractionation on Sephadex LH-20 reveals that while flavonoids (such as tri-, di-, and mono-glycosides of myricetin and quercetin, including myricitrin) dominate the early water and methanol fractions of the leaf, the subsequent acetone fractions are heavily dominated by highly polymerized proanthocyanidins (Xiong *et al.*, 2016). These leaf proanthocyanidins possess distinctive 5-deoxy extender units, predominantly robinetinidol and fisetinidol, which are covalently bonded through C4 positions to terminal catechin or galocatechin units, rendering their interflavanyl bonds highly resistant to standard acid-catalyzed cleavage (Xiong *et al.*, 2016). This tissue-specific heterogeneity is clear across other species; for instance, the leaves, stem bark, and root bark of *Acacia confusa* display a wide variation in total phenolics, with its leaves uniquely containing a mixture of propelargonidin, procyanidin, and prodelphinidin units linked via B-type interflavan bonds (Wei *et al.*, 2010). Similarly, phytochemical mapping of *Acacia nilotica* leaves reveals a substantial presence of diverse metabolites, including reducing sugars, terpenoids, alkaloids, phlobatannins, and pyrogallol (1,2,3-benzenetriol), which further amplifies the pharmacological versatility of the aerial tissues (Revathi *et al.*, 2017).

Likewise, flowers, leaves, and other plant parts have demonstrated distinct phytochemical profiles, highlighting the diversity of bioactive constituents found within the genus. In *Acacia dealbata*, hydroethanolic extracts of the flowers show a profile that is strongly dependent on the status of floral maturation (Paula *et al.*, 2022). The early flowering stage represents the most biochemically active phase, accumulating high levels of flavonols and chalcone derivatives (a group of polyphenols structured as β -unsaturated aromatic ketones whose open C-ring acts as a biological precursor to traditional flavonoids) (Paula *et al.*, 2022). Furthermore, evaluating the aerial residues and forest solid waste (leaves and inflorescences) of *Acacia mearnsii* has led to the successful isolation and qualitative characterization of cinnamic acid and coumarin (a lactone derivative generated via the cyclization of o-coumaric acid) (De Gonçalves Prietsch *et al.*, 2021).

Although bark is the most frequently investigated plant material due to its high concentration of condensed tannins, other tissues have also emerged as valuable sources of bioactive compounds. Polyphenolic profiling of *Acacia mearnsii* leaves identified several flavonoids, including myricetin, quercetin, (epi)fisetinidol, and their glycosylated derivatives (Xiong *et al.*, 2016). These compounds exhibited antioxidant and anti-inflammatory activities *in vitro*, indicating that biological activity is not restricted to tannin-rich bark extracts.

Overall, condensed tannins, proanthocyanidins, and flavonoids appear to be the main bioactive compounds identified in *Acacia spp.* Although their concentrations vary

among species, plant tissues, and extraction methods, these compounds are consistently associated with the antioxidant and biological activities reported in the literature.

Potential uses of *Acacia spp.* extracts.

Antioxidant activity

The proanthocyanidins derived from *Acacia spp.* extracts consistently demonstrate substantial antioxidant capacity across various *in vitro* models (Box 1). Proanthocyanidins purified from *Acacia mearnsii* bark exhibit potent free-radical scavenging capabilities, delivering an IC_{50} (Half Maximal Inhibitory Concentration) value of $25.6 \mu\text{g mL}^{-1}$ against the DPPH (1,1-diphenyl-2-picrylhydrazyl) radical (Shen *et al.*, 2010). This high efficiency is mirrored in other species of the genus, such as *Acacia seyal* bark methanolic extracts, which yielded an IC_{50} of $150 \mu\text{g mL}^{-1}$ in identical DPPH assays (Elmi *et al.*, 2020).

The radical scavenging proficiency of these extracts is strongly linked to a direct, positive correlation between the total concentration of phenolic compounds and their overall antioxidant capacity (Zhang *et al.*, 2010; Olajuyigbe & Afolayan, 2011). Chromatographic fractionation of *Acacia mearnsii* leaves on Sephadex LH-20 (a lipophilic-hydrophilic dextran gel) confirms that the distribution of these active principles dictates antioxidant power, for instance, the highly polymerized proanthocyanidins concentrated in the acetone fraction (L4) generated an elevated ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)] scavenging capacity of $7.0 \text{ mmol TE g}^{-1}$ (Trolox equivalent), whereas the lighter, flavonoid-rich fractions displayed intermediate values (Xiong *et al.*, 2016). Complementing these leaf-specific findings, De Gonçalves Prietsch *et al.* (2021) investigated the valorization of silvicultural waste from *Acacia mearnsii* by evaluating a phenolic compound-enriched extract (PCEE) obtained from combined leaves and inflorescences. This ethyl acetate fraction demonstrated a robust antioxidant profile, yielding an ABTS scavenging capacity of $621.748 \mu\text{mol TE g}^{-1}$, a DPPH scavenging activity of $314.085 \mu\text{mol TE g}^{-1}$, and a FRAP (ferric reducing antioxidant power) of $299.758 \mu\text{mol FSE g}^{-1}$ (ferrous sulfate equivalent), reinforcing the feasibility of reusing these discarded aerial parts. A similar tight correlation between polyphenolic density and antioxidant performance has been reported for *Acacia mangium* bark extracts, where higher total phenolic content directly translated into heightened anti-inflammatory and radical-quenching outcomes (Zhang *et al.*, 2010).

This high concentration of active components is also clear in *Acacia confusa*, where polyphenolic mapping across different plant tissues revealed that the root bark contains the highest density of extractable condensed tannins (280.70 mg g^{-1}), followed by the stem bark (247.76 mg g^{-1}) and leaves (64.17 mg g^{-1}) (Wei *et al.*, 2010). When evaluated against

the DPPH radical, these tissues achieved powerful IC₅₀ values of 89.03 µg mL⁻¹ (root bark), 87.85 µg mL⁻¹ (stem bark), and 113.06 µg mL⁻¹ (leaves). Remarkably, all *Acacia confusa* tissue extracts outperformed standard antioxidants, such as BHA (2,3-tert-butyl-4-hydroxyanisole) (IC₅₀ = 126.21 µg mL⁻¹) and ascorbic acid (IC₅₀ = 118.88 µg mL⁻¹), highlighting the raw efficiency of these natural polymers (Wei *et al.*, 2010).

From a mechanistic perspective, the antioxidant efficacy of *Acacia spp.* extracts is closely related to the structural characteristics of their flavan-3-ol subunits. Proanthocyanidins containing a pyrogallol-type B-ring, such as prorobinetinidins and prodelphinidins commonly found in *Acacia mearnsii* and *Acacia mangium*, exhibit a rapid initial free radical scavenging activity. In contrast, proanthocyanidins with a catechol-type B-ring tend to react more slowly but maintain antioxidant activity over longer periods, resulting in a progressive increase in radical scavenging capacity with extended reaction times. These findings suggest that differences in proanthocyanidin structure may influence both the kinetics and overall effectiveness of antioxidant activity in *Acacia spp.* extracts (Makino *et al.*, 2011).

In addition to leaves and bark residues, the flowers of the genus have also emerged as highly functional antioxidant matrices. In *Acacia dealbata*, hydroethanolic extracts of the blooms demonstrated a powerful radical-quenching and reducing capability that is directly driven by floral maturation stages and local environments. The non-mature phase (early flower) optimized this biochemical performance, delivering substantial DPPH (IC₅₀ = 6.79 mg mL⁻¹) and FRAP (IC₅₀ = 1.11 mg mL⁻¹) efficiencies driven by an elevated accumulation of chalcone derivatives, validating the target of harvesting invasive blooms early to mitigate both oxidative stress and plant proliferation (Paula *et al.*, 2022).

Furthermore, the choice of the primary extraction solvent exerts a dominant effect on the final antioxidant profile. In *Acacia nilotica* leaf extractions, the free-radical scavenging

capacity followed a strict solvent-dependent hierarchy, with acetone extractions capturing the most potent active principles, followed systematically by methanol and ethanol (Revathi *et al.*, 2017). Similarly, the reducing power of *Acacia mearnsii* bark shows a sharp dose-dependent response that varies by solvent polarity; purely aqueous extractions consistently yield the lowest reducing capabilities, whereas methanolic extractions optimize the retrieval of electron-donating reductones, although their absolute ferric reducing capabilities remain slightly below pure commercial reference standards like BHT (butylhydroxytoluene), rutin, and vitamin C (Olajuyigbe & Afolayan, 2011). This fractionation and purification effect was comprehensively mapped by Missio *et al.* (2017) through the single and sequential organic solvent extraction of industrial *Acacia mearnsii* bark powders. Their analytical characterization revealed that low-molecular-weight oligomers selectively isolated in the ethyl acetate fraction yielded a high oxygen radical absorbance capacity (ORAC) with an area under the curve (AUC) of 4982 µmol TE g⁻¹, whereas the higher molecular weight polyflavonoids recovered in subsequent alcoholic phases (such as pentanol) registered a lower total antioxidant effect (3189 µmol TE g⁻¹) due to the co-solubilization of non-tannin hydrocolloid gums. Generally, the concentration of the extract remains a primary driver of efficacy, and the observed values justify future research into *Acacia spp.* as potential natural alternatives to synthetic feed additives. However, *in vivo* shelf-life studies, matrix interaction assays, and palatability testing in commercial pet food formulations are necessary before industrial adoption can be realized.

Investigating the digestive stability of *Acacia mearnsii* bark polyphenols, Chen *et al.* (2018b) observed that while gastric environments preserve antioxidant profiles, subsequent intestinal alkaline conditions lead to a partial degradation of condensed tannins. Despite this degradation, the post-digestive bioaccessibility of proanthocyanidins reached approximately 17.9%, showcasing that a significant fraction remains stable and chemically active to exert functional antioxidant effects at the cellular level.

Box 1: Summary of antioxidant capacity and extraction methods of *Acacia spp.* extracts.

Species	Fraction	Method	Value	Reference
<i>Acacia mearnsii</i>	Bark (Purified PAs)	DPPH (IC ₅₀)	25.6 µg mL ⁻¹	Shen <i>et al.</i> , 2010
<i>Acacia mearnsii</i>	Bark	ORAC	Ethyl acetate fraction (AUC = 4982 µmol TE g ⁻¹); Pentanol fraction (AUC = 3189 µmol TE g ⁻¹)	Missio <i>et al.</i> , 2017
<i>Acacia mearnsii</i>	Bark (Digestive model)	DPPH (IC ₅₀)	61.5 µg mL ⁻¹	Chen <i>et al.</i> , 2018b
<i>Acacia mearnsii</i>	Leaves (acetone extract)	ABTS and Intracellular ROS	7.0 mmol TE g ⁻¹ ; All treatments significantly de-escalated LPS-induced cellular ROS to baseline.	Xiong <i>et al.</i> , 2016
<i>Acacia mearnsii</i>	Bark (Acetone, Methanol, Ethanol, Aqueous)	DPPH, ABTS and FRAP	Dose-dependent; hierarchy: Methanol > Acetone > Ethanol > Aqueous	Olajuyigbe & Afolayan, 2011
<i>Acacia seyal</i>	Bark (methanolic extract)	DPPH (IC ₅₀)	150 µg mL ⁻¹	Elmi <i>et al.</i> , 2020

<i>Acacia confusa</i>	Root Bark	DPPH (IC ₅₀)	89.03 µg mL ⁻¹	Wei <i>et al.</i> , 2010
<i>Acacia confusa</i>	Stem bark	DPPH (IC ₅₀)	87.85 µg mL ⁻¹	Wei <i>et al.</i> , 2010
<i>Acacia confusa</i>	Leaves	DPPH (IC ₅₀)	113.06 µg mL ⁻¹	Wei <i>et al.</i> , 2010
<i>Acacia nilotica</i>	Leaves	DPPH (Scavenging %)	Solvent efficiency hierarchy: Acetone (93.12%) > Methanol (83.49%) > Ethanol (83.25%) > Chloroform (63.84%)	Revathi <i>et al.</i> , 2017
<i>Acacia mangium</i>	Bark	DPPH and ABTS	Linear positive correlation between phenolic density and radical-quenching	Zhang <i>et al.</i> , 2010
<i>Acacia mearnsii</i>	Leaves and Inflorescences (Ethyl acetate - PCEE)	ABTS, DPPH and FRAP	621.748 µmol TE g ⁻¹ ; 314.085 µmol TE g ⁻¹ and 299.758 µmol FSE g ⁻¹ , respectively	De Gonçalves Prietsch <i>et al.</i> , 2021
<i>Acacia dealbata</i>	Flowers (hydroethanolic extract)	DPPH (IC ₅₀) and FRAP	6.79 mg mL ⁻¹ and 1.11 mg mL ⁻¹ , respectively	Paula <i>et al.</i> , 2022

ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt; AUC, Area Under the Curve; DPPH, 1,1-diphenyl-2-picrylhydrazyl; FRAP, Ferric Reducing Antioxidant Power; FSE, Ferrous Sulfate Equivalent; IC₅₀, half-maximal inhibitory concentration; LPS, lipopolysaccharide; ORAC, Oxygen Radical Absorbance Capacity; PAs, proanthocyanidins; PCEE, phenolic compound-enriched extract; ROS, reactive oxygen species; TE, Trolox equivalent. Lower numeric values for IC₅₀ designate a superior baseline antioxidant capacity.

Among the species evaluated, *Acacia mearnsii* exhibited particularly strong antioxidant activity in several of the assays reported; however, direct comparisons among species are limited by differences in plant material, extraction procedures, phenolic composition, assay conditions, and response metrics.

Inhibition of carbohydrate-digesting enzymes

Acacia spp. extracts have been the subject of study due to their ability to inhibit the enzymes α -glucosidase and α -amylase, which play important roles in regulating carbohydrate digestion and consequently in the absorption of glucose by the body (Box 2). Expanding on these properties, Xiong *et al.*, 2017 demonstrated that polyphenols isolated from *Acacia mearnsii* bark exhibit highly selective and preferential inhibition of α -glucosidase over α -amylase. In their study, IC₅₀ values for α -glucosidase inhibition ranged from 0.4 to 1.4 µg mL⁻¹ in different high-speed countercurrent chromatography fractions (HSCCC), far exceeding the pharmaceutical reference standard acarbose (IC₅₀ = 141.8 µg mL⁻¹). This selective inhibition profile appears to be particularly relevant to canine digestive physiology, as modulation of carbohydrate digestion directly influences postprandial metabolic responses. In dogs, postprandial glycemic excursions and associated methylglyoxal production are closely linked to starch quality and glycemic index, suggesting that the regulation of carbohydrate digestion through targeted enzyme inhibition may represent a biologically plausible strategy for modulating postprandial glycemic responses. In contrast, this rationale may be less applicable to cats, whose carbohydrate metabolism differs substantially from that of dogs. Felines exhibit lower expression of genes involved in starch digestion, glucose transport, and glycolysis, which is

consistent with their attenuated glycemic responses to dietary starch and suggests that the effects of enzyme inhibition may not be directly comparable between species (Weber *et al.*, 2018; Briens *et al.*, 2021).

The proanthocyanidins ((epi)catechin, (epi)fisetinidol, (epi)robinetinidol, and (epi)gallocatechin) present in the crude bark extracts of *Acacia mangium* exhibited significant α -amylase inhibitory activity, with an IC₅₀ value of 19.1 ± 3.4 µg mL⁻¹, and also strong inhibitory activity of the α -glucosidase enzyme, with an IC₅₀ value of 22.0 ± 1.7 µg mL⁻¹ (Chen *et al.*, 2019), suggesting a potential role in the modulation of postprandial glucose metabolism (Li *et al.*, 2022). This study established that, although the degree of polymerization (DP) is an important contributor to α -amylase restriction, it does not play a predominant role in α -glucosidase blockade, as demonstrated by the active inhibition retained by the depolymerized subunits and the isolated epicatechin monomer (IC₅₀ = 200 ± 3.2 µg mL⁻¹). This enzymatic performance is corroborated by the broader evaluation of *Acacia mearnsii* bark extracts carried out by Chen *et al.* (2018b), who reported an α -amylase IC₅₀ of 45.83 µg mL⁻¹ and a potent α -glucosidase blockade capable of inhibiting 40% of enzyme activity at 12.5 µg mL⁻¹ and approximately 80% at 25.0 µg mL⁻¹, significantly exceeding the acarbose glucosidase inhibition profile (IC₅₀ = 164.21 µg mL⁻¹). Furthermore, the inhibition of carbohydrate-digesting enzymes also occurs in flower extracts. In *Acacia dealbata*, hydroethanolic flower extracts exhibited a prominent dose-dependent inactivation of α -glucosidase, strongly influenced by floral maturation, where the initial flowering stage optimized this inhibitory action, presenting low IC₅₀ values of 27.03 µg mL⁻¹ (region A) and 31.60 µg mL⁻¹ (region B) due to the dense accumulation of bioactive chalcone derivatives,

which progressively decrease as the flowers mature in the maturation phase (Paula *et al.*, 2022).

Additionally, previous studies investigating the effects of simulated *in vitro* digestion on polyphenols present in the bark of *Acacia mearnsii* showed that, even after gastric digestion, the polyphenols remained stable, retaining their antioxidant activity and approximately 77% of their baseline α -glucosidase inhibitory capacity. During intestinal digestion, there was degradation of proanthocyanidins and a significant 26% decrease in total phenolic compounds, possibly due to chemical conditions, since polyphenols are sensitive in alkaline environments and can be converted into unidentifiable

compounds. The bioaccessibility of proanthocyanidins at the intestinal level in this study was approximately 17.9%. Simultaneously, ultra-fast liquid chromatography coupled with electrospray ionization quadrupole time-of-flight tandem mass spectrometry (UFLC-ESI-QTOF-MS²) analysis of this bioaccessible fraction confirmed that only monomeric, dimeric, and trimeric flavan-3-ols successfully cross the intestinal barrier, while the larger, unabsorbed polymers reach the colon, where they continue to actively interact with the local environment (Chen *et al.*, 2018a), suggesting potential intestinal accessibility of lower-molecular-weight phenolic compounds, although their absorption and biological effects *in vivo* remain to be established.

Box 2: Summary of carbohydrate-digesting enzymes inhibitory activities and digestive stability of *Acacia* spp. extracts.

Species	Fraction	Enzyme	Inhibitory activity (IC ₅₀ or % inhibition)	Reference
<i>Acacia mearnsii</i>	Crude extract bark and purified oligomeric fractions	α -glucosidase	0.4 to 1.4 $\mu\text{g mL}^{-1}$	Xiong <i>et al.</i> , 2017
<i>Acacia mearnsii</i>	Crude extract bark and purified oligomeric fractions	α -amylase	11.7 to 17.6 $\mu\text{g mL}^{-1}$	Xiong <i>et al.</i> , 2017
<i>Acacia mangium</i>	Ethanolic bark extract	α -amylase	19.1 $\pm$ 3.4 $\mu\text{g mL}^{-1}$	Chen <i>et al.</i> , 2019
<i>Acacia mangium</i>	Ethanolic bark extract	α -glucosidase	22 $\pm$ 1.7 $\mu\text{g mL}^{-1}$	Chen <i>et al.</i> , 2019
<i>Acacia mearnsii</i>	Ethanolic bark extract	α -amylase	45.83 $\mu\text{g mL}^{-1}$	Chen <i>et al.</i> , 2018b
<i>Acacia mearnsii</i>	Ethanolic bark extract	α -glucosidase	40% inhibition at 12.5 $\mu\text{g mL}^{-1}$ and ~80% inhibition at 25.0 $\mu\text{g mL}^{-1}$	Chen <i>et al.</i> , 2018b
<i>Acacia mearnsii</i>	Ethanolic bark extract - <i>in vitro</i> simulated digestion model	α -glucosidase	Gastric Phase: Retention of 77% of basal inhibitory capacity.	Chen <i>et al.</i> , 2018a
			Intestinal Phase: Decrease to 42% due to alkaline degradation; bioaccessibility of 17.9%.	
<i>Acacia dealbata</i>	Hydroethanolic Flowers extract	α -glucosidase	27.03 $\mu\text{g mL}^{-1}$ to 31.60 $\mu\text{g mL}^{-1}$	Paula <i>et al.</i> , 2022

IC₅₀, half-maximal inhibitory concentration.

The benefits associated with this potential include the regulation of glucose levels (Hossain *et al.*, 2020) and protection against oxidative stress (Chen *et al.*, 2025), supporting their potential relevance for nutritional strategies aimed at modulating postprandial glucose responses. In companion animal nutrition, natural enzyme inhibitors appear to be a plausible dietary strategy to delay starch digestion and attenuate postprandial glycemia. Furthermore, this inhibition pattern may offer additional advantages for companion animals. While strong α -glucosidase inhibition can effectively reduce postprandial glucose absorption, a more moderate inhibition of α -amylase may help avoid excessive amounts of undigested starch reaching the colon. This balance is essential, because excessive carbohydrate fermentation by intestinal microbiota can increase osmotic pressure within the gastrointestinal tract, potentially leading to digestive disturbances such as osmotic diarrhea. Therefore, selective modulation of carbohydrate-digesting enzymes may provide metabolic benefits while minimizing undesirable gastrointestinal effects in both dogs and cats (Weber *et al.*, 2018; Briens *et al.*, 2021). However, there is no direct

evidence from clinical trials with animals fed inhibitors, only for manipulation of the carbohydrate source (Briens *et al.*, 2021). Although a wide range of functional ingredients, including polyphenols, flavonoids, peptides, lipids, dietary fibers, and constituents of vegetable oils, have demonstrated inhibitory activity against carbohydrate-digesting enzymes *in vitro* or *in silico*, most of the available evidence remains in the preclinical stage. Consequently, important aspects such as optimal dosage, toxicity, bioavailability, and pharmacokinetic behavior are still poorly understood (Kashtoh & Baek, 2023; Rangel-Galván *et al.*, 2024). However, considering the high prevalence of obesity in companion animals and its close association with insulin resistance, *diabetes mellitus*, and other metabolic comorbidities (Chandler *et al.*, 2017), strategies aimed at modulating carbohydrate digestion and reducing rapid postprandial glucose absorption represents an important objective in nutritional management.

In this context, natural enzyme inhibitors derived from plant sources, including extracts of *Acacia* spp., represent promising candidates for the development of functional

and nutraceutical ingredients. Collectively, the available evidence indicates that *Acacia*-derived proanthocyanidins showed strong α -glucosidase inhibitory activity in the studies reviewed, while maintaining a more moderate effect on α -amylase. This selective inhibition profile may be advantageous for metabolic modulation, as it could attenuate postprandial glycemic responses without causing excessive starch fermentation in the hindgut. However, further studies are needed to confirm its efficacy, safety, and long-term effects under physiological conditions and in animal models before practical applications can be recommended.

Antimicrobial activity

The antimicrobial potential of *Acacia spp.* has attracted considerable scientific interest, with investigations focusing on leaf, bark, and floral matrices across various in vitro screening models (Box 3). Regarding the leaf profile of *Acacia nilotica*, organic solvent extractions demonstrated pronounced efficacy against a broad spectrum of clinical pathogens, with antimicrobial activity against different Gram-positive bacterial strains (*Staphylococcus aureus* MTCC 737, *Bacillus subtilis* MTCC 441, *Bacillus megaterium* MTCC 441, *Bacillus cereus* MTCC 6840, and *Bacillus aryabhattai* MTCC 14579) and Gram-negative counterparts (*Pseudomonas putida* MTCC 1194, *Escherichia coli* MTCC 1302, *Klebsiella pneumoniae* MTCC 4727, and *Serratia marcescens* MTCC 4822) (Revathi *et al.*, 2017). Similarly, Ziani *et al.* (2020) evaluated *Acacia tortilis ssp. raddiana* leaves against clinical multidrug-resistant (MDR) pathogens. Their experimental profiling revealed that both decoction and 80% ethanolic extracts significantly suppressed Gram-positive strains, with the ethanolic extract showing pronounced efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA) at a minimum inhibitory concentration (MIC) of 0.312 mg mL⁻¹, compared to 0.625 mg mL⁻¹ for the decoction, while maintaining a consistent MIC of 1.25 mg mL⁻¹ against several Gram-negative targets such as *Escherichia coli* and *Morganella morganii*.

This pathogen restriction is further complemented by the defense mechanisms identified in *Acacia seyal* bark extracts, which have displayed significant antimicrobial activity against different bacterial strains, including those multiresistant to conventional antibiotics (*Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Corynebacterium urealyticum*, *Shigella sonnei*, *Salmonella enterica* sv. *Typhi*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Streptococcus agalactiae*). Surprisingly, fractionation assays revealed that the methanolic fraction devoid of tannins retained significant antimicrobial activity against *Staphylococcus aureus*, *Corynebacterium urealyticum*, and *Pseudomonas aeruginosa*. This finding directly contradicted the performance of the tannin-containing crude methanolic fraction, suggesting that the antimicrobial activity may be

driven primarily by low-molecular-weight phytochemicals rather than condensed tannins. Consequently, tannins may contribute more substantially to antioxidant activity than to direct antimicrobial effects in certain biological environments (Elmi *et al.*, 2020), though more studies must be carried out to fully elucidate the underlying biochemical mechanisms. This anatomical variability is further illustrated by Yildiz *et al.* (2018), who explored the antimicrobial and anti-quorum-sensing properties of extracts obtained from different wood tissues (sapwood, heartwood, and bark) of *Acacia dealbata*. While activity against specific strains, such as *S. aureus* and *Listeria monocytogenes*, was observed, the bark extract displayed a broader spectrum of activity, inhibiting *Pseudomonas aeruginosa* and *Proteus mirabilis* and achieving an MIC of 156.25 μ g mL⁻¹ against *S. aureus*.

In addition to leaf and bark tissues, alternative anatomical structures such as flowers have emerged as potent antimicrobial reservoirs. Studies on the bioactive properties of phenolic compounds from *Acacia dealbata* flowers found that antimicrobial effects varied significantly according to flower maturation stages. The initial flowering stage optimized this secondary metabolite profile, possibly due to an elevated accumulation of bioactive chalcone derivatives. When evaluated against reference and resistant strains (*Escherichia coli* ATCC 29998, *Staphylococcus aureus* ATCC 43300, *Candida albicans* ATCC 10231, *E. coli* ESA37, *S. aureus* ESA111, and amphotericin-B-resistant *Candida albicans* ESA100), the early flower hydroethanolic extracts achieved marked antimicrobial activity. Live-cell microdilution testing confirmed that MIC values reached low concentrations, such as 0.79 $\pm$ 0.11 μ g mL⁻¹ against *S. aureus* and 4.57 $\pm$ 0.29 μ g mL⁻¹ against *E. coli*, showing substantial antimicrobial activity under the experimental conditions and, in some cases, values comparable to those reported for reference antimicrobial agents (Paula *et al.*, 2022).

The antimicrobial activity reported for *Acacia spp.* extracts appears to involve mechanisms operating at distinct levels of experimental evidence. Phenolic compounds and other phytochemicals have been shown to interact directly with bacterial cell envelopes, disrupting membrane integrity and cell wall structures, which may result in leakage of intracellular components and impairment of essential cellular functions. These compounds can also interfere with transmembrane proton gradients, compromising energy metabolism and microbial viability (Elmi *et al.*, 2020; Ziani *et al.*, 2020). In addition to direct bactericidal effects, extracts obtained from different *Acacia spp.* tissues have demonstrated anti-quorum sensing activity, interfering with bacterial communication systems involved in virulence, biofilm formation, and pathogen colonization (Yildiz *et al.*, 2018). Furthermore, molecular docking studies conducted with compounds

tentatively identified in *Acacia tortilis* extracts predicted that epigallocatechin derivatives could interact with penicillin-binding protein 2a (PBP2a), a transpeptidase associated with β -lactam resistance in MRSA. However, these docking results represent a predicted molecular interaction and do not constitute experimental confirmation of PBP2a inhibition (Ziani *et al.*, 2020). Importantly, these different approaches

represent complementary tiers of evidence, ranging from *in silico* predictive modeling to phenotypic antimicrobial inhibition, and should not be interpreted as equivalent confirmation of a definitive mode of action. Taken together, these mechanisms may contribute to the antimicrobial effects reported for *Acacia spp.* extracts against various bacterial species, including both susceptible and resistant strains.

Box 3: Summary of antimicrobial activities across *Acacia spp.* extracts.

Species	Fraction	Antimicrobial activity (MIC or inhibition zone)	Reference
<i>Acacia dealbata</i>	Hydroethanolic Flowers extract: Early Flower (EF); Mid Flower (MF);	MIC Range EF → MF → LF	Paula <i>et al.</i> , 2022
	Late Flower (LF);	<i>S. aureus</i> (ATCC 43300): 0.79 – 1.57 $\mu\text{g mL}^{-1}$;	
		<i>S. aureus</i> (ESA111): 2.63 – 4.05 $\mu\text{g mL}^{-1}$;	
		<i>E. coli</i> (ATCC 29998): 4.57 – 8.46 $\mu\text{g mL}^{-1}$;	
		<i>E. coli</i> (ESA37): 9.30 – 13.77 $\mu\text{g mL}^{-1}$;	
		<i>C. albicans</i> (ATCC 10231): 8.37 – 13.40 $\mu\text{g mL}^{-1}$;	
		<i>C. albicans</i> (ESA100): 15.00 – 25.61 $\mu\text{g mL}^{-1}$;	
<i>Acacia tortilis</i>	Aqueous leaves extract;	MIC	Ziani <i>et al.</i> , 2020
	Ethanolic leaves extract;	Aqueous:	
		<i>E. coli</i> : 1.25 mg mL^{-1} ;	
		<i>K. pneumoniae</i> : 2.50 mg mL^{-1} ;	
		<i>M. morgani</i> : 1.25 mg mL^{-1} ;	
		<i>P. mirabilis</i> : 2.50 mg mL^{-1} ;	
		<i>P. aeruginosa</i> : 2.50 mg mL^{-1} ;	
		<i>E. faecalis</i> : 5.00 mg mL^{-1} ;	
		<i>L. monocytogenes</i> : 1.25 mg mL^{-1} ;	
		MRSA: 0.625 mg mL^{-1}	
		MSSA: <0.15 mg mL^{-1}	
		Ethanolic:	
		<i>E. coli</i> : 1.25 mg mL^{-1} ;	
		<i>K. pneumoniae</i> : 1.25 mg mL^{-1} ;	
		<i>M. morgani</i> : 1.25 mg mL^{-1} ;	
		<i>P. mirabilis</i> : 1.25 mg mL^{-1} ;	
		<i>P. aeruginosa</i> : 1.25 mg mL^{-1} ;	
		<i>E. faecalis</i> : 2.50 mg mL^{-1} ;	
		<i>L. monocytogenes</i> : 1.25 mg mL^{-1} ;	
		MRSA: 0.312 mg mL^{-1} ;	
		MSSA: <0.15 mg mL^{-1} ;	
<i>Acacia seyal</i>	Aqueous bark extract;	MIC	Elmi <i>et al.</i> , 2020
	Methanolic bark extract;	Aqueous:	
		<i>S. aureus</i> : 512.0 $\mu\text{g mL}^{-1}$;	
		<i>P. aeruginosa</i> : 1024.0 $\mu\text{g mL}^{-1}$;	
		<i>C. urealyticum</i> : 64.0 $\mu\text{g mL}^{-1}$;	
		Methanolic:	
		<i>S. aureus</i> : 64.0 $\mu\text{g mL}^{-1}$;	
		<i>P. aeruginosa</i> : 512.0 $\mu\text{g mL}^{-1}$;	
		<i>C. urealyticum</i> : 64.0 $\mu\text{g mL}^{-1}$;	

Acacia nilotica	Acetone leaves extract;	Zone of Inhibition Diameter	Revathi <i>et al.</i> , 2017
	Methanol leaves extract;	Acetone:	
		<i>B. cereus</i> : 20.0 ± 0.1 mm;	
		<i>S. aureus</i> : 10.0 ± 0.1 mm;	
		<i>P. putida</i> : 9.8 ± 0.1 mm;	
		<i>B. aryabhattai</i> : 9.7 ± 0.3 mm;	
		<i>B. subtilis</i> : 9.5 ± 0.2 mm;	
		<i>B. megaterium</i> : 9.5 ± 0.1 mm;	
		<i>S. marcescens</i> : 6.5 ± 0.3 mm;	
		<i>E. coli</i> : 6.2 ± 0.3 mm;	
		Methanol:	
		<i>S. aureus</i> : 12.0 ± 0.1 mm;	
		<i>P. putida</i> : 7.3 ± 0.5 mm;	
		<i>B. aryabhattai</i> : 9.3 ± 0.5 mm;	
		<i>B. subtilis</i> : 10.3 ± 0.1 mm;	
		<i>B. megaterium</i> : 8.0 ± 0.1 mm;	
		<i>S. marcescens</i> : 9.6 ± 0.1 mm;	
		<i>E. coli</i> : 5.5 ± 0.2 mm;	
Acacia dealbata	Methanol and Hot water tissues extract;	MIC	Yildiz <i>et al.</i> , 2018
		Bark:	
		<i>S. aureus</i> : 156.25 µg mL ⁻¹ ;	
		<i>P. aeruginosa</i> : 625.0 µg mL ⁻¹ ;	
		<i>C. albicans</i> : 2500.0 µg mL ⁻¹ ;	
		<i>P. mirabilis</i> : 156.25 µg mL ⁻¹ ;	
		<i>K. pneumoniae</i> : 312.5 µg mL ⁻¹ ;	
		<i>L. monocytogenes</i> : 312.5 µg mL ⁻¹ ;	
		Heartwood:	
		<i>S. aureus</i> : 39.1 µg mL ⁻¹ ;	
		<i>K. pneumoniae</i> : 625.0 µg mL ⁻¹ ;	
		<i>L. monocytogenes</i> : 625.0 µg mL ⁻¹ ;	
		Sapwood:	
		<i>S. aureus</i> : 78.13 µg mL ⁻¹ ;	
		<i>K. pneumoniae</i> : 625.0 µg mL ⁻¹ ;	
		<i>L. monocytogenes</i> : 625.0 µg mL ⁻¹ ;	

MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

Antimicrobial resistance has become an important concern in veterinary medicine, particularly in companion animals, where resistant pathogens such as MRSA and multidrug-resistant *Enterobacteriaceae* have been increasingly reported (Palma *et al.*, 2020). The activity reported against multidrug-resistant microorganisms further highlights the relevance of *Acacia*-derived phytochemicals for future veterinary applications. Although the current evidence is restricted to *in vitro* studies, the identification of natural compounds capable of inhibiting resistant pathogens may provide a basis for future investigations exploring alternative approaches to mitigate antimicrobial resistance, an increasingly important challenge in companion animal health.

From a companion animal nutrition perspective, the broad-spectrum antimicrobial activity reported for *Acacia spp.* extracts may have potential technological applications in minimally processed feeding systems. Although raw feeding practices, such as Raw meat-based diets (RMBDs), remain controversial among veterinary professionals due to concerns regarding nutritional adequacy and microbiological safety, these products continue to be widely used by pet owners and are commercially available in many markets (Davies *et al.*, 2019). Because raw diets are not subjected to thermal processing, they present a greater risk of contamination by pathogenic microorganisms than conventional extruded

foods. In this context, the antimicrobial activity demonstrated by Acacia-derived phytochemicals suggests that these compounds may deserve further investigation as potential complementary tools for improving the microbiological quality and safety of raw pet food products. Nevertheless, it is critical to emphasize that such applications remain hypothetical at present. To date, no direct canine or feline feeding trials have been conducted to evaluate their efficacy, appropriate dosage, palatability, gastrointestinal tolerance, nutrient interactions, or long-term safety.

Therefore, although the antimicrobial potential of *Acacia* spp. is well supported by in vitro evidence, further studies are needed to determine whether these effects can be translated

into practical applications in companion animal nutrition and food safety.

Cytotoxicity, cytoprotection, and cellular biological activities

Evidence from cell culture models indicates that *Acacia* spp. extracts exhibit diverse cellular biological activities, including cytotoxic and antiproliferative effects, antioxidant and anti-inflammatory responses, and differential effects on tumor and non-tumor cells (Box 4). The magnitude and selectivity of these effects vary according to Acacia species, plant tissue, extraction method, phenolic composition, and molecular characteristics of the compounds present in the extracts.

Box 4: Cellular biological activities of *Acacia* spp. Extracts.

Acacia species	Plant material / extract	Cellular model	Biological effect evaluated	Key finding	Main phenolic fraction/ compound	Reference
<i>Acacia mearnsii</i>	Bark / EtOAc fraction (PAE) and H ₂ O fraction (PAW)	MDA-MB-231, BEL-7402, HeLa, A549	Antitumor / growth inhibition	PAE: ↑ inhibition of BEL-7402 and MDA-MB-231 at 200 µg mL ⁻¹ ; PAW: ↓ activity	Proanthocyanidins (enriched in trimers)	Shen <i>et al.</i> , 2010
<i>Acacia chundra</i>	Leaves, bark and flowers / H ₂ O, EtOH and CHCl ₃ extracts	Human RBCs	Cytotoxicity / hemolysis	↓ hemolysis (<1%) in all extracts	Phenolics, flavonoids and tannins	More <i>et al.</i> , 2026
<i>Acacia mearnsii</i>	Leaves / crude extract (L) and fractions L1–L4	LPS-stimulated RAW 264.7	Antioxidant; anti-inflammatory	Non-cytotoxic ≤100 µg mL ⁻¹ ; ↓ ROS at 50 µg mL ⁻¹ ; L3/L4 ↓ NO and IL-1β, COX-2, iNOS and IL-6 expression	Proanthocyanidins and flavonoids	Xiong <i>et al.</i> , 2016
<i>Acacia nilotica</i>	Leaves / acetone and MeOH extracts	MDA-MB-231, HEP-2, Vero	Anticancer / antiproliferative	↑ concentration-dependent cell death in cancer cells (25–100 µg mL ⁻¹); ↔ Vero viability	Phenolics, predominantly pyrogallol	Revathi <i>et al.</i> , 2017
<i>Acacia mearnsii</i>	Bark / crude extract (B) and HSCC fractions (B1–B7)	RAW 264.7; THP-1	Anti-inflammatory; bioenergetic modulation	Non-cytotoxic ≤100 µg mL ⁻¹ ; B4–B7 ↓ ROS, NO, IL-1β and iNOS; B ↓ inflammatory metabolic switch	Monomeric and oligomeric proanthocyanidins (catechin, galocatechin, fisetinidol, robinetinidol)	Xiong <i>et al.</i> , 2017
<i>Acacia mearnsii</i>	Bark / Ethanol extract (ABE)	HepG2	CAA; cytotoxicity	No cytotoxicity ≤500 µg mL ⁻¹ ; ↓ intracellular peroxyl stress (EC ₅₀ = 0.30 ± 0.003 mg mL ⁻¹)	B-type oligomeric PACs (DP 1–11)	Chen <i>et al.</i> , 2018a
<i>Acacia dealbata</i>	Flowers / EtOH extract and sequential fractions	A549, HCT-116, PSN1, T98G, B16-F10, HFF-1, human neutrophils	Antitumoral; antimelanogenic; fibroblast growth; oxidative burst modulation	ERWA: ↑ cytotoxicity toward A549/HCT-116 (IC ₅₀ = 250 µg mL ⁻¹); ↓ oxidative burst (62.5–500 µg mL ⁻¹)	Flavonoid- and chalcone-rich fractions	Casas <i>et al.</i> , 2020
<i>Acacia mearnsii</i>	Bark / Proanthocyanidins (PAC) encapsulated in biodegradable PLGA microparticles	Vero, T24	Cytotoxicity; biocompatibility	PLGA and PLGA/PAC: ↔ viability/proliferation after 24 h	Proanthocyanidins	Grasel <i>et al.</i> , 2019

<i>Acacia seyal</i>	Bark / H ₂ O and MeOH extracts; tannin precipitate (PW) and tannin-free fraction (FW)	MRC-5	Cytotoxicity / safety	MeOH extract safe $\leq 128 \mu\text{g mL}^{-1}$; PW: dose-dependent cytotoxicity ($\text{IC}_{50} = 241.2 \pm 16.8 \mu\text{g mL}^{-1}$); FW: non-toxic $\leq 1024 \mu\text{g mL}^{-1}$	Condensed tannins; catechin- and gallic acid-based oligomers	Elmi <i>et al.</i> , 2020
<i>Acacia tortilis</i> ssp. <i>raddiana</i>	Whole plant / decoction and EtOH extracts	NCI-H460, HeLa, HepG2, MCF-7, PLP2, RAW 264.7	Cytotoxicity; anti-inflammatory	$\uparrow$ cancer-cell growth inhibition ($\text{GI}_{50} = 33.3\text{--}53.0 \mu\text{g mL}^{-1}$); $\downarrow$ toxicity toward PLP2 ($\text{GI}_{50} > 250 \mu\text{g mL}^{-1}$); $\downarrow$ NO in RAW 264.7	Gallic acid and epigallocatechin derivatives	Ziani <i>et al.</i> , 2020
<i>Acacia mearnsii</i>	Aerial parts (PCEE)	HaCaT	Cytotoxicity	$\uparrow$ toxicity with concentration; lysosomal/membrane damage (NR $\text{IC}_{50} = 358.8 \mu\text{g mL}^{-1}$); MTT $\downarrow$ only at $2500 \mu\text{g mL}^{-1}$	Flavonoids and organic acids (isolated cinnamic acid and coumarin)	De Gonçalves Prietsch <i>et al.</i> , 2021
<i>Acacia catechu</i>	Leaves / 50% hydro-MeOH extract (ACLE)	Primary chicken PBL	Immunomodulation; lymphocyte proliferation	MNC dose = 0.3 mg mL^{-1} ; $\uparrow$ basal proliferation (5.33%) and LPS-stimulated proliferation (14.75%)	Flavonoids and tannins	Thakur <i>et al.</i> , 2025

ABE, *Acacia mearnsii* bark extract; ACLE, *Acacia catechu* leaf extract; CHCl₃, chloroform; ERWA, ethyl acetate fraction of the water-acid extract; EtOAc, ethyl acetate; EtOH, ethanol; FW, filtrate devoid of tannin from water extract; H₂O, water; MeOH, methanol; PAE, ethyl acetate fraction of proanthocyanidins; PAW, water fraction of proanthocyanidins; PCEE, phenolic compound-enriched extract; PW, precipitate of tannins from water extract; A549, human lung adenocarcinoma cell line; B16-F10, mouse melanoma cell line; BEL-7402, human hepatocellular carcinoma cell line; HaCaT, human keratinocyte cell line; HCT-116, human colorectal carcinoma cell line; Hep-2, human laryngeal/cervical epidermoid carcinoma cell line; HepG2, human hepatocellular carcinoma cell line; HFF-1, human foreskin fibroblast cell line; HeLa, human cervical epithelial carcinoma cell line; MCF-7, human breast adenocarcinoma cell line; MDA-MB-231, human triple-negative breast adenocarcinoma cell line; MRC-5, human embryonic lung fibroblast cell line; NCI-H460, human non-small cell lung carcinoma cell line; PBL, primary chicken peripheral blood lymphocytes; PLP2, primary porcine liver cell culture; PSN1, human pancreatic adenocarcinoma cell line; RAW 264.7, murine macrophage cell line; RBCs, red blood cells; T24, human urinary bladder carcinoma cell line; T98G, human glioblastoma multiforme cell line; THP-1, human monocytic leukemia cell line; Vero, African green monkey kidney epithelial cell line; CAA, cellular antioxidant activity; COX-2, cyclooxygenase-2; DP, degree of polymerization; EC₅₀, half maximal effective concentration; GI₅₀, concentration causing 50% inhibition of cell growth; HSCCC, high-speed countercurrent chromatography; IC₅₀, half maximal inhibitory concentration; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MNC, maximum non-cytotoxic dose/concentration; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NO, nitric oxide; NR, Neutral Red assay; PAC/PACs, proanthocyanidins; PLGA, poly(lactic-co-glycolic acid); ROS, reactive oxygen species;

Several studies have reported differential sensitivity between tumor and non-tumor cells, suggesting a potential degree of selectivity of *Acacia*-derived phenolic compounds. Extracts from *Acacia tortilis*, for example, inhibited several tumor cell lines at GI₅₀ (growth inhibition of 50%) values between 33.3 and 53.0 $\mu\text{g mL}^{-1}$, whereas normal primary porcine liver cell culture (PLP2) cells exhibited substantially lower sensitivity, with GI₅₀ values above 250 $\mu\text{g mL}^{-1}$ (Ziani *et al.*, 2020). A similar tendency was observed for *Acacia nilotica*, whose leaf extracts induced concentration-dependent cell death in human triple-negative breast adenocarcinoma (MDA-MB-231) and human hepatocellular carcinoma (Hep-2), while producing comparatively lower effects on African green monkey kidney epithelial cell line (Vero) (Revathi *et al.*, 2017). These findings are consistent with the antiproliferative effects reported for *Acacia dealbata* flower extracts against human lung adenocarcinoma cell line (A549), human laryngeal/cervical epidermoid carcinoma cell line (HCT-116), human pancreatic adenocarcinoma cell line (PSN1), and human glioblastoma multiforme cell line (T98G), although the magnitude of inhibition varied considerably among cell types (Casas *et al.*, 2020). Thus, cellular selectivity appears to be a recurrent but not universal

characteristic, since differences in susceptibility among tumor cell lines indicate that the response is influenced by both the extract and the biological characteristics of the target cell.

The composition and molecular characteristics of proanthocyanidins appear to be particularly important in determining these responses. In *Acacia mearnsii*, proanthocyanidin-rich fractions obtained using different solvents exhibited markedly different antiproliferative activities, with the ethyl acetate fraction showing stronger effects against human hepatocellular carcinoma cell line (BEL-7402) and MDA-MB-231 cells than against human cervical epithelial carcinoma cell line (HeLa) and A549 cells. The greater activity of this fraction was associated with its enrichment in proanthocyanidin trimers (Shen *et al.*, 2010). This observation is relevant because it indicates that the biological activity of phenolic extracts may be related to specific molecular structures rather than simply to the amount of phenolic compounds present. A similar relationship was observed in cellular antioxidant studies, in which highly polymerized proanthocyanidins showed lower cellular effectiveness than smaller molecules, probably because their larger molecular size limits membrane passage and intracellular accessibility (Chen *et al.*, 2018a).

The influence of chemical composition becomes even more evident when cytotoxicity is evaluated in non-tumor cells. *Acacia seyal* provides an important example, as the aqueous bark extract produced pronounced toxicity in human embryonic lung fibroblast cell line (MRC-5), whereas the methanolic extract caused little or moderate toxicity at comparable concentrations. Fractionation demonstrated that the tannin-containing fraction exhibited an IC_{50} of $241.2 \pm 16.8 \mu\text{g mL}^{-1}$, while the tannin-free fraction was not toxic (Elmi *et al.*, 2020). Importantly, the similar tannin contents of the aqueous and methanolic extracts but markedly different cellular responses indicate that total tannin concentration alone does not adequately explain cytotoxicity. Instead, the chemical nature of the phenolic compounds and their interactions with other constituents may determine whether an extract produces a toxic or comparatively well-tolerated response.

This concentration-dependent behavior is also evident in *Acacia mearnsii*. A phenolic-enriched extract from aerial parts caused a stronger reduction in human keratinocyte cell line (HaCaT) viability in the neutral red assay than in the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, with an IC_{50} of approximately $358.8 \mu\text{g mL}^{-1}$ in the former and a substantial reduction in viability only at $2500 \mu\text{g mL}^{-1}$ in the latter (De Gonçalves Prietsch *et al.*, 2021). In addition, hemolytic activity in human erythrocytes has been investigated as another indicator of cellular compatibility, highlighting the importance of considering membrane-related effects when evaluating the safety of phenolic-rich extracts (More *et al.*, 2026). The different responses among assays indicate that the biological effects of the extract may involve multiple cellular targets and reinforce the importance of using complementary methods when evaluating cytotoxicity. Conversely, proanthocyanidins from *Acacia mearnsii* incorporated into poly(lactic-co-glycolic acid) microparticles (PLGA) did not produce significant toxicity in Vero or human urinary bladder carcinoma cell line (T24) after 24 hours, demonstrating that the delivery system can also influence cellular exposure and biological response (Grasel *et al.*, 2019).

Taken together, these findings suggest that cytotoxicity is not an intrinsic and constant property of *Acacia spp.* extracts, but rather the result of interactions among concentration, phenolic structure, extract matrix, and cellular susceptibility. This is particularly relevant for proanthocyanidins, for which increasing polymerization may modify both antioxidant potential and cellular accessibility. Therefore, extracts with high phenolic or tannin contents should not automatically be considered either more biologically active or more toxic. Instead, the relationship between phenolic concentration and biological effect appears to be nonlinear and highly dependent on molecular characteristics.

In parallel with cytotoxicity, increasing evidence indicates that *Acacia spp.* phenolic compounds can modulate cellular oxidative and inflammatory responses at non-cytotoxic concentrations, providing a more relevant basis for discussing potential cytoprotective effects. Proanthocyanidins from *Acacia mearnsii* bark showed cellular antioxidant activity in human hepatocellular carcinoma cell line (HepG2) without inducing cytotoxicity at concentrations up to $500 \mu\text{g mL}^{-1}$ (Chen *et al.*, 2018a). Likewise, extracts and fractions from *Acacia mearnsii* leaves reduced Reactive Oxygen Species (ROS) and nitric oxide (NO) production in lipopolysaccharide-stimulated murine macrophage cell line (RAW 264.7) without affecting cell viability at concentrations up to $100 \mu\text{g mL}^{-1}$. The most active fractions also reduced Interleukin-1 beta (IL-1 β), Inducible Nitric Oxide Synthase (iNOS), Cyclooxygenase-2 (COX-2), and Interleukin-6 (IL-6) expression, indicating simultaneous modulation of oxidative and inflammatory pathways (Xiong *et al.*, 2016).

The effects observed in *Acacia mearnsii* bark further support this interpretation. Extracts and fractions reduced ROS and NO production in lipopolysaccharide-stimulated macrophages without compromising cell viability, while monomeric and oligomeric proanthocyanidins were associated with stronger cellular activity. In addition, the extract modulated the metabolic reprogramming associated with inflammatory activation in human monocytic leukemia cell line (THP-1) derived macrophages (Xiong *et al.*, 2017). These findings are important because they suggest that the biological activity of *Acacia* phenolic compounds may extend beyond direct radical scavenging to modulation of intracellular inflammatory and metabolic pathways, particularly when smaller proanthocyanidin structures are present.

Similar cellular modulation has been observed in other models. *Acacia dealbata* flower extracts inhibited Phorbol 12-myristate 13-acetate-induced oxidative burst in human neutrophils in a concentration-dependent manner, indicating an ability to modulate cellular oxidative responses (Casas *et al.*, 2020). The same study also evaluated mouse melanoma cell line (B16-F10) and human foreskin fibroblast cell line (HFF-1), including endpoints related to melanogenesis and fibroblast growth, demonstrating that the biological effects of the flower extracts extend beyond direct tumor-cell inhibition and oxidative stress modulation. Similarly, an aqueous-methanolic leaf extract of *Acacia catechu* maintained lymphocyte viability at 0.3 mg mL^{-1} while modifying basal and mitogen-stimulated lymphocyte proliferation, indicating immunomodulatory activity within a non-cytotoxic concentration range (Thakur *et al.*, 2025). These findings reinforce the concept that the concentration range at which an extract is administered is critical, since immunomodulatory, antioxidant, or anti-inflammatory effects may occur at concentrations below those associated with cellular toxicity.

However, it is important to distinguish cellular antioxidant or anti-inflammatory activity from true cytoprotection. Inhibition of ROS production, oxidative burst, or inflammatory mediators indicates modulation of cellular stress responses, but does not necessarily demonstrate that the extract protects cells against a defined cytotoxic insult. Therefore, although the findings from *Acacia mearnsii* and *Acacia dealbata* support a potential protective role of their phenolic compounds, direct evidence of cytoprotection should be interpreted according to experimental models in which preservation of cellular viability or function is demonstrated under oxidative or other defined stress conditions. This distinction is particularly important because antioxidant activity measured in chemical systems or isolated cellular pathways cannot be directly extrapolated to protection of tissues or organisms.

Another relevant biological effect is the inhibition of acetylcholinesterase reported for phenolic compounds from *Acacia dealbata* flowers. Because acetylcholinesterase regulates acetylcholine degradation, its inhibition may contribute to maintaining cholinergic neurotransmission and therefore supports a potential neuroprotective relevance of these compounds (Paula *et al.*, 2022). Nevertheless, this activity should not be interpreted as evidence that *Acacia spp.* extracts prevent or delay neurodegenerative diseases, since enzyme inhibition alone does not demonstrate neuronal protection. Rather, it identifies a potential biological mechanism that warrants further cellular and *in vivo* investigation.

Overall, the evidence indicates that the cellular biological effects of *Acacia spp.* are governed by a complex interaction between phenolic composition, molecular structure, degree of polymerization, concentration, extraction method, delivery system, and cellular model. Proanthocyanidins illustrate this complexity particularly well: highly polymerized molecules may contribute substantially to antioxidant capacity in chemical assays but show reduced cellular accessibility, whereas monomeric and oligomeric structures may exhibit greater cellular activity because of their higher accessibility to intracellular targets (Xiong *et al.*, 2017; Chen *et al.*, 2018a). Thus, phenolic content alone should not be used as a predictor of cytotoxicity or cytoprotective potential.

From a pharmaceutical perspective, the selective antiproliferative effects observed in several tumor models and the cellular antioxidant and anti-inflammatory activities support the potential of *Acacia*-derived phenolic fractions as sources of bioactive compounds. In the context of companion animal health, the absence of cytotoxicity at specific concentrations, combined with antioxidant, anti-inflammatory, and immunomodulatory effects observed in cellular models, indicates potential for further investigation as functional ingredients or nutraceutical candidates. However, the current

evidence is predominantly based on *in vitro* models and does not establish safe or effective doses for pharmaceutical, food, or companion animal-health applications. Further studies integrating chemical characterization, cellular mechanisms, bioaccessibility, pharmacokinetics, and *in vivo* safety and efficacy are necessary before practical applications can be proposed.

Conclusions and future perspectives

Acacia spp. extracts represent a diverse source of phenolic compounds, particularly proanthocyanidins, condensed tannins, and flavonoids, whose composition varies according to species, plant tissue, extraction procedure, and molecular structure. The available evidence indicates that these extracts exhibit a broad range of biological activities *in vitro*, including antioxidant, carbohydrate-digesting enzyme inhibitory, antimicrobial, antiproliferative, anti-inflammatory, and immunomodulatory effects. However, these activities should not be interpreted as intrinsic properties of the genus as a whole, since the magnitude and direction of the biological response depend strongly on the chemical profile and structural characteristics of the phenolic constituents.

A key finding emerging from the literature is that phenolic concentration alone is insufficient to predict biological activity. In particular, proanthocyanidins illustrate the importance of molecular size and degree of polymerization: highly polymerized structures may contribute substantially to antioxidant activity in chemical assays, whereas lower-molecular-weight monomers and oligomers may exhibit greater cellular accessibility and biological interaction. Similarly, differences in phenolic composition and extraction procedures can substantially modify antioxidant, enzymatic, antimicrobial, and cellular responses.

The biological evidence also indicates a concentration-dependent relationship between activity and cellular effects. At non-cytotoxic concentrations, *Acacia*-derived phenolics have been associated with reductions in ROS, NO, and inflammatory mediators, as well as modulation of immune-cell responses. Conversely, higher concentrations may result in loss of cell viability and other cytotoxic effects. Importantly, antioxidant or anti-inflammatory activity should not automatically be equated with cytoprotection, as direct evidence of cytoprotection requires preservation of cellular viability or function under a defined damaging condition.

From an application perspective, these results corroborate the promising potential of *Acacia spp.* phenolic fractions as sources of functional bioactive ingredients, particularly for applications involving antioxidant, antimicrobial, metabolic, and cellular effects. The inhibition of α -glucosidase and α -amylase is particularly relevant as a mechanistic basis for future research into metabolic modulation, while antimicrobial activity against both susceptible and multidrug-resistant

microorganisms suggest potential use in companion animal health and nutrition sectors. However, these possibilities remain at a preclinical stage and should not be interpreted as evidence of therapeutic efficacy.

Furthermore, *Acacia spp.* extracts may represent promising candidates for the development of functional ingredients or nutraceuticals aimed at modulating oxidative and inflammatory status, immune responses, or carbohydrate digestion. Their antimicrobial properties may also warrant investigation as complementary strategies to enhance microbiological food safety. However, their application in companion animal nutrition must be preceded by studies specifically designed to determine dose-response relationships, bioavailability and bioaccessibility, palatability, gastrointestinal tolerance, nutrient interactions, physiological efficacy, and long-term safety for each target species.

The main obstacle to translating *in vitro* evidence regarding *Acacia spp.* phenolic compounds into practical applications is confirming whether the active molecules are bioaccessible and retain their efficacy after ingestion. To overcome this bottleneck, future research must combine detailed chemical characterization with investigations into gastrointestinal stability, metabolism, cellular uptake, pharmacokinetics, and dose-response relationships. In this context, *in vivo* studies will be essential to validate these bioactivities and establish safe, effective exposure ranges.

In summary, *Acacia spp.* constitute a complex reservoir of structurally diverse phenolic compounds, the biological actions of which depend on molecular characteristics, bioaccessibility, concentration, and physiological context. Future studies should move beyond general screening and focus on molecular mechanisms, dose-response relationships, and targeted *in vivo* assays. This refined approach is essential for reliably assessing efficacy and safety, paving the way for practical applications in companion animal health and nutrition sectors.

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Data Availability Statement

Data sharing is not applicable to this article, as all data generated or analyzed during this study are included in this published manuscript.

Artificial Intelligence

During the preparation of this manuscript, the authors used ChatGPT (OpenAI) to assist with English language editing, formatting, and text conciseness, and Leapspace to assist with literature search and identification of relevant references for the discussion. After using these tools, the authors reviewed, validated, and edited all content as needed, taking full responsibility for the integrity and accuracy of the published work.

Conflicts of Interest

The authors declare no conflicts of interest.

Author Contribution Statement

JND: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing; LTr: Conceptualization, Investigation; LGD: Data curation, Visualization; JFB: Data curation, Visualization; MVS: Writing – review & editing; ARZ: Writing – review & editing; LTr: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – original draft, Writing – review & editing. All authors have read and agreed to the published version of the manuscript.

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