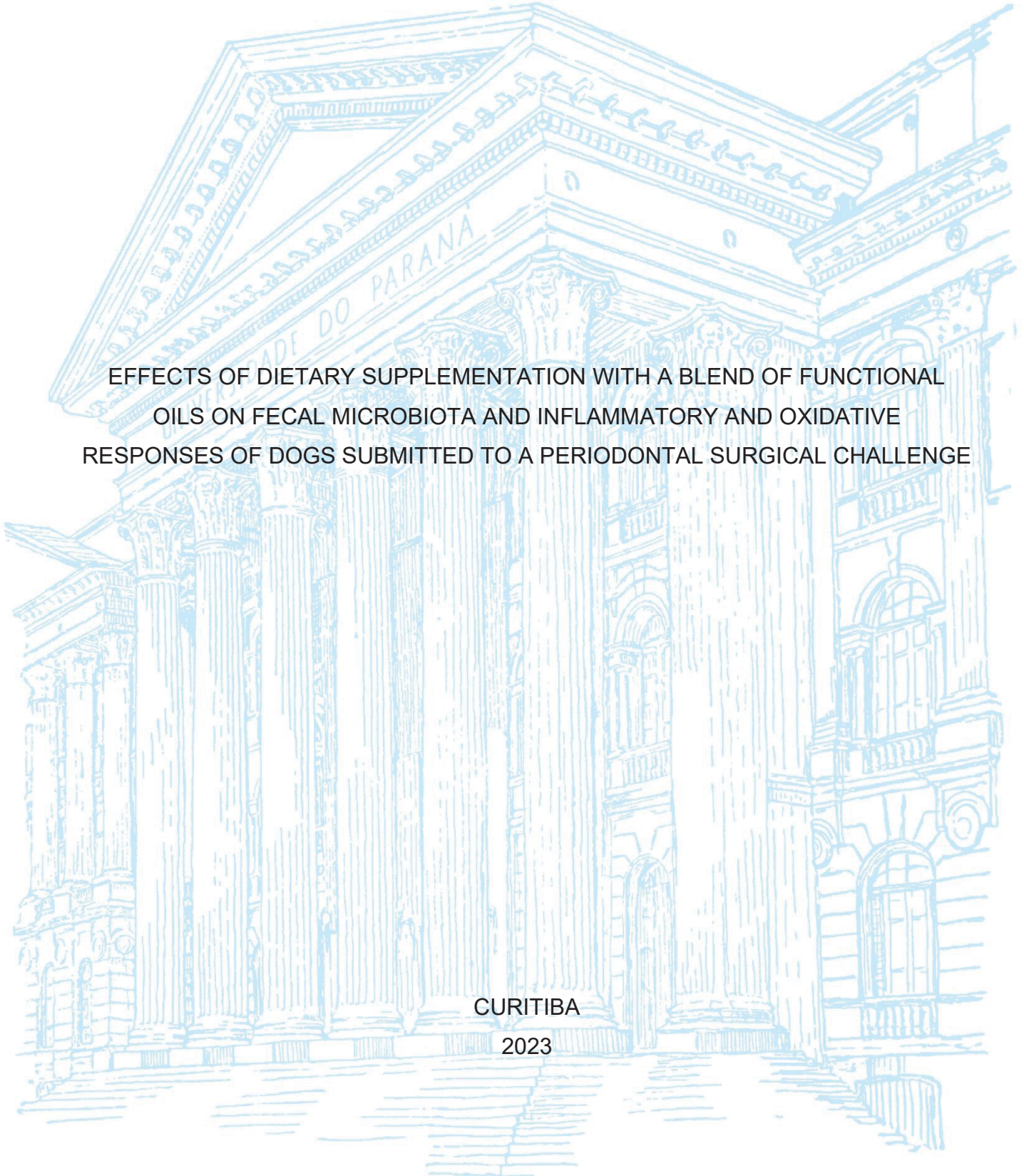UNIVERSIDADE FEDERAL DO PARANÁ

RENATA BACILA MORAIS DOS SANTOS DE SOUZA

EFFECTS OF DIETARY SUPPLEMENTATION WITH A BLEND OF FUNCTIONAL OILS ON FECAL MICROBIOTA AND INFLAMMATORY AND OXIDATIVE RESPONSES OF DOGS SUBMITTED TO A PERIODONTAL SURGICAL CHALLENGE

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Dissertação apresentada ao curso de Pós-graduação em Ciências Veterinárias, Setor de Ciências Agrárias, Universidade Federal do Paraná, como requisito parcial à obtenção do título de Mestre em Ciências Veterinárias.

Orientadora: Profª. Drª. Ananda Portella Félix

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TERMO DE APROVAÇÃO

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Dedicate to:

João Paulo and Samuel

My family

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To God, for the strength and peace that He gives me in the face of adversities.

To my father Marcos Aurelio Morais dos Santos, who has never measured efforts for my professional formation and always encouraged me.

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RESUMO

Opções de alimentos com ingredientes funcionais são um nicho de grande potencial de mercado. Levando em consideração essa demanda, os compostos vegetais e os óleos funcionais podem ser utilizados como aditivos zootécnicos. Os óleos funcionais são definidos como óleos que têm uma ação além do seu valor nutricional. Devido à presença de compostos bioativos, os óleos funcionais têm diferentes ações terapêuticas, atuando como antioxidantes, anti-inflamatórios e reguladores de microbiota intestinal. O Brasil apresenta uma rica biodiversidade com grande potencial para a obtenção destes compostos alternativos. Diante disso, objetivamos avaliar os efeitos dos óleos funcionais de copaíba (*Copaifera* spp.), casca de caju (*Anacardium occidentale*), e espécies de pimenta (*Schinus molle* L. e *Capsicum annum* L.) sobre os coeficientes de digestibilidade aparente (CDA) de nutrientes, metabólitos fermentativos intestinais, microbiota fecal, e marcadores inflamatórios e oxidativos em cães submetidos à cirurgia periodontal. Foram avaliados dois tratamentos: controle e teste, contendo o blend de óleos funcionais (0,1 g/animal/dia). Os tratamentos foram oferecidos durante 35 dias a 12 cães adultos da raça Beagle, distribuídos inteiramente ao acaso (n=6). No dia 30, os cães foram submetidos à cirurgia periodontal. Foram coletadas amostras de fezes (dias 30 e 35) e sangue (dias 0, 30, e 35) para a avaliação de metabólitos fermentativos intestinais, microbiota fecal, e respostas inflamatórias e antioxidantes no sangue. Os cães do grupo controle apresentaram uma redução mais pronunciada nos gêneros *Prevotella* e *Faecalibacterium* após a cirurgia (dia 35) do que o grupo de teste (P<0,05). Além disso, os cães do grupo controle também apresentaram maior abundância de *Streptococcus* no dia 35 (P<0,05). Houve aumento na concentração de NF-κB no sangue após cirurgia apenas no grupo controle (P<0,05). Além disso, os cães alimentados com o blend de óleos mostraram menor peroxidação lipídica (P<0,05) e uma tendência (P=0,059) para maior atividade da glutationa transferase. O blend de óleos funcionais não altera a digestibilidade dos nutrientes e pode modular a microbiota intestinal. Além disso, controla os mecanismos inflamatórios e oxidativos após o desafio cirúrgico em cães.

Palavras-chave: *Capsicum annuum* L; compostos bioativos; microbiota intestinal; NF-κB. *Schinus molle* L.

ABSTRACT

Food options with functional ingredients are a niche of great market potential. Considering this demand, the plants compounds and functional oils can be used as zootechnical additives. Functional oils are defined as oils that have an action in addition to their nutritional value. Due to the presence of bioactive compounds, functional oils have different therapeutic actions, acting as antioxidants, anti-inflammatory and gut microbiota regulators. Brazil presents a rich biodiversity with great potential to obtain these alternative compounds. Considering this, we aimed to evaluate the effects of functional oils from copaiba (*Copaifera* spp.), cashew nut shell (*Anacardium occidentale*), and pepper species (*Schinus molle* L. and *Capsicum annum L.*) on coefficients of total tract apparent digestibility (CTTAD) of nutrients, intestinal fermentative metabolites, fecal microbiota, and inflammatory and oxidative markers in dogs submitted to periodontal surgery. Two treatments were evaluated: control and test, containing the blend of functional oils (0.1 g/animal/day). The treatments were offered for 35 days to 12 adult Beagle dogs, distributed in a completely randomized design (n=6). On day 30, the dogs were submitted to periodontal surgery. Fecal (days 30 and 35) and blood (days 0, 30, and 35) samples were collected for the evaluation of intestinal fermentative metabolites, fecal microbiota, and inflammatory and antioxidant responses in the blood. Dogs of the control group presented a more pronounced reduction in the genera *Prevotella* and *Faecalibacterium* after surgery (day 35) than the test group ($P<0.05$). Besides, dogs of the control group also presented a greater abundance of *Streptococcus* on day 35 ($P<0.05$). There was an increase in NF-κB concentration in the blood after surgery only in the control group ($P<0.05$). Additionally, dogs fed the oil blend showed lower lipid peroxidation ($P<0.05$) and a tendency ($P=0.059$) to higher glutathione transferase activity. The blend of functional oils does not alter the digestibility of nutrients and may modulate the intestinal microbiota. Furthermore, it controls the inflammatory and oxidative mechanisms after the surgical challenge in dogs.

Keywords: *Capsicum annuum L;* gut microbiota; metabolic compounds; NF-κB; *Schinus molle L.*

FIGURE LIST

TABLE LIST

LIST OF ABBREVIATIONS

AHEE - acid-hydrolyzed ether extract

BCFA - branched-chain fatty acids

CAT - catalase

CB2 - cannabinoid receptor 2

CF - crude fiber

CNSL- cashew nut shell oil

CP - crude protein

CRP - C-reative protein

COX-2 - cyclooxygenase 2

CTTAD - coefficients of total tract apparent digestibility

DAMPs - damage-associated molecular patterns

DM - dry matter

DMf - fecal dry matter

GALT- gut-associated lymphoid tissue

GE - gross energy

GRAS - generally recognized as safe

GSH - reduced glutathione

GST - glutathione transferase

IKα β - inhibitory protein

IKK - protein kinases

IL-1 - interleukin -1

IL-6 – interleukin - 6

INOS - inducible NO synthase

LPO - lipid peroxidation

ME - metabolizable energy

NF-kB - nuclear factor kB

Nrf2 - nuclear factor erythroid 2

NO - nitric oxide

OM - organic matter

OTUs - observed taxonomic units

PAMP - pathogen-associated molecular patterns

PCoA - principal coordinate analysis

PPARs α - peroxisome proliferator-activated receptor alpha

PPARs γ - peroxisome proliferator-activated receptor gamma

PRRS - receptor recognition patterns

PUFA - polyunsaturated fatty acids

RelA - rel-related proteins A

ROS - reactive oxygen species

SCFA - short-chain fatty acids

SEM - standard error of the mean

SOD - superoxide dismutase

TBARS - modulate thiobarbituric acid reactive species

TLR4 - toll-like receptor

TRVP1 - transient receptor potential vanilloid 1

TNF - α - tumor necrosis factor alpha

LIST OF SIMBOLS

® - registered brand

α - alpha

β - beta

μ - micro (10^{-6})

γ- gamma

SUMMARY

CHAPTER I – GENERAL CONSIDERATIONS

1. INTRODUCTION

Pets are more "humanized", and concerning pet food, there is a replication of human food trends (VIANA; MOTHÉ; MOTHÉ, 2020). In this context, the industry is investing to develop foods that attend nutritional needs, but also provide health and reduce the risk of diseases (WERNIMONT et al., 2020). This increased interest in more natural and sustainable feed ingredients, combined with an increase in demand for the treatment of dogs with chronic degenerative diseases, have resulted in new food options with functional ingredients, as a niche of high marketing potential. Considering this demand, plant compounds and functional oils can be used not only as technological additives, improving the quality and safety of food, but also as zootechnical, contributing to the animal's health (KARÁSKOVÁ; SUCHÝ; STRAKOVÁ, 2016).

Functional oils present different therapeutic properties acting as antioxidants, anti-inflammatory and regulators of the gut microbiota (KARÁSKOVÁ; SUCHÝ; STRAKOVÁ, 2016). Due to these actions, the use of phytogenic additives for pets has been studied, both for its therapeutic potential as well as in a preventive mode, since inflammatory processes, oxidative stress and gut dysbiosis are commonly present in aged and obese animals. Moreover, these conditions are related to the progression of most chronic degenerative diseases such as arthritis, cancer, diabetes, and kidney disease (VALACCHI et al., 2018).

Brazil has a wide biodiversity with great potential to obtain these alternative compounds. Among these products are: Copaiba oil-resin, obtained from the tree of the species *Copaifera* spp.; the liquid extracted from the shell of cashew nuts; and the oils from the *Schinus molle* L. and the pepper tree *Capsicum annuum* L. Therefore, the aim of this review is to present how oxidative stress and inflammation occur in the animal organism and contribute, through literature, with new information about the action of these functional oils in these conditions.

1.1. OBJECTIVES

1.1.2 General objective

Through the literature review in chapter 1, the general objective is to understand the activity of functional oils from the Brazilian biodiversity in the animal organism. Through chapter 2 the aim of the study was to evaluate the effects of a blend composed by four functional oils on gut functionality and inflammatory and oxidative markers in dogs submitted to surgical challenge.

1.1.3 Specific objective

To evaluate the digestibility and palatability of a diet containing a blend of functional oils from Copaiba oil-resin, Cashew nut shell oil, and oils from pepper species of *Capsicum annuum* L. and *Schinus molle* L. Also, to evaluate the influence of these oils on the gut microbiota composition and diversity, fermentative metabolites, and parameters of inflammatory and oxidative response in dogs submitted to dental prophylaxis surgery.

2. LITERATURE REVIEW

2.1 Phytogenic feed additives

Phytogenic additives are substances derived from plants that, when incorporated into feed, have a positive effect on the diet and animal organism (PERIĆ; ŽIKIĆ; LUKIĆ, 2009). According to processing and origin, phytogenic may be classified into four subclasses: I) Herbs (flowering product, non-woody and from non-persistent plants); II) Plants (entire or processed parts of a plant, e.g., root, leaves, and bark), III) Essential oils (hydrodistilled extracts of volatile compounds from plants as leaves, seeds, roots, and flowers); and IV) Oil-resin (natural solution of resin dissolved in essential oil) (HASHEMI; DAVOODI, 2011).

In animal nutrition, these compounds are designated additives and, according to their function, they can be included in the classification defined by the European Community (EC 1831/2003), as sensory phytogenic additives, conferring flavor or odor to the food; technological additives, improving quality and safety of food; and as zootechnical additives, which can increase the performance and quality of animal products (KARÁSKOVÁ; SUCHÝ; STRAKOVÁ, 2015).

Phytogenic additives can be formed by a single plant or through a combination of species. As each plant and its derivatives have several active substances, it is considered that the effect of a phytogenic product is due to the synergy among its compounds, and that these effects can be potentiated when species are used in combination (HASHEMI; DAVOODI, 2011).

In animal feed, the use of plant products emerged from the demand for more natural and sustainable feed ingredients (MARTIN; FERASYI, 2016). This occurred mainly from 2006, after the prohibition of the use of antibiotics by the European Union and discussion on the restriction of the use of this class of drugs in other countries. Since then, a new concept "Clean Green and Ethical" (MARTIN; FERASYI, 2016) has been applied in livestock production, valorizing a drug-free production, to reduce the risk of resistance, and valorizing the use of coproducts, which contributes to a reduced environmental impact (SALAMI et al., 2019).

In livestock, the use of phytogenics is not only an alternative to replace growth promoters, but also has demonstrated functions such as: improved palatability of food, benefits for digestive functions, gut microbiota and animal performance (KARÁSKOVÁ; SUCHÝ; STRAKOVÁ, 2015). In pet food, the concept of "natural and sustainable" has also been applied, and as a result, the use of phytogenics as an alternative to synthetic antioxidants has been studied (ROZENBLIT et al., 2018; SCHLIECK et al., 2021). Despite this, it is due to their pharmacological effects on the body, proving anti-inflammatory, antioxidant, and antimicrobial action (KARÁSKOVÁ; SUCHÝ; STRAKOVÁ, 2015) that the use of these additives has been receiving attention. Although most studies in dogs demonstrate effects of plant compounds through topical application (Table 1), the use of this type of additive as a dietary therapeutic alternative has already been demonstrated (Table 1).

TABLE 1 – EXAMPLES OF PHYTOGENIC ADDITIVES USE IN DOGS AND ITS BENEFITS

Phytogenic additive	Mode of use	Animal	Action	References
Habanero pepper extract	Diet supplement	Dogs with different tumors	Favorable effects on different tumors and is well tolerated by the animals	Adaszek et al. (2017)
Blend of copaiba oil-resin, CNSL, and pepper species	Diet supplement	Beagle dogs submitted to a surgical challenge	↓NF-κB, lipid peroxidation, *Streptococcus* genus in dog feces ↑ GST	Souza et al. (2023)
Microencapsulated thymol, carvacrol, and cinnamaldehyde	Diet supplement	Beagle dogs	Neutrophils, lymphocytes, globulins, nitrogen oxide, GSH-PX ↓ ROS, fecal bacterial count, *Salmonella*, *Escherichia coli*	Campigotto et al. (2022)
Blend of essential oils of clove, rosemary, oregano, and vitamin E	Diet supplement	Beagle dogs	↓ROS, Non-protein thiols and ↑ GST	Schlieck et al. (2021)
Curcumin extract	Diet supplement	4-month-old beagles	↑ Total antioxidant capacity, anti-inflammatory effect	Campigotto et al. (2020)
Green tea polyphenols	Diet supplement	Male Dogs	Anti -obesity and anti -inflammatory effects, improve gastrointestinal immunity	Li et al. (2020)
Copaiba oil	Oral topical application	Dogs and *in vitro*	↓ halitosis and gingivitis, inhibition of the adherence of *Streptococcus mutans* and plaque forming bacteria	Pieri et al. (2010)
Menthol and thymol oils	Applied as an oral gel	Adult dogs	↓ buccal halitosis	Low et al. (2014)
Thymol and eugenol essential oils	Applied all over the skin and hair	English cocker spaniel dogs	↓ Reduced the number of tick larvae on dogs (*Rhipicephalus sanguineus*)	Monteiro et al. (2021)

Essential oils/product		Model	Effect	Reference
Dermoscent BIO BALM® Neem, rosemary, lavender, clove, tea tree, oregano, peppermint essential oils, cedar bark extract, and PUFAs	Topical administration	Dogs with low, medium, and severe atopic dermatitis	↓ canine atopic dermatitis and pruritus score ↑ beneficial in ameliorating the clinical signs of atopic dermatitis	Blaskovic et al. (2014)
Citrus, basilic, eucalyptus, cinnamon, lemon balm, lemongrass, lemon verbena, tea tree, savory, myrrh, and cannabis essential oils	*S. pseudintermedius* strains isolated from dogs suffering from pyoderma	Dogs (*in vitro*)	↑ bactericidal activity against methicillin-resistant Staphylococcus	Nocera et al. (2020)
Thyme and oregano essential oils	Bacterial and fungal isolates from canine otitis externa	Dogs (*in vitro*)	↑ bactericidal and fungicidal activity	Sim et al. (2019)
Cinnamon essential oil	Staphylococcus strains from canine otitis	Dogs (*in vitro*)	Effective antimicrobial and antibiofilm activity	Albuquerque et al. (2021)

SOURCE: Adapted from Ruiz-Cano et al. (2022).

2.2 Functional Oils

Among the group of phytogenic additives are functional oils, which are compounds extracted from aromatic plants, usually found in Mediterranean and tropical countries, where they represent an important part of the local biodiversity. Functional oils are liquid, volatile at temperature ranges between (28 and 38 °C) (TUREK; STINTZING 2012; OLADIMEJI; ORAFIDIYA; OKEKE, 2004), clear, lipid-soluble, and soluble in organic solvents. They can be synthesized by all tissues of the plant (buds, flowers, leaves, stems, twigs, seeds, fruits, roots, wood or bark), being stored in secretory cells, cavities, canals, epidermic cells or glandular trichomes (BAKKALI et al., 2008).

Functional oils are defined as oils that have an action in addition to their nutritional value (MURAKAMI et al., 2014). In the category of functional oils are oil-resin and essential oils, which differ in the method of extraction (HASHEMI; DAVOODI, 2011). The oil-resin is usually extracted from different parts of plants (such as trunks and shells) directly or extracted in non-aqueous solvents. Oil-resin is composed of a resinous part and a volatile part. For isolation of the volatile fraction, called essential oil, the most conventional methods are: hydrodistillation or steam distillation, cold pressing method, and the extraction methods with organic solvents. Among the innovative extraction methods are: supercritical fluid extraction, subcritical liquid extraction using H_2O and CO_2, ultrasound-assisted extraction, microwave-assisted extraction, solventless microwave extraction, and microwave hydrodiffusion and gravity (ASBAHANI et al., 2015).

Due to the volatile and reactive nature of functional oils, their effectiveness in the body can be influenced by different conditions. During production and storage processes, functional oils can be degraded by oxidation, volatilization, temperature heating or by lighting (STEVANOVIĆ et al., 2018). In addition, it is necessary that the oil is able to be delivered to the intestine to be metabolized. In consideration of this, to ensure the stability of these compounds and their effective use in animal nutrition, functional oils must be microencapsulated. The benefits of microencapsulation are exemplified in figure 1.

The microencapsulation process ensures, in addition to stability to external factors, thermostability at the temperature of the animal's body and a slow digestion of the

carrier matrix. Thus, oil carriers can be classified as polymer-based particles or lipid-based particles (STEVANOVIĆ et al., 2018).

Polymer-based particles are generally composed of natural polymers, such as protein polysaccharide hydrogels. In addition to being rigid enough to ensure mechanical stability during mixing with granular feed, the combination of the amphiphilic properties of proteins and the hydrophilic properties of polysaccharides ensures greater stability (STEVANOVIĆ et al., 2018). Commonly, the structure of a polymer is composed of an external layer of polysaccharides and an internal layer of protein (TORCELLO-GÓMEZ et al., 2011; XU et al., 2017).

The techniques used are: simple and complex coacervation of functional oil droplets; extrusion; and combination of simple coacervation and extrusion (STEVANOVIĆ et al., 2018).

Lipid-based particles include some vegetable oils and liposomes. Vegetable oils are a mixture of triglycerides, as main compounds, and secondary compounds such as glycerolipids, phospholipids, and non-glycerolipids (YARA-VARÓN et al., 2017). Vegetable oils with long-chain triglycerides such as corn oil and canola oil may be used due to the small digestion rate (MAJEED et al., 2016). Microemulsions, with droplet diameters less than 500 nm, are produced by microfluidization or micelle formation techniques (NAZZARO et al., 2012) that can be combined with spray cooling techniques, considered the most economical encapsulation technology (SILVA et al., 2014).

Liposomes are a system composed of one or more bilayers, usually formed using a phospholipid involving a water-based nucleus. The main methods for this technique include mechanical dispersion method, solvent dispersion method, and detergent removal method (AKBARZADEH et al., 2013). The types of functional oil carriers are exemplified in figure 2.

FIGURE 1– BENEFITS OF MICROENCAPSULATION ON FUNCTIONAL OILS IN ANIMAL FEED
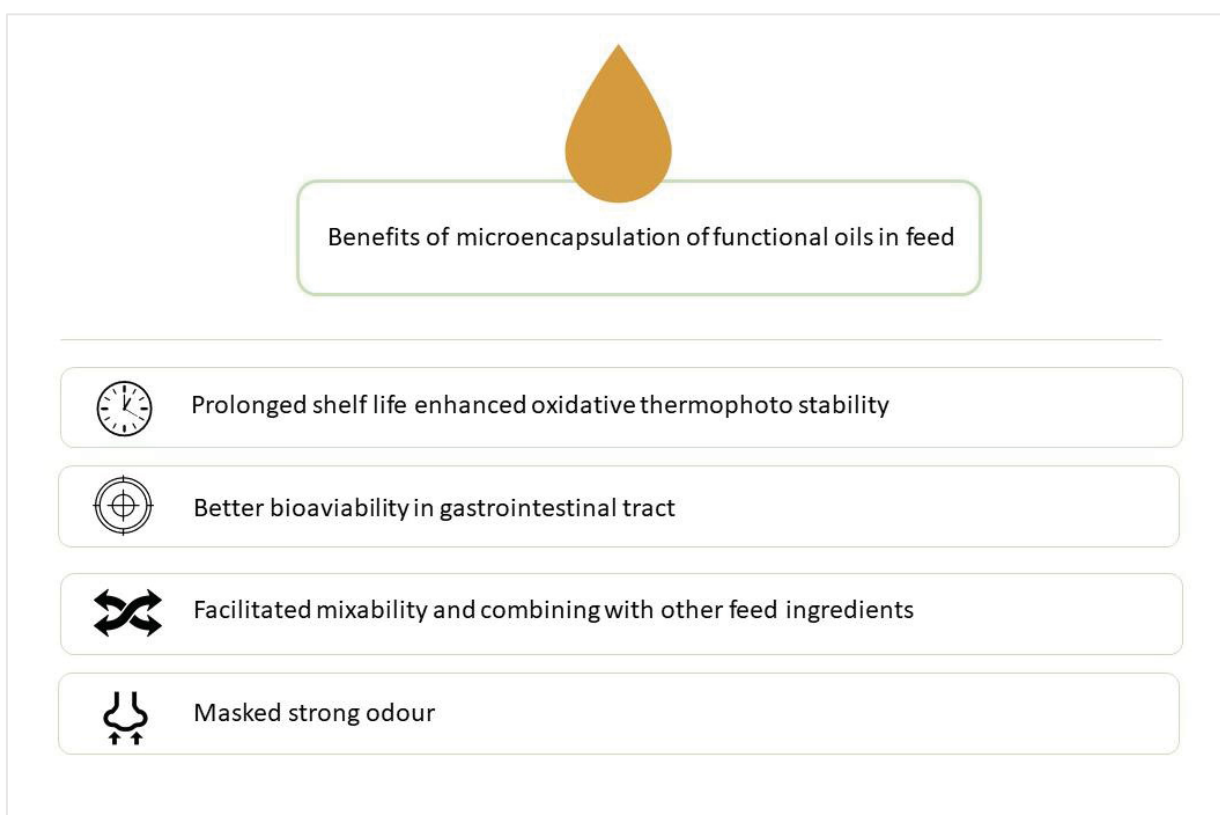
SOURCE: Adapted from Stevanović et al. (2018).

FIGURE 2 – APPROACHES FROM FUNCTIONAL OILS MICROENCAPSULATION
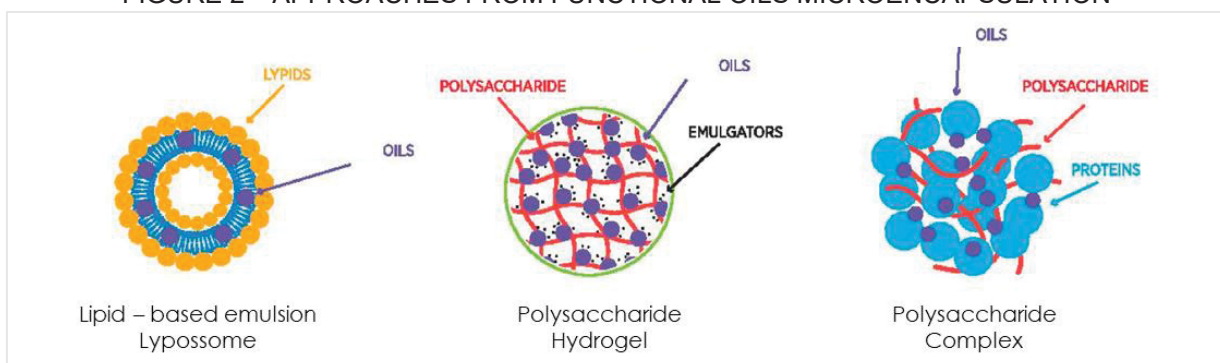
SOURCE: Adapted from Stevanović et al. (2018).

2.3 Bioactive compounds

The pharmacological action of functional oils is related to the secondary metabolites present in their composition. These metabolites are produced by different cells of the plant, and are responsible for the adaptation of the plant when they interact with the environment and for acting in the defense mechanisms of the plant (BAKKALI et al., 2008). These compounds can vary in their composition and concentration due to genetic and environmental factors, such as soil, light incidence, temperature, humidity, water, and nutrients availability. Usually, a functional oil has two or three components present in higher concentration (20 to 70%) and these components determine the main and unique pharmacological action of a variety of plants (BAKKALI et al., 2008; GANG et al., 2001)

There are three major groups of secondary metabolites present in functional oils: terpenes (predominantly monoterpenes, sesquiterpenes and diterpenes), phenolic compounds (phenylpropanoids and flavonoids), and nitrogen compounds (alkaloids, glycosides, glucosinolates and cyanogenic glycosine) (VOON; BHAT; RUSUL, 2012).

2.3.1 Terpenes

Among the bioactive compounds, terpenes are the largest family of plant secondary metabolites. Terpenes are basically hydrocarbons, that is, formed only of carbon and H_2O, and are the first line of defense of plants (CHO et al., 2017). When these terpenes are modified by oxidation of the methyl group and inclusion of different functional groups, they are named Terpenoids. Depending on their functional groups, terpenoids can have different chemical functions, such as: alcohols, acids, aldehydes, ketones, ethers, and phenols. Regardless of their functional group, their chemical structure is formed in blocks of 5 carbons, called isoprene unit (C5H8). Depending on the number of isoprene units, terpenes are classified as monoterpenes, sesquiterpenes, and diterpenes, as shown in figure 3. Terpenes have an enormous chemical structural diversity that is generated by both terpenoid metabolic pathways and the specialized cell types that participate in their biosynthesis (ZULAK; BOHLMANN, 2010).

These bioactive compounds are recognized for their anti-inflammatory action. This action occurs mainly through the suppression of pro-inflammatory enzymes and signaling of inflammatory pathways. In addition, a large number of studies demonstrate the antioxidant, antimicrobial, antiviral, anticancer, analgesic, and antidiabetic activity of these compounds (AMORATI; FOTI; VALGIMIGLI, 2013; ASTANI; REICHLING; SCHNITZLER, 2010; BHALLA; GUPTA; JAITAK, 2013; GUIMARÃES; QUINTANS; QUINTANS-JÚNIOR, 2013; HABTEMARIAM, 2017; NAZZARO et al., 2013; OZ et al., 2015).

FIGURE 3 – CHEMICAL STRUCTURE OF ISOPRENE AND MONOTERPENES AND SESQUITERPENE
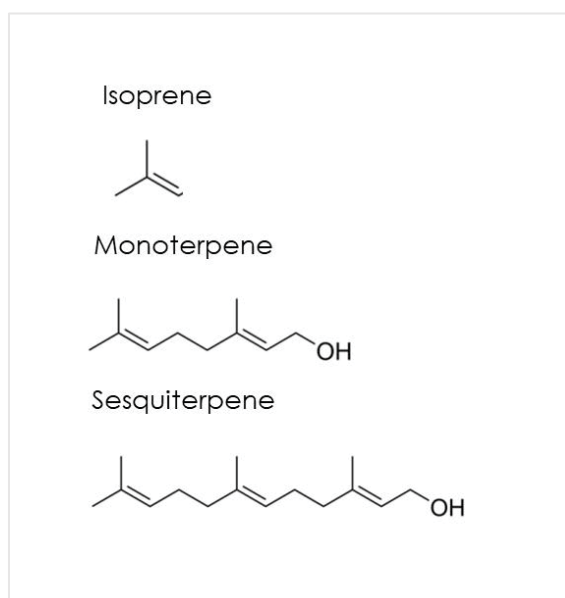
SOURCE: Adapted from Mewalal et al. (2017).

2.3.2 Phenolic compounds

Phenolic compounds are originated from the secondary metabolism of plants, and are considered essential for their growth and reproduction, being formed under conditions of plant stress, such as infection, injury and UV radiation (ANGELO; JORGE, 2007; NACZK; SHAHIDI, 2004). Phenolic compounds are a very diverse group of phytochemicals, chemically defined as substances that have at least one aromatic ring

with one (or more) hydroxyl. Phenolic compounds can be separated into two major groups: Flavonoids, formed by two aromatic rings, and non-flavonoids. The non-flavonoids, also called phenolic acids, contain an aromatic ring, at least one hydroxyl group, and different functional groups such as aldehydes, alcohols, or acids that can form esters with organic acids or bind to sugars (KARAKAYA, 2004; LUNA-GUEVARA et al., 2018). Among the most commonly known phenolic compounds are: resveratrol, quercetin, luteolin, and catechins (SHEN et al., 2022). The complete classification of phenolic compounds is represented in figure 4.

In a functional oil the different phenolic compounds act by different mechanisms, and may act synergistically or not. Thus, the majority action of the oil will depend on the concentration and type of compounds that are present in the oil. In general, the phenolic compounds have as their main characteristic the antioxidant action, mainly related to the presence of the aromatic ring with oxireduction capacity. In addition, phenolic compounds also have antimicrobial, anti-inflammatory, antitumor, hypoglycemic, cholesterol-reducing, antidiabetic, and digestive action, through the increased secretion of bile (ALI GHASEMZADEH, 2011; PANCHE; DIWAN; CHANDRA, 2016).

FIGURE 4 – CLASSIFICATION OF PHENOLIC COMPOUNDS
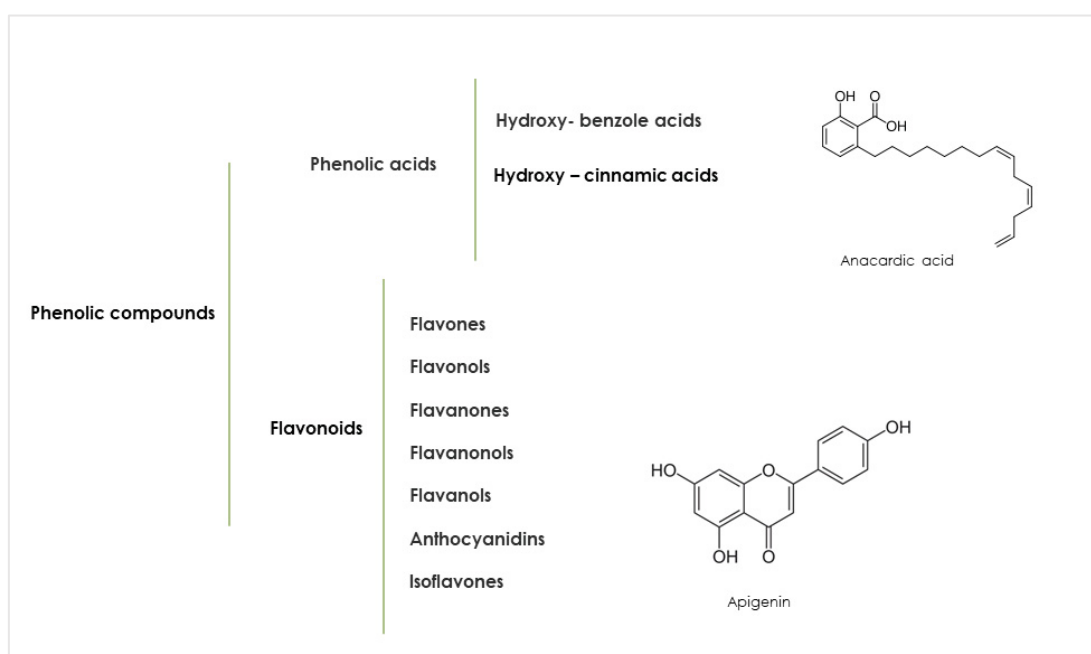
SOURCE: Adapted from Karakaya (2004).

2.3.3 Alkaloids

Plant alkaloids are a large class of secondary metabolites, containing more than 20,000 molecules (FAISAL et al., 2023). They are characterized as cyclic organic compounds that have at least one nitrogen atom in their ring, and do not have nitrogen in an amide or peptide bond (O'CONNOR, 2010). They are predominantly found in angiosperms, synthesized in the endoplasmic reticulum, and concentrated in vacuoles. The definition for this class of bioactive compounds is difficult, since there is no clear separation between alkaloid compounds properly and naturally occurring complex amines (HENRIQUES; KERBER; MORENO, 1999). According to their chemical composition, alkaloids can be classified into "true alkaloids", protoalkaloids and pseudoalkaloids (Figure 5) (BRUNETON, 1995).

Plant species that contain more than 0.001% of alkaloids are recognized as sources of these compounds. Plant groups such as Solanaceae, Fabaceae, Asteraceae, Papaveraceae, Amaryllidaceae, Rutaceae, Apocynaceae and Rubiaceae have potential to be used in pharmaceuticals (YANG; STÖCKIGT, 2010).

Generally, plants have a variety of alkaloid compounds, forming a complex mixture that can be dominated by one main component. The quantities and composition present can vary depending on the plant. Many of these compounds have recognized pharmacological effects, such as the analgesic effects of morphine and codeine. In addition to these analgesic effects, many antiviral and antimicrobial drugs have been developed from these metabolites (BASITH et al., 2016; BRIBI et al., 2016; FAISAL et al., 2023). Moreover, new findings have attributed to glucosinolate alkaloids, present in brassica vegetables such as broccoli and cauliflower, apoptosis-stimulating effects in human tumor cells (FAHEY; ZALCMANN; TALALAY, 2001).

FIGURE 5 – CHEMICAL STRUCTURE OF SOME WELL-KNOWN ALKALOID COMPOUNDS
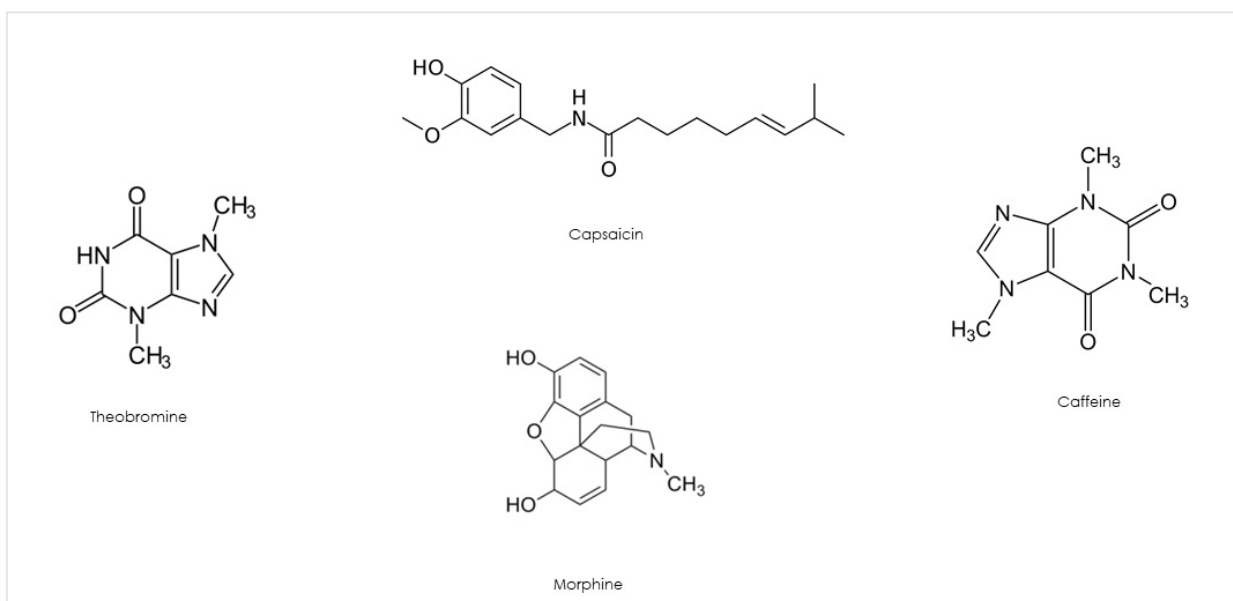
SOURCE: Adapted from Silva et al. (2020).

2.4 Biological action of functional oils on the animal organism

2.4.1 Anti-inflammatory action

2.4.1.1 Inflammatory processes

Inflammation and oxidative stress are correlated events in the animal organism. The inflammatory response is induced from exogenous or endogenous signals. The exogenous signals are linked to pathogen-associated molecular patterns (PAMPs), which are for example lipopolysaccharides and exotoxins. PAMPs are recognized by the host organism through receptor recognition patterns (PRRs), such as Toll-like receptors (TLRs). Endogenous signals are the damage-associated molecular patterns (DAMPs) that are produced when a tissue or organ is stressed or damaged. Among these endogenous factors are oxidized lipoproteins (LPO) (MEDZHITOV, 2008).

From the initial signaling of the inflammatory process, the immune system is recruited to contain the damage. Normally, the immune response consists of the innate

response and the adaptive response. In this review the focus will be only on the innate response, which aims to provide immediate protection against pathogens or tissue damage (VAN DYKE; KORNMAN, 2008). The innate response initiates with the recognition of the initial inflammatory triggers (PRRS, DAMPS) by macrophages. The macrophages release cytokines, chemokines, and inflammatory mediators that induce an increase in inflammatory transcription factors, such as NF-κB. In this process there is also a recruitment of neutrophils. In the neutrophils the enzyme xanthine oxidase and the TLR4 will induce the production of reactive oxygen species (ROS) in order to eliminate the pathogen and resolve the inflammation (LORNE et al., 2008). When inflammation is not controlled, the excessive release of ROS, and the incapability of neutralization by the antioxidant system, leads to oxidative stress, increased translocation of NF-κB, and the death of neutrophils, amplifying the inflammatory response, and potentially triggering chronic inflammation (WINTERBOURN; KETTLE; HAMPTON, 2016).

2.4.1.2 NF-κB pathways

In the inflammatory process, the activation of the NF-κB pathway is a determining factor, and for this reason it has been widely studied. NF-κB is a protein that represents a family that is involved with the transcription of genes responsible for the inflammatory response (OECKINGHAUS; GHOSH, 2009) such as IL-1, IL-6, iNOS, and COX-2 (ROTHSCHILD et al., 2018). In mammals this family is composed of five members, and the most present and abundant in cells is RelA, also called p65 (ZHANG et al., 2015). NF-κB activation has two signaling pathways: the non-canonical pathway and the canonical pathway. The canonical pathway responds to a diversity of stimuli from different immune receptors such as: cytokines, growth factors, microbial components, and stressors (ISRAEL, 2010). The primary mechanism for this activation is the degradation of the inhibitory protein IkBα, which is triggered via a complex of multiple subunit IκB kinase (IKK). After phosphorylation of IkBα the NF-κB makes a rapid translocation to the nucleus, to stimulate gene transcription (SUN; LEY, 2008).

There are several therapeutic strategies to inhibit the signaling activity of this transcription factor, these are: I. inhibition of IKK activity; II. inhibition of protease activity;

III. inhibition of nuclear translocation; IV. inhibition of DNA binding (LIU et al., 2017). Some bioactive metabolites present in functional oils have specific function on the NF-κB pathway, controlling the inflammatory response. The group of terpenes, for example, specifically inhibit IKK and prevent the degradation of Ikα (LIU et al., 2017; LUCCA et al., 2018). The anti-inflammatory action of 32 metabolites belonging to the group of terpenes, through the inhibition of the NF-κB pathway, was widely discussed by Silveira e Sá et al. (2013). In this study, the authors concluded that terpenes act by decreasing the concentrations of ROS and inflammatory cytokines such as TNF-α, IL-1β, and IL-6, demonstrating great potential to act as an anti-inflammatory drug.

This mechanism of anti-inflammatory action occurs not only systemically, but also in the gut mucosa. Phenolic compounds, for example, can suppress the TLR4 receptor pathway in the gut, decreasing the production of pro-inflammatory cytokines induced by NF-κB. The excessive production of pro-inflammatory cytokines causes damage to the gut mucosa, including increasing its permeability. These effects have implications for modulation of the gut microbiota, since the integrity of the mucosa and the activity of the gut-associated immune system interfere with eubiosis (LI et al., 2021). Both the action of terpenes and the action of polyphenols on the NF-κB pathway are demonstrated in figure 7. In the same way that the nuclear transcription factor NF-κB acts by transcribing inflammatory genes, another transcription factor, Nrf2 acts in the opposite pathway, playing a role in protecting the endothelium against ROS damage (CHEN et al., 2006). Terpenes and phenolic compounds are able to induce the activation of Nrf2 (AMES-SIBIN et al., 2018) regulating positively the antioxidant response.

FIGURE 6 – ACTION OF TERPENES AND POLYPHENOLS AS INHIBITORS OF NF-ĸB PATHWAY
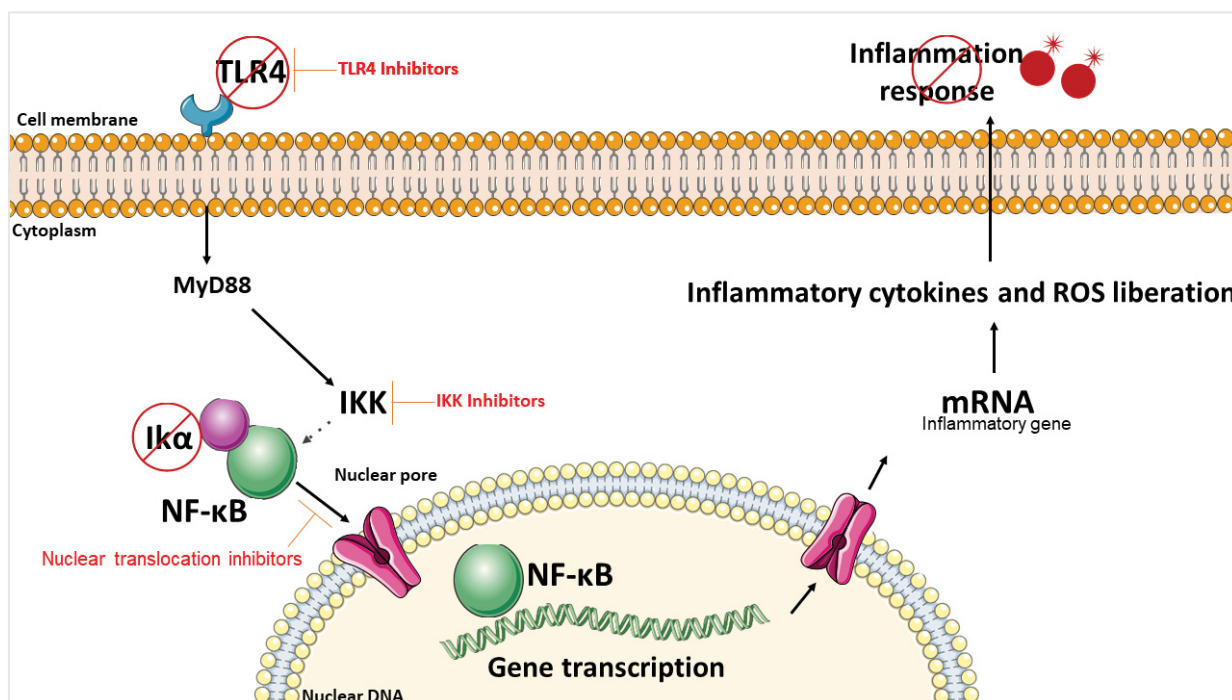
SOURCE: Adapted from Liu et al. (2017).

2.4.2 Antioxidant action

The antioxidant activity of functional oils is related to their capacity to act as an anti-inflammatory agent. A significant amount of ROS is produced by monocytes, neutrophils, eosinophils, and macrophages through the process of bacterial phagocytosis (SOEHNLEIN et al., 2017). In addition, ROS are involved in modulating the transcription factors Nrf2 and NF-ĸB, which are involved in the expression of important cytokines (SUN; LEY, 2008). Thus, through the inhibition of these transcription factors, functional oils may be able to decrease the production of ROS, reducing oxidative tissue damage. However, besides this indirect action on the production of free radicals through the anti-inflammatory action, bioactive metabolites also have a direct antioxidant action through some mechanisms of action: I. Oxireduction, the bioactive compounds of functional oils have free radical scavenging action, produced during metabolism, preventing the formation of superoxide anions, hydroxyl anions, and lipid peroxides (CALLEJA et al., 2013). This

effect occurs by the oxireduction ability of bioactive compounds, such as phenolic compounds for example, where an H^+ atom from the hydroxyl group of the aromatic structure is donated to the free radical. This mechanism is represented in figure 7. II.Sparing consumption of endogenous antioxidant enzymes. As a consequence of the free radical scavenging action, bioactive compounds promote less degradation of endogenous antioxidant enzymes (ERYIGIT et al., 2017). The endogenous antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH), and glutathione transferase (GST) are an important part of the antioxidant system and act together with the GSH system, contributing to oxidative balance (Figure 8). SOD acts by transforming two superoxide radical anions into hydrogen peroxide. CAT transforms hydrogen peroxide into water and oxygen (MASELLA et al., 2005). GSH cycles between its oxidized (GSH Px) and reduced (GSH- Rd) form catalyzes the dismutation of hydrogen peroxide into water and oxygen (MASELLA et al., 2005). GST is an enzyme that has high specificity for GSH. GST plays a physiological function in triggering the detoxification of pharmacologically active compounds, which are generated intracellularly or present in the form of xenobiotics. The GST-catalyzed conjugation reaction of glutathione with xenobiotic compounds turns the compounds in the reactions less toxic and more soluble in water, facilitating their excretion (WHEATLEY et al., 1994). Some studies evaluating the levels of cellular activity of endogenous enzymes have observed that bioactive compounds are able to stimulate the activity of these enzymes such as SOD, CAT, and GST (CAMPOS et al., 2021; ERYIGIT et al., 2017; MORAIS et al., 2010).III. The chelation of metal ions such as iron, copper, chromium, and cobalt by polyphenol compounds prevents oxidative damage (SÁNCHEZ-VIOQUE et al., 2013). Pro-oxidative metals in excess react with reactive compounds such as the superoxide anion radical, and nitric oxide, which leads to oxidative stress which is responsible for lipid peroxidation, DNA damage, protein modification, and other effects (Figure 8). IV. Some bioactive compounds are capable of suppressing a variety of pro-oxidant enzymes involved in the production of ROS, preventing oxidative damage in cells (TREVISAN et al., 2006). Among these enzymes is the xanthine oxidase, responsible for the metabolism of uric acid, which is one of the main producers of superoxide anions and hydrogen peroxide (MASUOKA; KUBO, 2004; TREVISAN et al., 2006). Xanthine oxidase is formed from xanthine dehydrogenase

under oxidative conditions. This enzyme catalyzes the oxidation of hypoxanthine to xanthine and uric acid (BRAY 1975; PORRAS et al., 1981). Superoxide anion and hydrogen peroxide are formed from oxygen. The reaction progresses and depending on the oxidation state of the xanthine oxidase, more superoxide anions and hydrogen peroxide are generated, causing cell damage (EPSTEIN; MCCORD, 1985; FONG et al., 1973) (Figure 9).

FIGURE 7 – MECHANISMS OF FREE RADICAL SCAVENGING OF FUNCTIONAL OILS
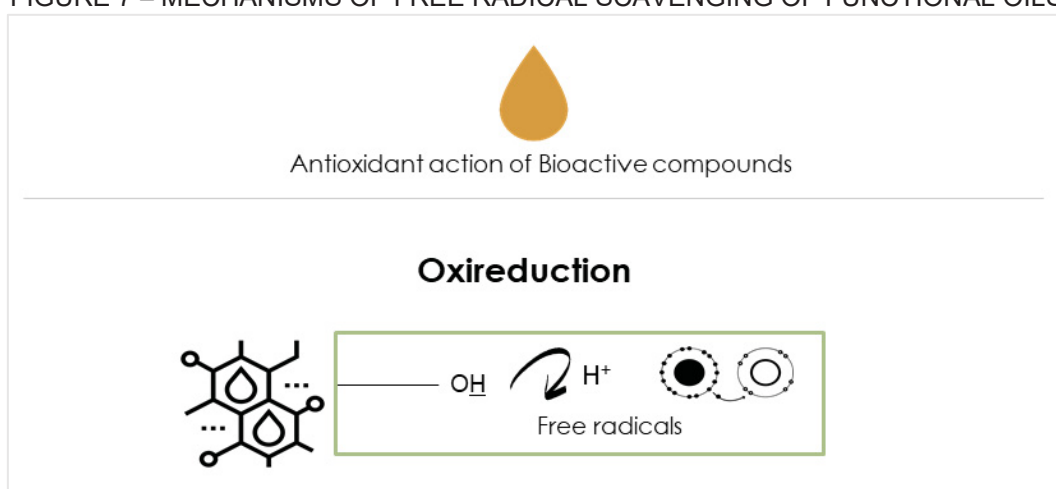
SOURCE: Trevisan et al. (2006).

FIGURE 8 – CHELATION OF METAL IONS THAT PARTICIPATE IN THE REACTIONS OF THE ENZYMATIC ANTIOXIDANT SYSTEM

SOURCE: The author (2023).
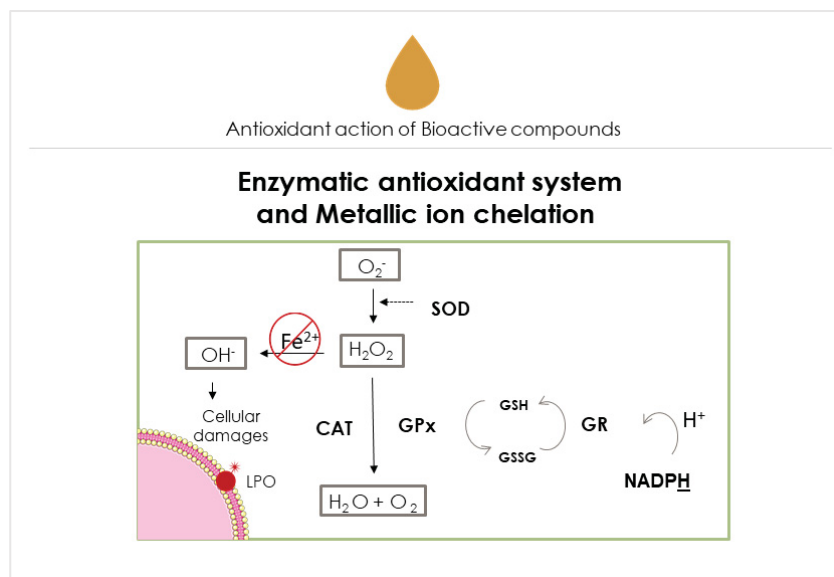
FIGURE 9 – REPRESENTATION OF THE INHIBITION OF THE XANTHINE OXIDASE ENZYME

SOURCE: The author (2023).
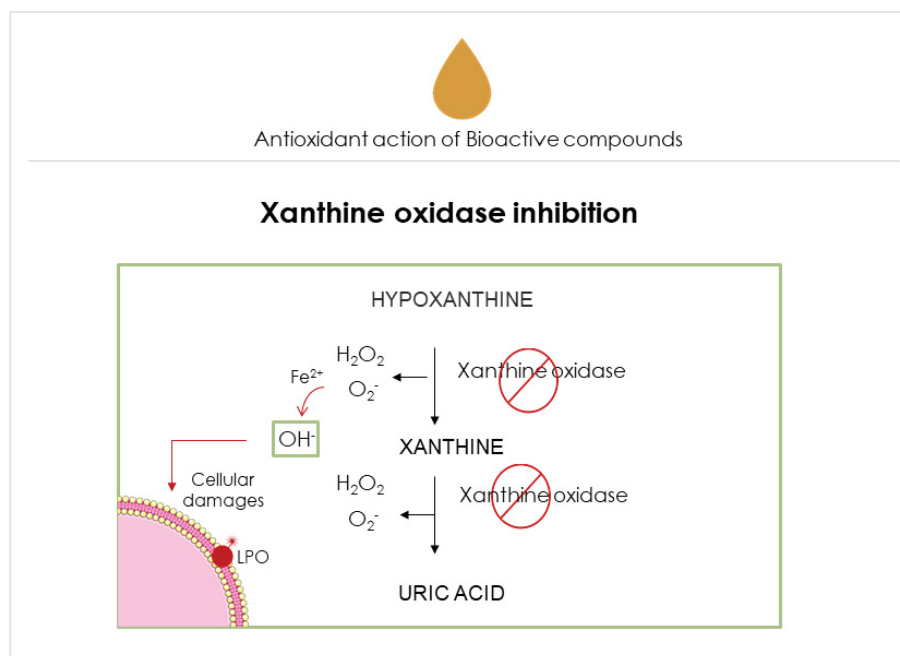
2.4.3 Gut microbiota modulation action

The gut microbiota communicates with inflammatory metabolic and oxidative stress pathways through direct and indirect mechanisms. As physiological changes in these three axes are cross-regulated, the gut microbiota can be influenced by the anti-inflammatory action of bioactive compounds present in plants (LI et al., 2020).

In addition to this indirect modulating action, bioactive compounds such as polyphenols and terpenes have antimicrobial characteristic and can alter the composition of the gut microbiota (BURT, 2004; LI et al., 2018). Considering that functional oils have different compounds, there is agreement that their antibacterial activity is not attributable to one specific mechanism, but to several cellular targets (Figure 10). Moreover, the mechanisms do not act separately, but may act as a consequence of others (CARSON; MEE; RILEY, 2002; SKANDAMIS et al., 2001). One of the most discussed modes of action is related to the hydrophobicity of plant compounds, which act on the lipids of the cell membrane of potentially pathogenic bacteria, such as *Clostridium perfringens*, for example (FRIEDMAN; JUNEJA, 2010). This mechanism makes the membrane more permeable, causing leakage of ions and other cell contents, leading to cell death (BURT, 2004; CARSON; MEE; RILEY, 2002; SKANDAMIS et al., 2001). Gram-positive bacteria are more susceptible to this action (BURT, 2004; TIWARI et al., 2009). Gram-negative bacteria have a hydrophilic membrane of lipopolysaccharides creating a barrier to functional oils, which are hydrophobic, which gives more resistance to this type of bacteria (HUQ et al., 2014).

Some studies report this modulating activity that functional oils have on the gut microbiota of domestic animals. Ruzauskas et al. (2020) demonstrated that pigs fed a combination of terpenes had lower abundance of the genus *Streptococcus* spp. This genus, when increased, is related to intestinal dysbiosis and inflammatory bowel disease in dogs (ALSHAWAQFEH et al., 2017). Also in pigs, by investigating the composition of the microbiota of weanling piglets, Li et al. (2018) observed that the group fed a mixture of carvacrol and thymol essential oils showed higher abundance of genera considered beneficial for the species. In dogs, an extract rich in polyphenols obtained from green tea

also provided a modulating effect on the microbiota, increasing bacteria considered beneficial that belong to the phylum firmicutes (LI et al., 2020).

Despite the results, it is important to consider that the antimicrobial action of functional oils depends on factors such as the minimum concentration and chemical structure of the compounds that are present. Some studies show that oils with higher concentration of phenolic compounds have greater antimicrobial activity (DORMAN; DEANS, 2000). Furthermore, there are investigations related to the presence and positioning of hydroxyl in the phenolic structure, demonstrating that according to the positioning of the ring, the bioactive compound may have different action on gram-positive and gram-negative bacteria (DORMAN; DEANS, 2000).

FIGURE 10 – LOCATIONS AND MECHANISMS OF FUNCTIONAL OILS IN THE BACTERIAL CELL
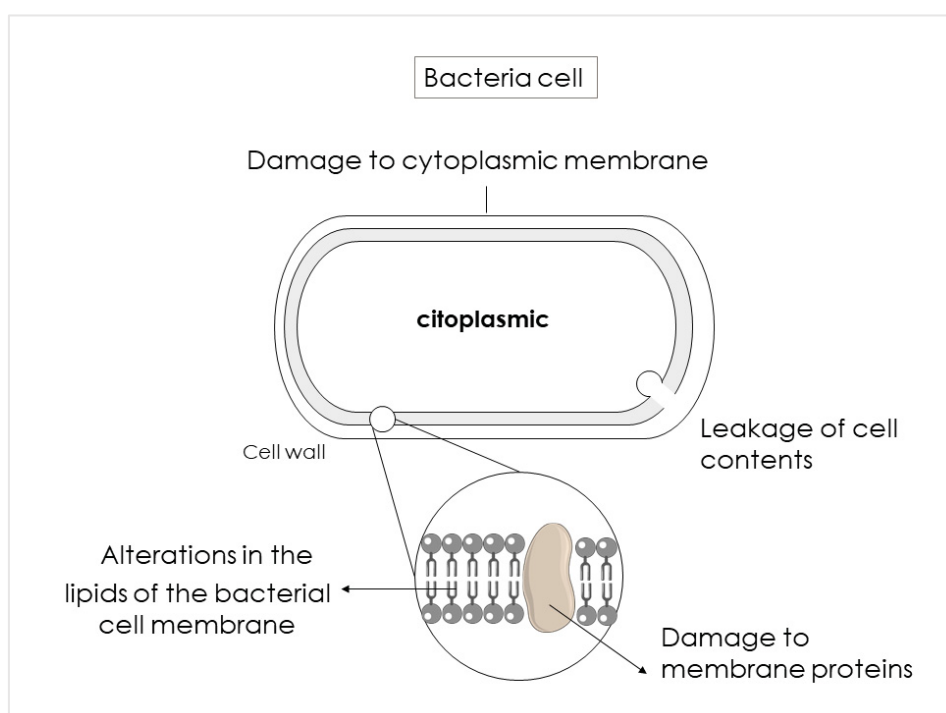
SOURCE: Adapted from Burt (2004).

In addition to the action of secondary metabolites on the gut microbiota, through anti-inflammatory and antimicrobial activity, some bioactive compounds of functional oils

have potential to stimulate the digestive system. Physiologically, proteins are digested in the stomach and small intestine, resulting in only small amounts of proteins reaching the large intestine (QAISRANI et al., 2015). When the proteins reach the distal segments of the gastrointestinal tract, the amino acids are fermented by proteolytic bacteria, producing compounds such as ammonia, amines, and branched chain fatty acids (RÍOS-COVIÁN et al., 2016). If protein digestion does not occur efficiently, these compounds are produced in excess, and can be toxic to the gut mucosa (BLACHIER et al., 2007), and also contribute to the odour of feces (WINDEY; DE PRETER; VERBEKE, 2012).

According to Mellor (2000) some bioactive compounds, such as capsaicin for example, have the capacity to stimulate gastric and pancreatic enzymatic activity. Moreover, there is evidence that some bioactive plant compounds also stimulate the secretion of saliva, mucus and bile, contributing to intestinal functionality (PLATEL & SRINIVASAN, 2004). This action on digestion, by increasing the action of enzymes, such as pancreatic proteases and pepsin, optimizes the digestion of proteins, reducing the substrate for proteolytic bacteria. This fact modulates the composition of the microbiota, since some proteolytic bacteria, such as *Clostridium perfringens* for example, can be potentially pathogenic (SUCHODOLSKI et al., 2012). Furthermore, there is a correlation between increased proteolytic bacteria and decreased abundance of bacteria considered beneficial such as *Lactobacillus* and *Bifidobacterium* (ALESSANDRI et al., 2019). Also, the increase in mucus production stimulated by functional oils, can decrease the adherence of pathogenic bacteria to the intestinal mucosa, indirectly modulating the gut microbiota (FRANZ; BASER; WINDISCH, 2010).

2.5 Oils from Brazilian biodiversity

2.5.1 Copaiba oil-resin

Copaiba oil-resin is a light yellow-brown exudate extracted from the trunk of the Copaifera tree (Figure 11), consisting of a non-volatile resinous part and a portion of volatile compounds. Copaifera is a tree of the genus *Copaifera* L., family Leguminosae, commonly distributed in regions of the African continent and in tropical and subtropical

regions of Latin America. The trunk of the Copaiba tree, from where the oil is extracted, has aromatic bark and can measure up to 0.4 to 4 meters in diameter. There are 72 described species of Copaiba, 16 of which are located exclusively in Brazil. The largest concentration of trees is in the Amazonas and Pará states (VEIGA JUNIOR; PINTO, 2002), making this region the main commercial producer of Copaiba oil. Among the species belonging to the Brazilian flora, the most prominent are *Copaifera officinalis* L.; *Copaifera reticulata* Ducke; *Copaifera multijuga* Hayne; *Copaifera langsdorffii*; and *Copaifera cearensis* Huber ex Ducke (PIERI; MUSSI; MOREIRA, 2009; VEIGA JUNIOR; PINTO, 2002).

The extraction of the oil-resin of copaiba must be performed using the correct technique, to avoid damaging the tree permanently. The trunk must be drilled with an auger of approximately 2 meters in diameter, in two holes (Figure 11). To obtain the oil, a PVC pipe is inserted into the hole, through which the oil flows. After the extraction is complete, the hole is closed with a sealing cover that is easy to remove, or with clay, so that the hole can be used for other harvests (VEIGA JUNIOR; PINTO, 2002).

The concentration of bioactive compounds present in copaiba oil-resin can vary according to: tree species, biological factors (presence of insects and fungi) or abiotic factors such as light, solar radiation, temperature and soil composition (OLIVEIRA et al., 2006). Despite this variation, studies conducted with different resin-oils show that the pharmacological properties have remained the same (VEIGA et al., 2007) because there is a common pattern in the main compounds found. About 80% of the substances found in oil-resins are sesquiterpenes and 20% are diterpenes. Among the volatile sesquiterpenes, the most present is β-caryophyllene, corresponding to about 50% of the compositions. Among the diterpenes, copalic acid predominates, and its concentration varies among copaiba species (LUCCA et al., 2018; VEIGA et al., 2007). Table 2 shows some of the main compounds present in copaiba oil-resin.

Several pharmacological properties are attributed to these bioactive compounds such as: anti-inflammatory effect (CARVALHO et al., 2005; VEIGA et al., 2007) , analgesic (CARVALHO et al., 2005), antimicrobial (PIERI; MUSSI; MOREIRA, 2009), and anti-tumor properties (LIMA et al., 2003).

2.5.1.1 Anti-inflammatory activity of the Copaiba oil-resin

Although β-caryophyllene is not the only compound present in copaiba oil-resin with anti-inflammatory action, it is the main compound responsible for this action (AMES-SIBIN et al., 2018).

Studies show that β-cariophyllene can negatively regulate the expression of cyclooxygenase 2, tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and IL-1β in models of neuroinflammation *in vitro* and *in vivo*. This is because this compound alone, as well as in conjunction with copaiba oil-resin, is able to inhibit the NF-κB pathway through a mechanism involving the activation of cannabinoid receptor (CB2) (GUO et al., 2014; LUCCA et al., 2018; OJHA et al., 2016). This effect was proven by Ames-Sibin et al. (2018) who observed a reduction in liver metalloproteinases, which activity is an indicator of polymorphonuclear cell infiltration. Similarly, a study evaluating both *in vitro* inflammatory parameters and the effect of copaiba oil-resin via oral and topical administration in humans with chronic psoriasis, observed neutralization of NF-κB translocation and reduced pro-inflammatory cytokine release, as well as a reduction in the characteristic clinical signs of the disease with doses of 0.1 to 10 µM of the oleoresin from *Copaifera langsdorffii* Delf.(GELMINI et al., 2013).

2.5.1.2. Antioxidant activity of copaiba resin oil

With regard to antioxidant capacity, it is possible that copaiba oil-resin acts by reducing oxidative stress through three main mechanisms already described in this review: I. Reduction of the inflammatory process, II. Stimulation of the endogenous antioxidant system III. Scavenging of free radicals (CALLEJA et al., 2013; OJHA et al., 2016)

These mechanisms were demonstrated in a study evaluating the isolated action of 430 mg/kg of β-caryophyllene, demonstrating reduction of ROS and increase of GSH (AMES-SIBIN et al., 2018), and in a study using the oil-resin of *C. reticulata* Ducke, demonstrating reduction of oxidative stress in rats with induced colitis (BARBOSA et al., 2018). Similarly, a study using Wistar rats as experimental models of skin flaps to simulate

necrosis caused by ischemia and reperfusion syndrome, showed increased GSH activity and reduced thiobarbituric acid-reactive substances (TBARS) when supplemented with *Copaifera langsdorffii* Desf resin oil (DE LIMA SILVA et al., 2009).

2.5.1.3 Antimicrobial activity

This action is related to the combination between sesquiterpenes and diterpenes of copaiba oil-resin and occurs through the loss of integrity of the bacteria cell wall (LIMA et al., 2003; SANTOS et al., 2008).

This antimicrobial action has been demonstrated on many pathogens, including gram-negative and mainly gram-positive bacteria, such as *Staphylococcus* spp. (ALENCAR et al., 2015) and *Streptococcus* spp. (SIMÕES et al., 2016). In dogs, a study using topical oral copaiba oil (10ml) (PIERI et al., 2010) demonstrated an effect against the bacteria: *Streptococcus salivarius*, *Streptococcus pyogenes* and *Enterococcus faecalis*, potential causes of periodontal disease in this specie. Furthermore, the use of oil-resin from *Copaifera reticulata* Ducke exercised bacteriostatic and bactericidal activity even in multidrug-resistant strains of coagulase-positive *Staphylococcus* isolated from dogs with external otitis (ZIECH et al., 2013).

Many of these medicinal properties were previously known by the indigenous population and the people who live in the northern, northeastern, and mid-western regions of Brazil. For this reason, the topical and oral use of the oleoresin is considered popular. However, despite the cultural use, scientific investigations, and support from researchers in the processes of extraction and characterization of the oils and their properties are necessary. This is currently in progress at the regional federal universities and institutions such as a Brazilian Agricultural Research Corporation (EMBRAPA).

FIGURE 11 – COPAIBA TREE (*COPAIFERA LANGSDORFFII*); AUGER DRILLING, OIL RESIN

SOURCE: Pieri (2009); https://www.gentedeopiniao.com.br/meio-ambiente/oleo-de-copaiba-riqueza-da-amazonia-e-do-brasil; https://blog.useorganico.com.br/conheca-os-beneficios-e-usos-do-oleo-vegetal-de-copaiba/

2.5.2 Cashew nut shell oil (CNSL)

Cashew (*Anacardium occidentale* L.) belongs to the family *Anacardiaceae* and is a native plant of northeastern Brazil. Although it can be found in other regions of South America like Colombia, Costa Rica, Honduras, El Salvador and in other continents like Asia and Africa.

The cashew tree has several functionalities, both food and pharmacological. The cashew consists of the pseudo-fruit (peduncle) of yellow to red color, and the nut, its true fruit (Figure 12) (PAIVA et al., 2000).

The cashew nut is an aquenium fruit and consists of three parts: shell, skin and almond. The shell is rigid and straight. The region between the kernel and the shell, called mesocarp, has a spongy and alveolar structure, which contains a viscous, caustic, dark brown oil, known as cashew nut shell liquid (CNSL), considered a by-product of low added value, which represents 25% of the weight of the nut (MAZZETTO; LOMONACO; MELE, 2009; PAIVA et al., 2000).

From the cashew nut processing, the kernel and the shell are obtained, which are the raw material for the production of the CNSL. After the extractive industrial process, 18% of CNSL and 55% of a "residual cake" is obtained, which is used as a combustible in boilers (PAIVA, 2010). The CNSL is a natural source of phenolic lipids, such as anacardic acid, cardanol, cardol and metylcardanol (MAZZETTO; LOMONACO; MELE, 2009).

Different processes can be used to obtain the CNSL: cold extraction (presses), solvent extraction, supercritical CO_2 extraction and thermal-mechanical process (hot oil process) (CORREIA; DAVID; DAVID, 2006; PHANI KUMAR et al., 2002). In the hot oil process, generally employed in industrial scale factories, the hot CNSL is used as a vehicle to heat the raw nuts to approximately 190°C. In this way, the outer shell is ruptured, which releases the alkylphenols present in the mesocarp, followed by the removal of the shell, which allows the recovery of almonds (PATEL; BANDYOPADHYAY; GANESH, 2006). When subjected to high temperatures (180° C), the anacardic acid undergoes a reaction of decarboxylation converting to cardanol, producing the called CNSL technical (MAZZETTO; LOMONACO; MELE, 2009)

According to the extraction method, the composition of the CNSL changes. The natural CNSL contains a high quantity of anacardic acid, and does not present polymeric material in its composition. However, the technical CNSL showed a high percentage of cardanol and also polymeric material, present in all samples analyzed (GEDAM; SAMPATHKUMARAN, 1986).

Although the almond is the part of the cashew tree that is considered the most famous and which generates the most money, the CNSL has several industrial applications, such as paints, varnishes, resins, insulators and pharmacological applications (LUBI; THACHIL, 2000). Regarding pharmacological activities, phenolic lipids present in CNSL apparently exhibit activities: antitumoral (CORREIA; DAVID; DAVID, 2006; WU et al., 2011), antioxidant, (KUBO et al., 2006; STASIUK; KOZUBEK, 2010; TAN; CHAN, 2014), antibacterial, gastroprotective and anti-inflammatory (HAMAD; MUBOFU, 2015). In a recent study, Sahin et al. (2022) showed that phenolic lipids from CNSL have the potential to modulate PPAR α and γ transcription factors, and may be favorable for the treatment of obesity and diabetes.

2.5.2.1 Anti-inflammatory and antioxidant activity of CNSL

Regarding anti-inflammatory activities, the CNSL compounds can prevent the release of TNF-α, decrease the gene expression of cytokines, and enzymes, such as prostaglandin synthase and lipoxygenase, through the inhibition of the NF-κB pathway (PARAMASHIVAPPA et al., 2001).

The cashew shell liquid also has antioxidant properties, mainly due to the presence of anacardic acid. Its phenolic structure has capacity of oxireduction, donating hydrogen, removing the ROS, in addition to inhibiting the pro-oxidative enzyme xanthine oxidase (TREVISAN et al., 2006).

These actions were proven by Souza et al. (2018) analyzing the phenolic lipids present in CNSL. Through in vitro assay, the authors demonstrated that CNSL reduced the gene expression of inflammatory markers and the production of nitric oxide and IL-6. Another study, with an animal model, evaluated the effect of anacardic acid, extracted from the CNSL. The authors evaluated anti-inflammatory and antioxidant parameters in rats that received an intraperitoneal dose of compounds causing inflammation and edema. The authors of the mentioned study observed that the animals that received the dose of anacardic acids before the induction of edema, showed reduced migration of leukocytes and neutrophils to the intraperitoneal cavity, lower concentration of malondialdehyde (MDA - a parameter to measure oxidative stress) and increased levels of GSH. In nociceptive tests, anacardic acids also decreased licking, abdominal contortions and latency to thermal stimulation, possibly via interaction with opioid receptors (GOMES JÚNIOR et al., 2020).

2.5.2.2 Antimicrobial activity of CNSL

The antimicrobial properties of CNSL are due to the high quantity of anacardic acid in its composition. As they are amphiphilic molecules, they act on the lipoprotein membrane of bacteria (BURT, 2004).

This action has already been demonstrated in broilers, supplemented with CNSL, showed control of proliferation of intestinal *Escherichia coli* (LÓPEZ et al., 2012). Also, broilers challenged with *Eimeria* showed a lower impact on the gut microbiota when fed a mixture of CNSL and castor oil (0.15% of the blend) (VIEIRA et al., 2020). In pigs, the association of CNSL with Castor oil has been shown to benefit the intestinal functionality of nursery piglets by increasing potentially beneficial bacteria and reducing potentially pathogenic bacteria in the jejunal mucosa. In addition to maintaining villus height, without affecting overall growth performance (MOITA et al., 2021).

FIGURE 12 – CASHEW APPLE (FRUIT), NUT AND SHELL. LONGITUDINAL SECTION OF CASHEW NUTS.
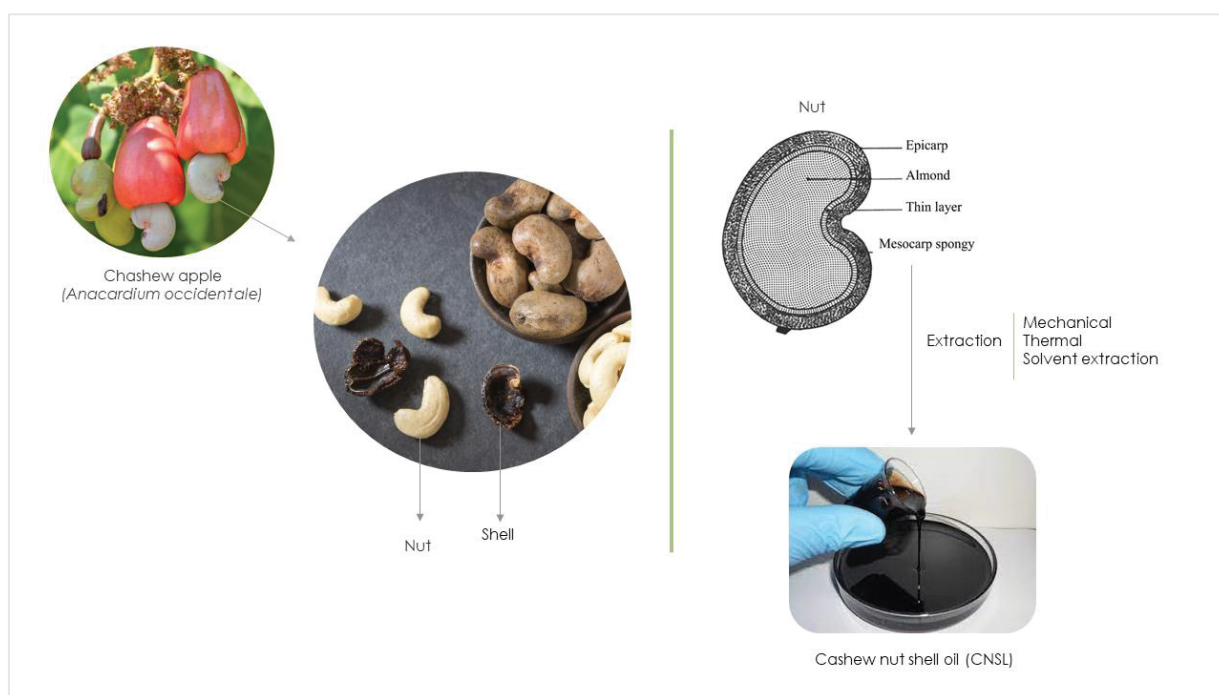
SOURCE: Adapted from Soares (1986)

2.5.3 Oil from the pepper specie *Schinus molle* L.

Pink pepper, mastic, or red mastic fruit are the names used for *Schinus molle* L., a plant from the family Anacardiaceae, which includes about 30 species. *Schinus molle* L.

is native to southern Brazil but is distributed in several countries in Central and North America.

The essential oil can be extracted from the fruit or leaves of *Schinus molle* L. by hydrodistillation or steam distillation. This oil is rich in monoterpenes such as: β-felandrene, α-felandrene, myrcene, limonene and α-pinene (ZAHED et al., 2011).

Its bioactive compounds exhibit antioxidant, antimicrobial, anti-inflammatory, anti-parasitic, anti-viral and anti-allergic action (EL-NASHAR et al., 2022; ERYIGIT et al., 2017) (Figure 13). In addition, the use of *Schinus molle* L. essential oil is known for its larvicidal effect against *Rhipicephalus sanguineus* and *Aedes Aegypti* (BITENCOURT et al., 2022; REY-VALEIRÓN et al., 2018).

2.5.3.1 Anti-inflammatory, antioxidant activity of *Schinnus molle* L.

To the compound α-pinene is attributed the anti-inflammatory capacity of pink pepper oil. This compound attenuates inflammation by inhibiting NF-κB. This action has already been demonstrated in mice with induced allergic rhinitis. The animals treated with α-pinene showed improvement in clinical signs, and reduced levels of TNFα, IL-1, and IgE. In addition, the compound was able to inhibit IκB kinase (IKK)-β and nuclear factor-κB (NF-κB) activation in mast cells (NAM et al., 2014). The antioxidant action of this oil is due to its ability to eliminate free radicals, as demonstrated by Eryigit et al. (2017) who observed free radical reduction through Trolox Equivalent Antioxidant Capacity (TEAC).

2.5.3.2 Antimicrobial activity and gut functionality

Due to the presence of terpenes as bioactive compounds, the oil of *Shinus molle* L. seems to exhibit antimicrobial activity (BURT, 2004). An in vitro study demonstrated antimicrobial capacity of *Schinnus molle* L. on *Staphylococcus* spp. and *Streptococcus* spp. bacteria which caused periodontal disease in dogs (ALVES et al., 2020). Another study, however, *in vivo*, using orange essential oil, which main active compound is limonene, also present in *Schinnus molle* L, achieved interesting results in the intestinal functionality of broiler chickens. The authors observed improvement in feed efficiency and

intestinal morphometric change, characterized by increased villus height in the jejunum (SOUZA et al., 2021). Similarly, Silva et al. (2011) also observed improvement in the intestinal absorptive surface of broilers fed with 0.4% essential oil of *Schinnus molle* L.

2.5.4 *Capsicum annuum* L. oil-resin

The species *Capsicum annum* L. is a member of the *Solonaceae* family and is one of the five most commercialized pepper species in the world. Of the well-known pepper genera, *C. annuum* is the pepper with the most variation in shape, size and color of its fruits, so its botanical identification can be difficult (PERRY et al., 2007). The *Capsicum* genus has a diversity of chemical compounds, such as: capsaionoides, carotenoids, flavonoids, vitamins and minerals (GÓMEZ-GARCÍA; OCHOA-ALEJO, 2013). Due to its characteristic flavor and odor, and the variety of phytochemicals in its composition, the use of its fruits and seeds is widely used as raw material for food and pharmaceutical agroindustries.

Pepper plants, since they are specialties, are subject to microbial and insect contamination (KURMUDLE et al., 2013). As an alternative to this, many food industries use oil resin as raw material to produce of sauces, snacks, instant noodles and meat products, instead of chili peppers *in natura* (ATTOKARAN, 2011). This is because the oil-resin ensures more stability and biological control, since they are composed of little amount of water. Also, the use of oil-resin, because it is a concentrated product, requires fewer logistics of transport and storage, and gives uniformity of color, flavor and odor to the food. In addition, it is possible to dilute oil according to the type of food produced. This alternative, in addition to benefits for industries, such as the commercialization of excess oil-resin, also provides better use of raw material that is out of specification for consumption *in natura* (FERNÁNDEZ-RONCO et al., 2013).

From a pharmacological point of view, the oil-resin is a rich source of bioactive compounds of great availability and has many applications for pharmaceutical industries. Extraction of the resin oil can be done by supercritical fluids or organic solvents and filtration (KURMUDLE et al., 2013).

The functional oil of *Capsicum Annum* L. presents as its main bioactive compound the capsaicin (8-methyl-N-vanillyl-6-nonenamide), belonging to the group of alkaloids, followed by the capsinoids dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin (PERRY et al., 2007). Their main functions are: antipruritic, anti-inflammatory, antiapoptotic, anticancer, antioxidant, and neuroprotective functions (ADASZEK et al., 2019; ANAND; BLEY, 2011; BAENAS et al., 2019; BOGUSZ et al., 2018; CHUNG; CAMPBELL, 2016) (Figure 13).

2.5.4.1 Mechanisms of capsaicin action

The mechanisms of action leading to the pharmacological effects attributed to Capsaicin are complex and involve the activity of transient receptor potential vanilloid (TRPV1) ion channels. TRPs are a family of cation channels that are non-selective of several different stimuli such as, temperature, pH, ROS production, osmotic stress, and bacterial toxins (BUJAK et al., 2019). In addition, their activity can be regulated by some phytochemicals such as capsaicin (NILIUS; OWSIANIK, 2011). TRPs are present in various tissues of the human and animal body, and recent findings have shown their expression also in immune cells, such as dendritic cells, macrophages or T lymphocytes (WANG; SIEMENS, 2015). Thus, it is known that the TRPV1 canal is not only involved in thermal and pain sensation, but also in other physiological processes (SZALLASI et al., 2007).

Regarding pain control, according to Adaszek et al. (2019) capsaicin, after binding to the TRPV1 receptor, causes the opening of the cation channels. This results in the active potential of cations flowing into the cell and depolarizing it. This results in the active potential being passed to the spinal cord and is responsible for the sensation of heat and pain. However, if the alkaloid is administered several times, the vanilloid receptor is desensitized and the conduction of pain stimuli to the spinal cord is blocked, resulting in pain relief. It has been proven that TRPV1, if exposed to capsaicin for a longer period, changes its spatial conformation and becomes inactivated. This means that the receptor is no longer stimulated, even if the activating stimulus is present (WINTER et al., 1995).

The role of TRPV1 in inflammation is not fully established yet. Studies have related an overexpression of these receptors in inflammatory diseases such as: obesity, diabetes, cancer, asthma, rheumatoid arthritis, and inflammatory bowel diseases (CSEKŐ et al., 2019; HSIEH et al., 2017; KIM, 2018;FENG et al., 2017). Similarly, the literature shows that there is suppression of inflammation with the use of substances binding these channels, such as capsaicin, which acts by suppressing COX2 formation (KOBAYASHI et al., 2012), probably by inhibiting the transcription factor NF-κB (KIM et al., 2003).

Besides the anti-inflammatory action, capsaicin also has antioxidant action, through the inhibition of nitric oxide (NO), which by reacting with superoxide anions, potentializing cellular oxidative damage (TSAI; TSAI; HO, 2005) In addition, phenolic compounds, also present in the functional oil of *Capsicum annum* L., have oxireduction capacity, scavenging free radicals (OLATUNJI; AFOLAYAN, 2019; SIM; SIL, 2008).

In veterinary medicine, capsaicin was widely used for pain control in racing horses (Seino et al.,2003). However, due to welfare reasons and to prevent injuries, capsaicin was banned by the International Equestrian Federation. In broilers, McElroy et al. (1994) and Orndorff et al. (2005) attributed to capsaicin antimicrobial effect, especially against *Salmonella.* Similarly, in ruminants, Capsaicin showed effects on rumen bacteria (CALSAMIGLIA et al., 2007). This action occurs due to the hydrophobicity of the phenolic group present in capsaicin (BURT, 2004).

In dogs, in a preliminary study, Adaszek et al. (2017) demonstrate that capsaicin supplemented via oral administration is well tolerated, and may have an anticancer effect, due to its antioxidant and antiproliferative actions.

FIGURE 13 – *CAPSICUM ANNUM* L. AND *SCHINUS MOLLE* L. AND THEIR MAIN PHARMACOLOGICAL EFFECTS
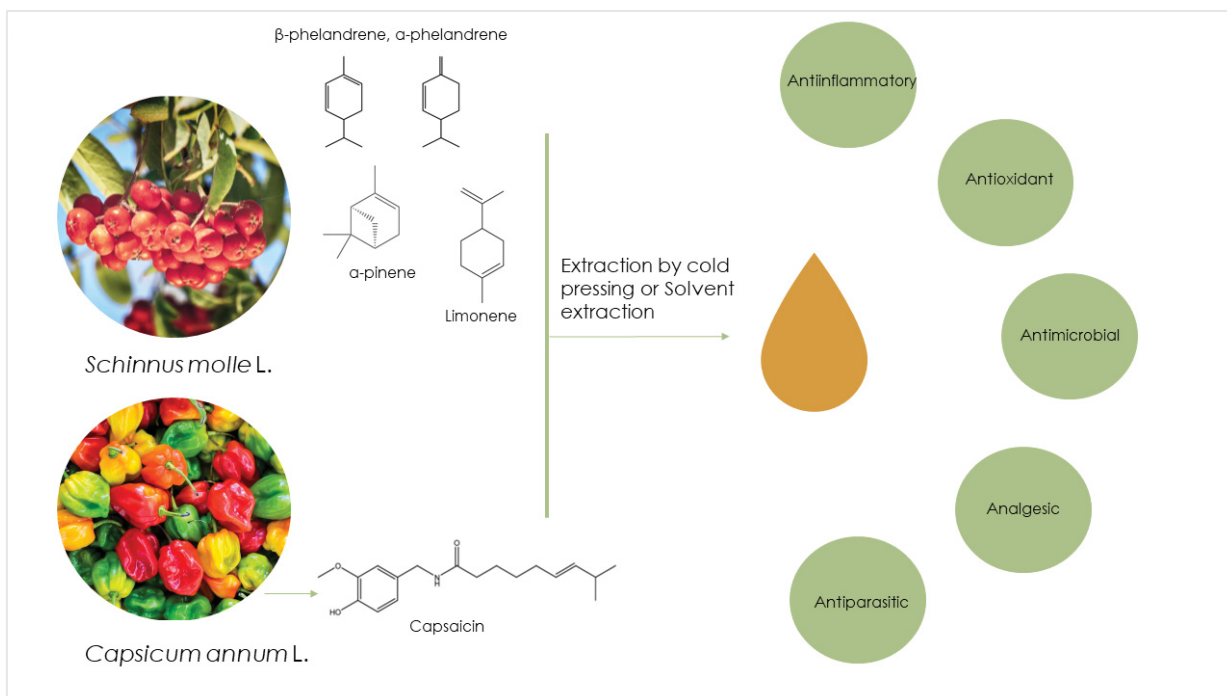
SOURCE: Adapted from Adaszek et al. (2017)

TABLE 2 – MAJOR BIOACTIVE COMPOUNDS PRESENT IN FUNCTIONAL OILS FROM BRAZILIAN BIODIVERSITY

Functional oil	Major Bioactive Compounds	References
Copaifera spp. oil-resin	β cariophyllene, β-bisabolene, α-bergamotene; δ-cadinene, α-humulene, α-copaene, β-sesquifelandreno, β-selinene, α-selinene,ciperene copalic acid, polyalthic acid, hardwickiic acid, clorechinic acid, kaurenoic acid, kolavenic acid	Aguilar et al. (2013); Lucca et al. (2008); Veiga e Pinto (2002); Veiga et al. (2007)
Cashew nut shell oil (CNSL)	Anacardic acids, cardanol, cardol, and 2-methylcardol	Mazzeto et al. (2009)
Schinnus molle L.	β-phellandrene, αphellandrene, myrcene, limonene, and α-pinene	Baser et al. (1997); Zahed et al. (2011); Eryigit et al. (2017)
Capsicum annum L.	Capsaicin,dihydrocapsaicin, nordihydrocapsaicin, homocapsaicin, and homodihydrocapsaicin	Perry et al. (2007); Adaszek et al. (2017)

SOURCE: The author (2023)

2.6 Legislation and Challenges

Concerning legislation, international regulatory organizations such as the Food and Drug Administration (FDA, 2015) and the Council of the European Union (Directive 70/524/EEC Cap. III) establish that functional oils and natural extracts are recognized as safe for use (GRAS – generally recognized as safe) (BURDOCK; CARABIN, 2004). In Brazil, there is a specific legislation (IN 42, law 6.198 of 26/12/1974) of the Ministry of Agriculture Livestock and Food Supply (MAPA), which regulates the inspection and supervision of ingredients used in animal feed. Because of this, some phytogenic compounds have already been released by MAPA, as flavoring additives (Normative ordinance No. 359, of July 9, 2021), bringing in not only benefits for animal health, but also competitiveness for the pet food industry. This is due to the fact that dog and cat tutors are increasingly interested in knowing the ingredients used in pet foods, showing preference for those denominated as functional (DI CERBO et al., 2017).

Despite the pharmacological effects and the support of legislation, some aspects of the use of functional oils in animal feed may need to be discussed more widely: I. According to the EC (European Community), all phytogenic additives, including herbs and functional oils must follow safety standards for animals, employees and the environment. The extraction of CNSL for example, despite being a co-product with wide applicability on different fronts, faces sustainability challenges to the environment and occupational health. This is because, in addition to the causticity of CNSL, the artisanal burning of cashew nut shells to fire the boilers of the mini-factories can lead to the inhalation of toxic compounds (DE OLIVEIRA GALVÃO et al., 2014) Therefore, procedures to ensure the safety of the employee and the knowledge and development of new extraction methods are important. II. Obstacles in evaluating published results. These difficulties occur especially when commercial products are used in experimentation. Some authors have difficulty in identifying and distinguishing between herbs, extracts, oil resins, essential oils, compounds isolated from essential oils, etc. In addition, botanical identification can be a challenge. An example of this are the many popular names given to the plants *Schinnus Molle* L. and *Capsicumm Annum*. L, as well as the dozens of species of the genus Origanum called Oregano. For this, the identification of bioactive compounds presents in

the functional oil, through gas chromatography, is essential. III. Observe environmental concerns. Regarding the copaiba oil-resin, although the oil extraction is one of the most traditional non-timber forest products extracted from the Amazon, there are gaps regarding its technique and frequency of extraction (SANTOS et al., 2011). Similarly, also considering a better use of the plant, and attempting to reduce the environmental impact, Chen and Kang (2013) evaluated the pharmacological activity of the stalks of pepper plants of the genus *Capsicum annum*. The extract of the stalks, which is usually discarded in rivers and landfills, contributing to environmental problems, showed higher antioxidant and anti-inflammatory effects than other parts of the fruit. This information highlights the importance of knowledge of the beneficiation and extraction processes, for researchers, incentive institutions, private industry and governmental agencies work together in pursuit of a sustainable production.

2.7 Cytotoxicity

Despite the support of the legislation, due to the large number of constituents, functional oils do not seem to have specific cellular targets (SAAD; MULLER; LOBSTEIN, 2013). As lipophilic they cross the wall and the cytoplasmic membrane, and may cause disruption of the cellular structure (BURT, 2004). Because of this, studies evaluating the cytotoxicity of these compounds are needed. In cases where the toxicity of the tested agent is unknown, it is recommended to evaluate doses up to 2,000 mg/kg (TICE et al., 2000).

With respect to CNSL, studies in rats prove that the use of up to 5 g/kg of animal weight is considered safe (SURESH AND RAJ et al., 1990). In addition, studies in broilers demonstrate the use of doses from 0.1 ml/kg to 0.3 ml/kg of food as safe (LÓPEZ et al., 2012). In ruminants, pharmacological effects were observed with doses of 3-4 g/100 kg body weight (MITSUMORI et al., 2014).

Evaluating copaiba oil-resin in rats, Gomes et al. (2007) observed that the 500 mg/kg body weight dose was well tolerated. The same researchers showed that the lethal dose (LD_{50}) was 3.9 - 4.3 g/kg body weight depending on the *Copaifera* species. Teixeira et al. (2017) using the dose of 2 g/kg body weight for albino rats observed for 48 hours,

reported no acute toxicity effects, and using 10% of the limit dose (200 mg/kg) already observed anti-inflammatory effects. In broilers Noleto et al. (2018) obtained improved performance using 2 g/kg (of food) of copaiba oil. Concerning the extracts and oils of *Schinnus molle*. L., no signs of acute or subacute toxicity were observed in Wistar rats (BRAS et al., 2010; FERRERO et al., 2007). The lethal dose (LD_{50}) of *Schinnus Molle* L. essential oil was determined by Martins et al. (2014) to be superior to 2000 mg/kg body weight. Capsaicin, on the other hand, the main component present in *Capsicum annum* L. pepper, was used at a dose of 74 mg/kg body weight in dogs. Of the 50 animals used, 9 of the test group and 5 of the control had a temporary reaction of vomiting, diarrhea, and anal itching for 3-4 days (ADASZEK et al., 2017). In rats, LD_{50} values of capsaicin is 161.2 mg/kg body weight in males and 148.1 mg/kg body weight in females (SAITO; YAMAMOTO, 1996). In dairy cows capsaicin supplementation at a much lower dose (250, 300 e 1000mg/ cow) has already shown increased immune cell activity (OH et al., 2015).

3. CONCLUDING REMARKS

Functional oils have the ability to modulate the inflammatory and antioxidant system, because of their compounds from the secondary metabolism of plants. These compounds, especially those from the Brazilian biodiversity, have the potential to be used as additives in dog and cat food. This is due to the fact that, in addition to providing health benefits, they attend a demand from tutors and industries which are concerned with the use of ingredients more natural and sustainable for the environment. However, it is still necessary to standardize and identify the type of compound used and optimize extraction processes. Furthermore, for functional oils to have better applicability, as phytogenic additives, it is important that more experimental studies evaluate the use of these compounds in dogs and cats, so that we can establish a greater correlation between in *vitro* and in *vivo* results.

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CHAPTER II - EFFECTS OF DIETARY SUPPLEMENTATION WITH A BLEND OF FUNCTIONAL OILS TO FECAL MICROBIOTA, AND INFLAMMATORY AND OXIDATIVE RESPONSES, OF DOGS SUBMITTED TO A PERIODONTAL SURGICAL CHALLENGE

Effects of dietary supplementation with a blend of functional oils to fecal microbiota, and inflammatory and oxidative responses, of dogs submitted to a periodontal surgical challenge

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Abstract

We aimed to evaluate the effects of functional oils from copaiba (*Copaifera* spp.), cashew nut shell (*Anacardium occidentale*), and pepper species (*Schinus molle* L. and *Capsicum annum L.*) on coefficients of total tract apparent digestibility (CTTAD) of nutrients, intestinal fermentative metabolites, fecal microbiota, and inflammatory and oxidative markers in dogs submitted to periodontal surgery. Two treatments were evaluated: control and test, containing the blend of functional oils (0.1 g/animal/day). The oil blend contained 280 g/kg cashew nut shell (*Anacardium ocidentalle*) oil, 60 g/kg *Capsicum annuum* L. and *Schinus molle* L. pepper species oils, and 60 g/kg copaiba (*Copaifera* spp.) oil. The treatments were offered for 35 days to 12 adult Beagle dogs, distributed in a completely randomized design (n=6). On day 30, the dogs were submitted to periodontal surgery. Fecal (days 30 and 35) and blood (days 0, 30, and 35) samples were collected for the evaluation of intestinal fermentative metabolites, fecal microbiota, and inflammatory and antioxidant responses in the blood. Dogs of the control group presented a more pronounced reduction in the genera *Prevotella* and *Faecalibacterium* after surgery (day 35) than the test group (P<0.05). Besides, dogs of the control group also presented a greater abundance of *Streptococcus* on day 35 (P<0.05). There was an increase in NF-κB concentration in the blood after surgery only in the control group (P<0.05). Additionally, dogs fed the oil blend showed lower lipid peroxidation (P<0.05) and a tendency (P=0.059) to higher glutathione transferase activity. The blend of functional oils does not alter the digestibility of nutrients and may modulate the intestinal microbiota. Furthermore, it controls the inflammatory and oxidative mechanisms after the surgical challenge in dogs.

Keywords: Capsicum annum L.; cashew nut shell oil; copaiba oil; intestinal microbiota; NF-κB; *Schinus molle* L.

Abbreviations: AHEE, acid-hydrolyzed ether extract; BCFA, branched-chain fatty acids; CAT, catalase; CF, crude fiber; CP, crude protein; CRP, C-reative protein; CTTAD, coefficients of total tract apparent digestibility; DM, dry matter; DMf, fecal dry matter; GALT, gut-associated lymphoid tissue; GE, gross energy; GSH, reduced glutathione; GST, glutathione transferase; IKα β, inhibitory protein; IKK, protein kinases; LPO, lipid peroxidation; ME, metabolizable energy; OM, organic matter; OTUs, observed taxonomic units; PCoA, principal coordinate analysis; ROS, reactive oxygen species; SCFA, short-chain fatty acids; SEM, standard error of the mean; SOD, superoxide dismutase; TLR4, Toll-like receptor.

1. Introduction

The correlation between the inflammatory process, oxidative stress, and intestinal dysbiosis in animals is already reported in the literature (Mittal et al., 2014; Minamoto et al., 2015). At the center of this relationship are the studies that evaluate the activation of transcription factors and especially their modulation through the diet.

Among the nuclear transcription factors, NF-κB has been widely studied because it responds to a large variety of immune and inflammatory receptors in the body (Sun and Ley, 2008). Activation of the NF-κB pathway is related to diseases in humans such as rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disease (Asahara et al., 1995; Schreiber et al., 1998; Hussman et al., 2016). In dogs, increased expression of this factor is suggested to be responsible for inflammation in aged animals (Alexander et al., 2018), obese patients (Li et al., 2019), and diseases such as chronic enteropathies (Luckschander et al., 2010) and cancer (Morrison et al., 2012). Besides these physiological stress conditions, surgical procedures (Desborough, 2020), including periodontal procedures in dogs (Cutando et al., 2007), and psychogenic stress situations can also alter the inflammatory and antioxidant balance of the organism (Juodžentė et al., 2018),

activating the NF-κB pathway and altering the composition of the intestinal microbiota (Topol and Kamyshny, 2013). Thus, targeting the NF-κB signaling pathway is an interesting therapeutic approach, which can be modulated by diet.

 In this context, functional oils from Brazilian biodiversity may provide benefits because they are rich in bioactive metabolites that can inhibit the NF-κB pathway (Liu et al., 2017). These additives are attracting interest from the pet food industry due to their biological action in animals, presenting the potential to be included in adjuvant foods or nutraceutical supplements. Moreover, these compounds satisfy demand from pet owners who are interested in the use of natural and environmentally sustainable ingredients (Di Cerbo et al., 2017).

In the feeding of livestock animals, functional oils from copaiba (*Copaifera* spp.), cashew nut shell (*Anacardium occidentale*), and pepper species such as *Schinus molle* L. and *Capsicum annum* L., or the use of their bioactive compounds, have been studied. Bioactive compounds include the sesquiterpene β-caryophyllene (copaiba oil) (Pinto et al., 2000; Veiga et al., 2007); monoterpenes limonene, β-phellandrene, α-phellandrene, myrcene, and α-pinene (*Schinus molle* L.) (Zahed et al., 2011; Gomes et al., 2013); polyphenols anacardic acid, cardanol, and cardol (cashew nut shell oil) (Trevisan et al., 2006; Mazzetto et al., 2009); and the alkaloid capsaicin (*Capsicum annum* L.) (Kobata et al., 1999; Nadi et al., 2020). Preliminary studies show that besides benefits for digestive function and gut microbiota, the use of functional oils provides improved productive performance in animals (Aguilar et al., 2013; Mitsumori et al., 2014; Moura et al., 2017). In dogs, studies are still lacking, but anti-inflammatory and antimicrobial actions (Pieri et al., 2010) and antioxidant and anticancer actions have been described (Adaszek et al., 2017).

Therefore, we hypothesize that the use of functional oils is beneficial for dogs undergoing post-surgical stress. In this context, we aimed to evaluate the effects of a blend of functional oils from copaiba (*Copaifera* spp.), cashew nut shell (*Anacardium occidentale*), and pepper species:

Schinus molle L. and *Capsicum annum* L. on the coefficients of total tract apparent digestibility of nutrients and palatability of the diet and on fermentative metabolites, intestinal microbiota, and inflammatory and oxidative markers in dogs submitted to periodontal surgery.

2. Material and methods

2.1 *Blend of functional oils*

The additive evaluated (Pet Pepper Phytus®, Phytus Feed, São José dos Campos, SP, Brazil) was a blend of microencapsulated functional oils powder containing cashew nut shell oil (*Anacardium ocidentalle*), *Capsicum annuum* L. and *Schinus molle* L. pepper species oils, and copaiba (*Copaifera* spp.) oil. The composition of the blend according to the manufacturer is described in Table 1

2.2 *Experiment I: Digestibility, fecal characteristics, intestinal fermentative metabolites, fecal microbiota, and blood parameters*

2.2.1. *Animals and facilities*

The use of animals for this study was approved by the Ethics Committee on Animal Use of the Agrarian Sciences Sector of the Federal University of Paraná, Curitiba, PR, Brazil, under protocol n. 018/2021. The study was conducted at the Research laboratory in canine nutrition – LENUCAN in Curitiba, Paraná, Brazil (25º 25' 40" S, 49º 16' 23" W).

Twelve adult Beagle dogs (6 years old) were used (6 males and 6 females) with a mean body weight of 13.1 ± 1.21 kg, and a mean body condition score of 5.91 ± 1.24, according to Laflamme (1997). All animals were submitted to previous clinical evaluation and were healthy.

The dogs were individually housed in brickwork kennels (5 m long x 2 m wide), containing a bed and free access to fresh water. During most of the experiment (until day 25), the dogs had free access to a grassy outdoor area of 1.137.84 m^2 for 4 hours/day for voluntary exercise and socialization. During the collection period (between days 25 and 30), the dogs were individually housed in kennels. The facilities had bars on the side walls that allowed visual and limited interaction with neighboring dogs, in addition to receiving extra attention and environmental enrichment inside the kennel during this period. The ambient temperature ranged from 16ºC to 28ºC, with a 12-h light-dark cycle (light from 6:00 am to 6:00 pm).

2.2.2. Diets

Two treatments were evaluated: control (3 males and 3 females), without supplementation of functional oils, and test (3 males and 3 females), with the supplementation of 0.1 g/animal/day of the blend of functional oils (Pet Pepper Phytus®, Phytus Feed, São José dos Campos, SP, Brazil). . The treatments were given to the animals for 35 days. The functional oil blend was weighed daily on a precision scale (MH-Series, PocketScale, China), added by coating on the diet, and homogenized by hand at the time of diet feeding. The basal diet for the experiment (used for both the control and test groups) was an extruded commercial dry food for adult dogs, that met the nutritional requirements for maintenance of adult dogs according to The European Pet Food Industry Federation (FEDIAF, 2019). The diet contained the following ingredients in its composition: poultry by-product meal, meat meal, corn, soybean meal, poultry fat, swine liver hydrolysate, sodium chloride, citric acid, antioxidants (BHT, BHA), propionic acid, vitamin A, vitamin D3, vitamin E, vitamin B1, vitamin B6, vitamin B12, vitamin K3, nicotinic acid, folic acid, biotin, calcium pantothenate, zinc sulfate, calcium iodate, sodium selenite, copper sulfate, iron

sulfate, manganese sulfate, and zinc oxide. The diet had no added functional additives that could interfere with the intestinal functionality of the animals. The chemical composition of the diet is described in Table 2.

2.2.3. Digestibility test and fecal characteristics

The digestibility assay followed the total fecal collection method recommended by the Association of American Feed Control Officials (AAFCO, 2016). The diets were offered during a 25-day adaptation period followed by 5 days of total fecal collection.

The animals were fed twice a day (08:00 a.m. and 05:00 p.m.) in amounts sufficient to supply the metabolizable energy (ME) requirement of adult dogs in maintenance as recommended by the National Research Council (NRC, 2006): ME (MJ/day) = $0.40 - 0.54 \times$ body weight$^{0.75}$. The cofactor varied among animals to maintain body weight throughout the study.

Feces were collected and weighed twice a day and stored in individual plastic bags previously identified, covered, and stored in a freezer (-14°C) to be analyzed later. At the end of the collection period, the feces were thawed at room temperature and homogenized separately, forming a composite sample from each animal. The feces were dried in a forced ventilation oven (320-SE, Fanem, São Paulo, Brazil) at 55°C for 72h or until reaching a constant weight. After drying, feces and the experimental diet were ground using a 1 mm sieve in a grinder (Arthur H. Thomas Co., Philadelphia, PA, USA) and analyzed for dry matter (DM) at 105°C for 12 hours, crude protein (CP, method 954.01), ash (method 942.05), and ether extract in acid hydrolysis (EEAH, method 942.05). All analyses followed the recommendations of the Association of Official Analytical Chemists (AOAC, 1995). The total dietary fiber, insoluble fiber, and soluble fiber of

the diet were analyzed according to Prosky (1988). Gross energy (GE) was determined in a calorimeter pump (Parr Instrument Co., Model 1261, Moline, IL, United States of America).

Fecal characteristics were evaluated during the collection period by total dry matter (DMf) content, fecal output, fecal consistency by score, ammonia, and pH. Fecal pH and ammonia were analyzed in feces collected up to 15 minutes after spontaneous defecation on days 30 and 35 of the experiment.

The fecal score was always evaluated by the same researcher, assigning points from 1 to 5, being: 1 = feces are soft and have no defined shape; 2 = feces are soft and poorly formed; 3 = feces are soft, formed, and moist; 4 = feces are well formed and consistent; 5 = feces are well formed, hard and dry, according to Carciofi et al. (2009). Fecal pH was measured using a digital pH-meter (331, Politeste Instrumentos de Teste Ltda, São Paulo, SP, Brazil) using 3.0 g of fresh feces diluted in 30 mL of distilled water. Fecal ammonia concentration was determined according to Brito et al. (2010). Briefly, 5 g of fresh feces were incubated in a 500 mL lidded glass balloon, containing 250 mL distilled water, for 1 h. Then, three drops of octyl alcohol (1-octanol) and 2 g of magnesium oxide were added to the solution, subsequently distilled in a Macro-Kjeldahl apparatus, and recovered in a beaker, containing 50 mL boric acid. Finally, ammonia was titrated using standardized sulphuric acid at 0.1N.

2.2.4 Intestinal fermentative metabolites and fecal microbiota

Stool samples for the analysis of intestinal fermentative metabolites and fecal microbiota were collected on days 30 and 35 of the experiment. For determination of short-chain (SCFA, acetate, butyrate, and propionate) and branched-chain (BCFA, isovalerate, and isobutyrate) fatty acids, fresh feces of the animals were collected up to 15 min after defecation. In a plastic container

with a lid, 10 g of stool sample was weighed and mixed with 30 mL of 16% formic acid. This mixture was homogenized and stored in a refrigerator at 4°C for a period of 3 to 5 days. After this period the solutions were centrifuged at 2500 gx (2K15, Sigma, Osterode am Hans, NI, Germany) for 15 min. At the end of centrifugation, the supernatant was separated and subjected to further centrifugation. Each sample underwent three centrifugations, and at the end of the last one, part of the supernatant was transferred to a properly labeled eppendorf tube for subsequent freezing at -14 °C. Afterward, the samples were thawed and underwent new centrifugation at 18000 gx for 15 min (Rotanta 460 Robotic, Hettich, Tuttlingen, BW, German). Both centrifugations were conducted under refrigeration (approximately 5ºC). Fecal SCFA and BCFA were analyzed by gas chromatography (Shimadzu, model GC-2014, Kyoto, Honshu, Japan), using a glass column (Agilent Technologies, HP INNO wax - 19,091N, Santa Clara, CA, United States of America) 30 m long and 0.32 mm wide. The injected volume of the supernatant was set to 1 µL. Nitrogen was used as the carrier gas with a flow rate of 3.18 mL/min. The working temperatures were 200 °C at the injector, 240 °C at the column (at a speed of 20 °C/min), and 250 °C at the flame ionization detector.

For evaluation of the fecal microbiota, approximately 2 g of sample was taken from the interior of the freshly collected stool, placed in a sterile eppendorf tube and stored in a -80 ºC freezer until the moment of the analysis.

For DNA extraction from the samples, the commercial kit "ZR Fecal DNA MiniPrep®" from Zymo Research (Zymo Research, Irvine, CA, USA) was used, following the protocol recommended by the manufacturer. The extracted DNA was quantified by spectrophotometry at 260 nm using the NanoDrop® 2000 spectrophotometer (Thermo Scientific, Wilmington, VA, USA). To evaluate the integrity of the extracted DNA, all samples were run by electrophoresis in

1% agarose gel, stained with a 1% ethidium bromide solution and visualized with ultraviolet light in a transilluminator.

A 460-base segment of the V4 hypervariable region of the 16S rRNA gene was amplified using the universal primers 515F and 806R and the following PCR conditions: 94°C for 3 min; 18 cycles of 94°C for 45 sec, 50°C for 30 sec, and 68°C for 60 sec; followed by 72°C for 10 min. From these amplifications, a metagenomic library was built using the commercial Nextera DNA Library Preparation Kit from Illumina® (San Diego, CA, USA). The amplifications were pooled and subsequently sequenced in the Illumina® "MiSeq" sequencer (Degnan and Ochman, 2012). The reads obtained on the sequencer were analyzed on the QIIME (Quantitative Insights into Microbial Ecology) platform (Caporaso et al., 2010; Caporaso et al., 2011), followed by a workflow of the removal of sequences from low quality, filtration, removal of chimeras, and taxonomic classification. To generate the classification of bacterial communities by operational taxonomic units (OTU) identification, 29600 reads per sample were used, in order to normalize the data and not compare samples with different number of reads. Sequences were classified into bacterial genera by recognizing the OTUs through identity (>97%) between sequences when compared against a database. The update named "SILVA 132" from the year 2018 of the ribosomal sequence database "SILVA database" (Yilmaz et al., 2014) was used to compare the sequences.

2.2.5 Blood parameters

Blood was collected on days 0, 30, and 35 of the experiment. Before the collections, the dogs were submitted to a 12-hours fasting period. After physical contention and antisepsis with 70% alcohol on the ventral region of the neck, 2.5 ml of blood was collected by jugular venipuncture and transferred to a tube without anticoagulant.

2.2.5.1 Pro-inflammatory and oxidative stress markers

Quantitative detection of canine NF-κB p65 (Cat No. MBS2608289) in serum was measured using a specific ELISA kit according to the manufacturer's protocol (MyBioSource, Inc, San Diego, CA, USA). The quantification of C-reactive protein was analyzed by immunoturbidimetry assay (Pesce and Kaplan, 1987).

Serum oxidative markers were evaluated by measuring the activities of the enzymes superoxide dismutase (SOD), catalase (CAT), glutathione transferase (GST), reduced glutathione (GSH), and measuring the lipid peroxidation (LPO) and plasmatic proteins. For SOD and CAT analysis, samples were homogenized in potassium phosphate buffer solution (pH 6.5) at a 1:10 dilution and centrifuged at a speed of 10000 g for 20 min under a temperature of 4˚C. SOD activity was quantified through its ability to inhibit the auto-oxidation of pyrogallol reagent (Gao et al., 1998). CAT activity was quantified according to Aebi et al. (1984). For GST analysis, samples were homogenized in potassium phosphate buffer solution (pH 6.5), at a dilution of 1:30, and centrifuged at a velocity of 10000 g for 20 min under a temperature of 4°C. GST catalyzes the conjugation reaction of the substrate CDNB (1-chloro-2,4-dinitrobenzene) with GSH, forming a thioether that can be monitored by increasing absorbance, according to the method of Habig et al. (1974). GSH levels were measured by the Sedlak and Lindsay (1968) technique. For this, samples were homogenized in potassium phosphate buffer (pH 6.5) at 1:10 dilution. Subsequently, 100μL was mixed with trichloroacetic acid (80 µL, purity grade 12.5%). The supernatant was separated by centrifugation at 3000 g for 15 min at 4°C. The LPO rate was measured by the ferrous oxidation−xylenol orange (FOX) method as described by Jiang et al. (1991). This method quantifies the formation of hydroperoxides during lipid peroxidation, as hydroperoxides oxidize iron to ferric ion and in turn, this ion binds to the xylenol orange dye. Quantification of protein in the samples was done in microplates (Bradford, 1976) using bovine albumin as a standard. 10 µL

of the sample (homogenized in potassium phosphate buffer, pH 6.5, centrifuged at 10000 g, under 4°C temperature, for 20 min, diluted 1:10) was used in each well of the microplate, which was reacted with 250 μL of Bradford's solution. The reading was performed in a microplate reader at 595 nm. The value measured for protein was used to calculate the previous parameters, expressed in mg of protein.

2.2.6 Periodontal surgery

To promote stress and inflammation in the organism, the animals were submitted to a dental prophylaxis surgery with general anesthesia on the 30th experimental day. This surgery was chosen as a challenge to the organism, considering that all dogs naturally presented periodontal disease. Previously (day 0), the animals had a clinical dental appointment to visually assess the extent of gingivitis, plaque, calculus, and any obvious signs of attachment loss, according to the American Animal Hospital Association dental care guidelines for dogs and cats (Bellows et al., 2019). This previous evaluation of the animals was used to allocate the dogs into the control and test groups, equalizing the groups according to the severity of the periodontal disease. Each experimental group (control and test) presented four dogs with degree 1 and two dogs with degree 2 of periodontal disease, according to Bellows et al. (2019).

The surgeries were performed at the Veterinary Hospital of the Federal University of Paraná (Curitiba, Brazil), after a 12-hour fasting period. The animals were premedicated with acepromazine (0.03 ml/kg body weight) (Acepran® 0.2%, Vetnil, SP, Brazil), methadone (0.3 mg/kg body weight) (Mytedom® 1%, Cristália, SP, Brazil), and ketamine (0.05-0.1 mg/kg body weight) (Ketamin®, Cristália, SP, Brazil). Anesthesia was induced with propofol (3-4 mg/kg body weight) (Propotil® 1%, BioChimico, RJ, Brazil) associated or not with an adjuvant of the

anesthesiologist's choice, such as fentanyl (2.5 µg/kg body weight) (Fentanest®, Cristália, SP, Brazil) or remifentanil (10 µg/kg body weight) (Remifas®, Cristália, SP, Brazil). After tracheal intubation, general anesthesia was maintained with isofluorane (Isoforine®, Cristália, SP, Brazil), through a universal vaporizer, dosed by bubbling. Together with isofluorane, adjuvants such as lidocaine (1 mg/kg body weight/1h) (Hypocaína® 2%; Hypofarma, MG, Brazil) and ketamine (0.6 mg/kg body weight/1h) (Ketamin®, Cristália, SP, Brazil) were used for maintenance, according to the individual needs of each animal and the anesthesiologist's choice.

Before the surgical procedure, the dogs were re-evaluated through a complete examination of each tooth and intra-oral radiography of the mouth, confirming their classification in stages 1 or 2 of periodontal disease, according to Bellows et al. (2019). The technique used in the dental prophylaxis procedure was the scaling (supragingival and subgingival plaque and calculus removal) using an ultrasonic scaler (iM3 P6, Serona Animal Health, Canada) followed by the instrumentation with a curette to further remove plaque and calculus, and tooth polishing with paste.

Postoperatively, the animals received an injectable single dose of meloxicam (0.1 mg/kg body weight) (Elo-xicam® 0.2%, Chemitec, SP, Brazil) and an injectable single dose of dipyrone (25 mg/kg body weight) (Febrax®, Lema-Injex, MG, Brazil). Oral hygiene was performed for 7 days using chlorhexidine digluconate spray solution (Periovet®, Vetnil, SP, Brazil).

2.2.7 Calculations and statistical analysis

The organic matter (OM) was calculated by: 100 – Ash.

The DMf = (DM at 55°C × DM at 105°C)/100.

The CTTAD and ME were estimated according to AAFCO (2016), based on the equations:

CTTAD = (g nutrient intake - g nutrient excreted)/g nutrient intake

ME (MJ/kg) = {kJ/g GE intake - kJ/g fecal GE - [(g CP intake - g fecal CP) × (5.23 kJ/g)]}/g feed intake.

Data were analyzed for normality by the Shapiro-Wilk test. Data with time effect (ammonia, fecal pH, SCFA, BCFA, and blood variables) and normal distribution were analyzed according to a completely randomized design in a split-plot arrangement (n=6), considering the effects of treatment, day, and the interaction between treatment and day ($P<0.05$). When an effect of the day (0, 30, and 35) or of the interaction (treatment × day) was observed, means were compared by Tukey`s test. Digestibility data and the difference (final – initial) in blood variables were analyzed by the Student t-test ($P<0.05$). Fecal score data were analyzed by Mann-Whitney's test ($P<0.05$). P-values >0.05 and <0.10 were considered a tendency.

Data of alpha-diversity indexes (Shannon, Chao1, and number of OTUs) and relative abundance of bacterial genera were analyzed by the Kruskal-Wallis test ($P<0.05$). To characterize the overall differences in fecal microbial communities among the groups, principal coordinate analysis (PCoA) was performed on unweighted UniFrac distances. The effect of treatments on beta-diversity was evaluated among groups by PERMANOVA (Permutational Multivariate Analysis of Variance) with $P<0.05$ (Anderson, 2001).

2.3 Experiment II: Palatability

2.3.1 Animals, housing, and experimental design

Sixteen adult Beagle dogs (8 males and 8 females), 6 years old with a mean body weight of 13.1± 1.21 kg were used. The health conditions and facilities were the same as described in Experiment I. The dogs were individually housed in the kennels only during the palatability test (for about 30 min per day). The experiment followed a completely randomized design.

2.3.2 Palatability test

For the palatability test, the control diet and the test diet containing the addition of 0.1g of the functional oil blend (Pet Pepper Phytus®, Phytus Feed, São José dos Campos, SP, Brazil) were compared. For each animal was offered the two diets simultaneously for two consecutive days. The amount of each diet provided was 30% higher than the NRC (2006) recommendations for maintenance of adult dogs, thus ensuring the presence of leftovers. The food remained available to the animals for 30 minutes or until they completely consumed one of the foods. The relative position of the feeders was alternated on the second day of the experiment so that the animals were not conditioned to the feeding location. The palatability test was determined using the first choice and intake ratio between the diets offered to the dogs. The first choice was defined by observing the first feeder the animal approached. To determine the intake ratio, the amount offered and the leftovers were quantified and then the following equation was used: Intake ratio = intake in g of diet A or B/ intake in g of diets A+B.

2.3.3 Statistical analyses

Intake ratio results were compared by Student t-test (P<0.05) and the first choice by Chi-square test (P<0.05), totaling 32 repetitions per test (16 dogs x 2 evaluation days).

3. Results

3.1 Experiment I

3.1.1 Digestibility test and fecal characteristics

No adverse effects to the diets were observed, such as episodes of vomiting, diarrhea, or feed refusal. There was no difference (P>0.05) in dietary intake between treatments during the 35 days of the experiment (P>0.05, Table 3). The dogs ate all the feed offered, without the presence of leftovers. The intake (mg/kg of body weight/day) of each functional oil was 2.1 mg of cashew nut shell oil, 0.5 mg of pepper species oil, and 0.5 mg of copaiba oil.

The blend of functional oils did not alter the CTTAD of nutrients and dietary ME (P>0.05, Table 3). However, there was a higher fecal score for dogs from the test group (P<0.05, Table 3) than for the control group. In addition, there was no influence of the treatments on fecal pH (P>0.05, Table 4).

3.1.2 Intestinal fermentative metabolites and fecal microbiota

There was a tendency for the fecal ammonia (P=0.050) and isobutyrate (P=0.062) concentrations to decrease in dogs fed the oil blend (Table 4). Dogs fed the oil blend had lower fecal acetate concentration (P<0.05; Table 4). Moreover, the animals fed the oil blend showed a lower concentration of isovalerate and total BCFA in the feces, regardless of the day (P<0.05; Table 4). Other fermentative metabolites did not differ between the groups (P>0.05).

A reduction in microbial diversity (Shannon index) and richness (number of OTUs and Chao1 index) after the surgical challenge was verified in both groups (P<0.05). However, dogs fed the oil blend on day 35 did not statistically differ from the control group on day 30 for all alpha-

diversity indexes (Figure 1). The PCoA analysis showed a significant (P<0.05) separation between the fecal samples from the control group after the surgical challenge (day 35) compared to the other groups (Figure 2).

A total of 146 bacterial genera were identified in fecal samples. There was a reduction in the relative abundance of *Prevotella* spp. and an increase in *Streptococcus* spp. only in the control group after surgery on day 35 (P<0.05). The *Faecalibacterium* spp. genus showed lower relative abundance in dogs of the control group after surgery (day 35) when compared to the test group on day 30 (P<0.05; Table 5).

3.1.3   Pro-inflammatory and oxidative stress markers

The NF-κB showed an effect for the period, with an increase in its concentration on day 35, after the periodontal surgery, regardless of the treatment (P<0.05; Table 6). However, when evaluating the variation in serum concentration of NF-κB between day 35 minus day 30 (before the periodontal surgery), the increase in the concentration of this marker occurred only in the control group (P<0.05; Table 6). No dietary influence on C-reactive protein was observed in any of the evaluated periods (P>0.05; Table 6).

Regarding the biomarkers of oxidative stress, there was a reduction in GSH, GST, and LPO and an increase in plasmatic proteins after the periodontal surgery in both groups (P<0.05, Table 7). Dogs fed the oil blend had lower LPO (P<0.05) and a tendency (P=0.059) to higher GST activity compared to the control group, regardless of the day. There was no difference in the other oxidative variables analyzed (P>0.05, Table 7).

3.2 *Experiment II: Palatability*

No difference was observed in the first choice, but there was a tendency (P=0.061) for a reduction in the intake ratio with the inclusion of the oil blend in the diet (P>0.05; Table 8).

4 Discussion

Due to the biological activity of functional oils in the animal, it is important to identify the impact of these additives on diet digestibility and fecal characteristics. The present study observed no effect of the use of functional oils on nutrient digestibility and dietary ME, which is consistent with studies with broiler chickens (Jamroz et al., 2005).

To better understand the biological effects of the compounds present in the oils blend, we submitted the animals to a stressful situation, through periodontal surgery with general anesthesia. It was observed that, even without the use of antibiotics, the method of stress induction used in this study caused alterations that may be suggestive of intestinal dysbiosis such as a reduction in the alpha-diversity and alterations in the composition of the intestinal microbiota (Félix et al., 2022). This result suggests three possible factors causing this unbalance: I. Tissue injury capable of activating NF-κB transcription, triggering the inflammatory response also in the gut (Alazawi et al., 2016); II. Psychogenic stressors, such as the dogs' stay in a hospital environment, different people, and noises. According to the literature, non-physiological types of stress have already been applied in dog studies, causing similar changes in the intestinal microbiota (Venable et al., 2016); III. The topical use of chlorhexidine gluconate on teeth may also provide changes in the intestinal microbiota. The solution is one of the most widely used antiseptics, acting against Gram-negative and Gram-positive bacteria, yeasts, and fungi (Leshem et al., 2022). Antibacterial properties with

activity against pathogens such as *Staphylococcus aureus* and *Enterococcus faecalis* have already been demonstrated in humans and *in vitro* (Mohammadi, 2008).

Despite the effects of surgery on the gut microbiota, the concentrations of ammonia, isovalerate, and total BCFA in the feces were lower in the animals fed the oil blend. This effect may be attributed to the fact that some compounds of functional oils, such as capsaicin, for example, are able to increase gastric and pancreatic enzyme activity, as well as saliva, mucus, and bile production (Jang et al., 2004; Manzanilla et al., 2004; Platel and Srinivasan, 2004; Windisch et al., 2008). This process may optimize protein digestion, decreasing the substrate for proteolytic bacteria, and consequently reducing the production of nitrogen compounds in the feces. This effect has already been demonstrated in pigs fed functional oils (Zhang et al., 2018), and is very important in dog nutrition. This is because excessive nitrogen compounds can be toxic to the intestinal mucosa and contribute to increasing fecal odor (Windey et al., 2012). The oil blend also had the effect of decreasing the concentration of fecal acetate. Acetate is a product of fiber fermentation, which like other SCFA can have beneficial effects on the host, such as modulating the immune system through intestinal epithelial cells (Fukuda et al., 2012; Brestoff and Artis, 2013), so the lower production associated with the oil blend was not expected. However, since the intestinal microbial ecosystem is complex, it is not possible to associate acetate production with intestinal functionality, since this SCFA is not produced by a specific group of bacteria (Félix et al., 2022).

Regarding the composition of the fecal microbiota, our study observed that the oil blend possibly influences the modulation of the intestinal microbiota, influencing some bacterial genera considered sentinel in the gastrointestinal tract of dogs, such as *Faecalibacterium* spp. and *Streptococcus* spp. (AlShawaqfeh et al., 2017). There was a decrease of the genus *Prevotella* spp. in the feces of dogs only from the control group after surgery. *Prevotella* spp. is present in the intestine of healthy dogs and its reduction may be related to intestinal dysbiosis (Guard et al., 2015).

Also, dogs fed the oil blend presented a lower relative abundance of *Streptococcus* spp. after the surgery (day 35) when compared to the control group. This genus is associated with intestinal dysbiosis in dogs and is also associated with inflammatory bowel disease (Vázquez- Baeza et al., 2016; AlShawaqfeh et al., 2017; White et al., 2017). In addition, *Streptococcus* are proteolytic bacteria, that at least in part may have contributed to the result of reduced BCFA in dogs fed the oil blend. This modulation of *Streptococcus* spp. was observed in a study with pigs (Ruzauskas et al., 2020) fed a combination of terpenes present in pepper and oregano oils, in which the control group had a higher relative abundance of this genus. One of the hypotheses for this effect is due to the antimicrobial action of terpenes, capable of acting on the stability of Gram-positive bacteria membranes, making them more permeable and causing cell death (Kubo et al., 1993; Burt, 2004; Tiwari et al., 2009; Nazzaro et al., 2013). This action has been proven both via oral topical application in dogs and *in vitro* in studies evaluating copaiba oil and *Schinus molle* L. Both studies observed the action of these oils on bacteria that cause periodontal diseases in dogs, such as *Streptococcus* spp. (Pieri et al., 2010; Alves et al., 2020).

There was a maintenance of the relative abundance of *Faecalibacterium* spp. in the feces of the dogs fed the oil blend after the surgery. *Faecalibacterium* spp. belong to the phylum Firmicutes and is considered a sentinel genus of gastrointestinal health considering that its abundance is reduced in dysbiosis and is increased when this condition improves (AlShawaqfeh et al., 2017; Félix et al., 2022). The modulation of bacterial genera of the phylum Firmicutes was also demonstrated in piglets fed functional oils (Li et al., 2018). The authors suggest that polyphenol compounds, such as anacardic acids present in cashew nut shell oil, act by suppressing the pro-inflammatory Toll-like receptor 4 (TLR4) and inhibitory protein (IκBα), regulating the NF-κB inhibition pathway. These effects have implications for the modulation of intestinal microbiota

since mucosal integrity and gut-associated lymphoid tissue (GALT) activity interfere with eubiosis (De Kivit et al., 2014; Li et al., 2019).

Dogs receiving the oil blend supplementation also presented less variation of the gut microbiota after the surgical challenge, as demonstrated by the beta-diversity results, in agreement with a study with broilers chickens (Vieira et al., 2020). The authors observed that a blend containing cashew nut oil also had the effect of maintaining the total number of bacteria after challenging the broilers (Vieira et al., 2020). Similarly, a polyphenol-rich extract increased the diversity and richness of the fecal microbiota of dogs with dysbiosis (Li et al., 2019). Such results are promising, as stressful situations are inherent in the lives of companion animals, and general changes in the microbiota can lead to acute gastrointestinal disorders (Guard et al., 2015).

The present study also observed that one action of the oil blend was to control inflammation through the NF-κB pathway. Studies have shown that this anti-inflammatory action can be attributed mainly to the compounds: copalic acid and β-cariophyllene (copaiba oil); anacardic acid, cardanol, and cardol (cashew nut shell oil); α-felandrene, β-felandrene, myrcene, limonene, and α-pinene (*Schinus molle* L.); and capsaicin (*Capsicum annum* L.) (Kim et al., 2003; Mazzetto et al., 2009; Zahed et al., 2010; Lucca et al., 2018). These compounds specifically inhibit the protein kinases (IKK) complex and prevent the degradation of the inhibitory protein Ikβ, thus preventing NF-κB transcription (Jain et al., 2016, Liu et al., 2017). Moreover, some of them show inhibitory activity superior to conventional anti-inflammatory drugs, such as dexamethasone and acetyl salicylic acid (De Souza et al., 2018).

Besides suppressing the NF-κB pathway, which has a mutual relationship with the formation of reactive oxygen species (ROS) (Valachi et al., 2018), the bioactive compounds in the blend are known to have a direct antioxidant action. This action may be related to the oxireduction capacity of the bioactive compounds, neutralizing ROS, or stimulating the action of antioxidant

enzymes such as SOD, CAT, and GST (Campos et al., 2021). In the present study, dogs receiving the oil blend presented lower LPO, than the control group, regardless of the day. A similar result was attributed to anacardic acids in the study of Carvalho et al. (2013) in mice. This happens because these phenolic compounds present in cashew nut shell oil are able to suppress a variety of pro-oxidant enzymes, involved in the production of ROS. Among these enzymes is xanthine oxidase, responsible for the metabolism of uric acid, which is one of the main producers of superoxide anions and hydrogen peroxide (Trevisan et al., 2006). In addition, these phenolic compounds can act as chelators of divalent metal ions, preventing the formation of up to 82% superoxide ions (Kubo et al., 2006).

The use of the functional oil blend in this study did not cause an increase in the activity of the antioxidant enzymes SOD and CAT probably because they were measured in the blood. Nevertheless, it is known that cashew nut shell oil, copaiba oil, and *Schinus molle* L. oil have an action on antioxidant enzymes (SOD, CAT, and GTS) when measured intracellularly (Morais et al., 2010; Eryigit et al., 2017; Campos et al., 2021). On another hand, the test group presented higher GST activity regardless of the day. GST is a family of enzymes that have catalytic functions, acting after the damage, preventing the progress, and terminating the lipid peroxidation phenomenon (Dias et al., 2004). This fact corroborates the result of the reduction in the concentration of LPO in the animals fed with the oil blend. Curiously, GST activity and LPO were lower in both control and test groups after the surgery. This may possibly have occurred through the reduction of periodontal disease which is characterized by the generation of ROS (Waddington et al., 2000) by activated phagocytes at the gingival sulcus (Katsuragi et al., 2003). From this, we suggest that the lower inflammation five days after the surgery might had attenuate the oxidation process in the body, "sparing" the consumption of GST.

In the present study, supplementation with the functional oil blend did not alter the concentration of C-reactive protein. Although this protein is synthesized in response to NF-κB-mediated cytokine release, its half-life is only 19 hours, normalizing around 36-50 hours after stimulation (Mitaka, 2005). For this reason, it is likely that its concentration returned to baseline at the time of collection, which was 5 days after the procedure.

Regarding diet palatability, it is already known that the use of functional oils may reduce consumption, due to their volatile compounds that may alter the odor or flavor of foods (Benchaar et al., 2007). Despite this, there was no difference in the consumption of the diets or refusal to feed by the dogs during the study. However, a tendency to lower intake ratio was observed during the palatability trial, probably because the blend was added by coating. Considering this result, we suggest studies adding the oil blend to the dough during the processing of diets, since it is resistant to the high temperatures of the extrusion and drying processes because it is microencapsulated (Stevanović et al., 2018).

The main limitations of the present study were the low number of animals used, which limited the statistical power for some outcomes and made unfeasible a dose-response evaluation of the blend; the lack of quantification of the bioactive compounds of the blend; and that was not conducted a metagenomic analysis of the fecal microbiota, which would bring new insights about functional information of the gut microbiome of dogs receiving the oil blend.

5   Conclusion

The inclusion of 0.1 g/animal/day of the blend of functional oils containing 280 g/kg cashew nut shell (*Anacardium ocidentalle*) oil, 60 g/kg *Capsicum annuum* L. and *Schinus molle* L. pepper species oils, and 60 g/kg copaiba (*Copaifera* spp) oil does not alter the apparent digestibility

of nutrients and the metabolizable energy of the diet. Furthermore, it may reduce the fermentation of nitrogenous compounds in the gut such as the production of ammonia and total branched-chain fatty acids. In addition, the blend seems to be able to modulate the gut microbiota, promoting the maintenance of the genus *Faecalibacterium* spp. and reducing the *Streptococcus* spp. after the surgical challenge. Finally, the use of the combination of these functional oils controlled the increase of the NF-κB and reduced the oxidative stress in dogs submitted to periodontal surgery.

Credit authorship contribution statement

Renata Bacila Morais dos Santos de Souza: Investigation, Data Curation, Writing - Original Draft, Writing - Review & Editing. **Nayara Mota Miranda Soares:** Investigation. **Taís Silvino Bastos:** Investigation. **Gislaine Cristina Bill Kaelle:** Investigation. **Simone Gisele de Oliveira:** Supervision, Writing - review & editing. **Ananda Portella Félix:** Conceptualization, Data Curation, Project administration, Writing - Review & Editing.

Declaration of competing interest

The authors declare no conflict of interest.

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Table 1.

Ingredients and chemical composition (g/kg of dry matter) of the blend of functional oils.

Item	g/kg of dry matter
Ingredients*	
Cashew nut shell oil	280
Pepper species oil	60
Copaiba oil	60
Amorphous silica	225
Cornstarch	125
Lithothamnium calcareum	250
Chemical composition	
Dry matter	970.2
Ether extract	396.5
Ash	427.5

*Each oil in the blend present 100% purity.

The ingredients and chemical composition were provided by the manufacturer.

Table 2.

Analyzed chemical composition (g/kg of dry matter) of the experimental diet.

Item	g/kg of dry matter
Dry matter	910.3
Crude protein	219.0
Ether extract in acid hydrolysis	92.7
Total dietary fiber	6.10
Insoluble fiber	4.89
Soluble fiber	1.21
Ash	78.7
Calcium	20.7
Phosphorus	10.9
Gross energy (MJ/kg of dry matter)	19.83

Table 3.

Means of feed intake, coefficients of total tract apparent digestibility (CTTAD), metabolizable energy (ME, MJ/kg), and fecal characteristics of dogs fed without (Control) or with (Test) the functional oil blend.

Item	Treatments		SEM[1]	P-*value*
	Control*	Test*		
Feed intake (g/dog/day)	190.0	181.0	5.97	0.222
CTTAD				
Dry matter	0.837	0.853	0.0069	0.467
Organic matter	0.882	0.894	0.0052	0.399
Crude protein	0.853	0.867	0.0076	0.772
Ether extract	0.912	0.924	0.0040	0.743
Gross energy	0.883	0.896	0.0051	0.512
ME (MJ/kg of dry matter)	17.50	17.76	0.102	0.512
Fecal characteristics				
Dry matter (g/kg)	375.1	406.0	11.02	0.408
Production[2] (g/day)	103.20	80.70	4.903	0.980
Score[3]	4 (3.5/4)	4 (4/4)	-	0.031

* n=6/treatment.
[1] SEM = standard error of the mean.
[2] Production = g feces produced as-is/animal/day.
[3] Score: Median (1˚/3˚ quartiles) analyzed by Mann-Whitney test (P<0.05).

Table 4.

Means of fecal pH and concentration of short-chain (SCFA) and branched-chain (BCFA) fatty acids and ammonia of dogs fed without (Control) or with (Test) the functional oil blend before (D30) and after (D35) surgery.

Item	Treatment (T)				SEM[1]	P- *value*		
	Control*		Test*			T	Day (D)	T × D
	D30	D35	D30	D35				
Fecal characteristics								
pH	6.62	6.52	6.70	6.70	0.073	0.220	0.645	0.633
SCFA (μmol/g)								
Acetate	155.34	143.56	148.18	137.80	3.951	0.016	0.213	0.935
Propionate	65.86	62.25	65.08	60.95	2.111	0.806	0.470	0.960
Butyrate	7.97	5.75	7.19	6.63	0.378	0.949	0.008	0.079
Valerate	2.38	2.23	2.07	2.00	0.083	0.198	0.395	0.767
Total SCFA	231.55	213.79	222.53	207.38	5.285	0.174	0.186	0.912
BCFA (μmol/g)								
Isovalerate	1.13	0.98	0.82	0.82	0.034	0.004	0.105	0.127
Isobutyrate	1.87	1.78	1.68	1.53	0.054	0.062	0.079	0.666
Total BCFA	3.00	2.76	2.50	2.35	0.078	0.017	0.013	0.532
Ammonia (μmol/g)	78.34	97.01	78.34	80.04	4.072	0.0502	0.170	0.267

* n=6/treatment.
[1] SEM = standard error of the mean.

Table 5.

Medians (minimum-maximum) of relative abundance (%) of the most abundant genera in the fecal microbiota of dogs fed without (Control) or with (Test) the functional oil blend before (D30) and after (D35) surgery.

Item	Control*		Test*		P-*value*
	D30	D35	D30	D35	
Prevotella	40.7[a]	11.9[b]	32.2[a]	39.5[a]	0.047
	(24.2-51.4)	(0.2-40.8)	(11.5-52.1)	(1.28-57.1)	
Megamonas	15.9	38.8	11.7	16.9	0.128
	(4.8-33.1)	(11.7-72.8)	(3.3-24.3)	(2.1-44.7)	
Faecalibacterium	5.1[ab]	2.0[b]	9.1[a]	5.5[ab]	0.005
	(1.5-8.3)	(0.6-5.3)	(5.2-13.5)	(4.4-8.4)	
Fusobacterium	5.7	3.5	4.0	3.6	0.692
	(1.8-12.5)	(1.3-15.6)	(2.5-11.5)	(2.1-14.9)	
Bacteroides	3.0	4.5	4.4	3.2	0.272
	(0.6-5.7)	(0.3-7.7)	(3.5-7.3)	(1.7-7.3)	
Blautia	1.3	1.8	2.6	2.8	0.177
	(0.8-1.6)	(0.2-2.8)	(0.8-7.0)	(1.4-8.3)	
Phascolarctobacterium	1.9	0.9	2.2	2.1	0.226
	(1.4-6.3)	(0.0-3.4)	(1.6-3.2)	(0.1-2.7)	
Collinsella	0.8	0.4	1.2	0.9	0.581
	(0.4-1.9)	(0.0-1.9)	(1.1-3.1)	(1.2-4.8)	
Catenibacterium	0.5	0.9	0.7	1.1	0.112
	(0.2-0.8)	(0.2-1.1)	(0.3-1.2)	(0.8-1.3)	
Holdemania	0.2	0.4	0.4	0.6	0.395
	(1.3-0.6)	(0.1-1.6)	(1.2-0.9)	(0.1-13.6)	
Allobaculum	0.6	1.2	0.4	0.7	0.375
	(0.1-2.5)	(0.2-2.3)	(0.3-1.2)	(0.6-0.9)	
Sutterella	1.0	0.5	0.9	0.6	0.145
	(0.5-2.3)	(0.0-1.5)	(0.8-1.3)	(0.0-1.0)	
Bifidobacterium	0.2	0.0	0.0	0.0	0.113
	(0.0-4.5)	(0.0-6.1)	(0.0-0.5)	(0.0-0.1)	
Turicibacter	0.4	0.7	0.4	0.5	0.835
	(0.1-1.0)	(0.1-1.2)	(0.2-1.0)	(0.2-1.0)	
Streptococcus	0.0[b]	0.5[a]	0.0[b]	0.1[b]	0.043
	(0.0-0.4)	(0.0-4.0)	(0.0-0.1)	(0.0-0.3)	
Clostridium	0.3	0.3	0.4	0.3	0.605
	(0.0-0.7)	(0.1-0.6)	(0.2-0.7)	(0.1-0.6)	
Dorea	0.1	0.2	0.3	0.2	0.616
	(0.1-0.3)	(0.1-0.3)	(0.1-2.0)	(0.1-0.8)	
Lactobacillus	0.1	0.1	0.0	0.0	0.784
	(0.0-1.0)	(0.0-0.7)	(0.0-0.1)	(0.0-0.1)	

* n=6/treatment.

a,b Medians followed by different superscript letters differ by Kruskal-Wallis test (P<0.05).

Table 6.

Means of concentration and serum variation of nuclear factor NF-κB (pg/ml) and C-reactive protein (CRP, mg/l) in dogs fed without (Control) or with (Test) the functional oil blend before (D30) and after (D35) surgery.

Item	Treatments (T)		SEM[1]	P-value		
	Control*	Test*		T	Day (D)	T × D
NF-κB						
Day 0	375.50[b]	421.24[a]	26.877			
Day 30	338.03[b]	417.61[a]	20.517	0.577	0.032	0.144
Day 35	510.84[a]	433.86[a]	30.448			
Variation NF-κB				P-value		
Day 30 - 0	-37.47	-3.63	34.018	0.642		
Day 35 - 30	172.82	16.25	40.637	0.047		
CRP						
Day 0	0.13[a]	0.13[a]	0.010			
Day 30	0.10[a]	0.10[a]	0.009	1.000	0.005	0.978
Day 35	0.06[b]	0.07[b]	0.019			
Variation CRP				P-value		
Day 30 - 0	-0.02	-0.03	0.010	0.880		
Day 35 - 30	-0.04	-0.03	0.018	0.870		

* n=6/treatment.
[1] SEM = standard error of the mean.
a.b Means in the same column followed by distinct letters differ by Tukey's test (P<0.05).

Table 7.

Mean concentrations of oxidative parameters and plasmatic protein concentration of dogs fed without (Control) or with (Test) the functional oil blend on day 0, before (D30), and after (D35) surgery.

Item	Treatments (T)		SEM[1]	P-*value*		
	Control*	Test*		T	Day (D)	T × D
GSH (µg GSH.ul-1)						
Day 0	52.93[a]	89.33[a]	19.019			
Day 30	7.55[b]	3.29[b]	3.977	0.605	0.001	0.345
Day 35	14.11[b]	6.49[b]	4.429			
GST (mmol.min-1.mg of protein-1)						
Day 0	10.48[a]	11.84[a]	0.840			
Day 30	10.83[a]	12.13[a]	0.937	0.059	0.006	0.832
Day 35	6.48[b]	9.02[b]	0.750			
CAT (mmol.min-1.mg of protein-1)						
Day 0	0.24	0.17	0.069			
Day 30	0.26	0.20	0.115	0.481	0.892	0.967
Day 35	0.33	0.21	0.088			
SOD (mmol.min-1.mg of protein-1)						
Day 0	162.49	157.33	4.517			
Day 30	157.38	152.78	5.363	0.305	0.720	0.550
Day 35	170.75	151.14	7.649			
LPO (mmol.min-1.mg of protein-1)						
Day 0	74.74[a]	56.50[a]	5.665			
Day 30	65.04[a]	53.64[a]	6.209	0.037	<0.001	0.860
Day 35	34.87[b]	23.33[b]	3.211			
Protein (mg.mL-1)						
Day 0	33.15[b]	34.95[b]	0.929			
Day 30	34.37[b]	34.16[b]	0.891	0.164	0.004	0.297
Day 35	36.30[a]	40.02[a]	1.145			

* n=6/treatment.

[1] SEM = standard error of the mean.

GSH= reduced glutathione; GST= glutathione transferase; CAT= catalase; SOD= superoxide dismutase; LPO= lipid peroxidation.

[a,b] Means in the same column followed by distinct letters differ by Tukey's test (P<0.05).

P>0.05 for variation (Day 30-0 and Day 35-30) for all the analyzed variables (data not shown).

Table 8.

First choice and intake ratio of the control and test diets containing the blend of functional oils.

Item	Control	Test	P-*value*
[1]First choice	21	11	>0.05
[2]Intake ratio	0.62 ± 0.42	0.38 ± 0.42	0.061

[1] First choice by Chi-square test (P< 0.05).

[2] Intake ratio by Student t-test (P<0.05).
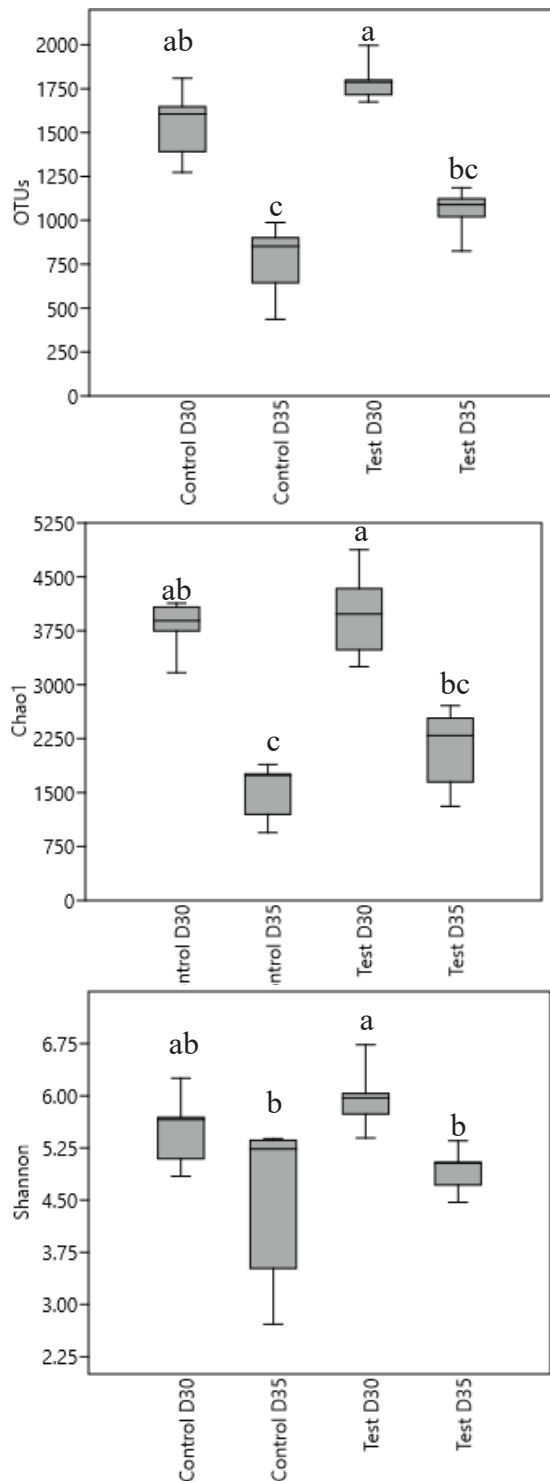
<superscript>a,b</superscript> Medians followed by distinct letters differ by the Kruskal-Wallis test (P<0.05).

Figure 1. Medians of alpha-diversity indexes of the fecal microbiota of dogs fed without (Control) or with (Test) the blend of functional oils before (D30) and after (D35) surgery.

Figure 2. Beta-diversity estimated by weighted Unifrac distance of the fecal microbiota of dogs fed without (Control) or with (Test) the blend of functional oils before (D30) and after (D35) surgery. Control group D35 differed from the other treatments by PERMANOVA (P=0.023).

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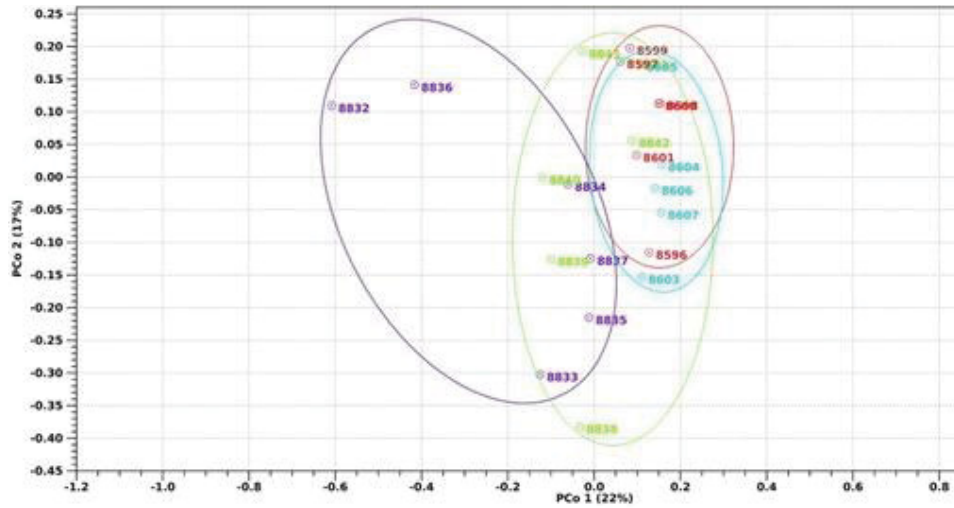ADASZEK, Ł. et al. Clinical assessment of the anti-cancer activity of the capsaicin-containing habanero pepper extract in dogs: A preliminary study. **Medycyna Weterynaryjna**, v. 73, n. 7, p. 404–411, 1 july. 2017. https://doi.org/ 10.21521/mw.5743

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APPENDIX I - ETHICS COMMITTEE

UNIVERSIDADE FEDERAL DO PARANÁ
SETOR DE CIÊNCIAS AGRÁRIAS
COMISSÃO DE ÉTICA NO USO DE ANIMAIS

CERTIFICADO

Certificamos que o protocolo número 018/2021, referente ao projeto de pesquisa **"Funcionalidade intestinal, imunidade e indicadores inflamatórios de cães alimentados com dietas contendo óleos funcionais"**, sob a responsabilidade de **Ananda Portella Félix** – que envolve a produção, manutenção e/ou utilização de animais pertencentes ao filo Chordata, subfilo Vertebrata (exceto o homem), para fins de pesquisa científica ou ensino – encontra-se de acordo com os preceitos da Lei nº 11.794, de 8 de Outubro de 2008, do Decreto nº 6.899, de 15 de julho de 2009, e com as normas editadas pelo Conselho Nacional de Controle da Experimentação Animal (CONCEA), e foi aprovado pela COMISSÃO DE ÉTICA NO USO DE ANIMAIS (CEUA) DO SETOR DE CIÊNCIAS AGRÁRIAS DA UNIVERSIDADE FEDERAL DO PARANÁ - BRASIL, com grau 2 de invasividade, em 29/04/2021.

Finalidade	Pesquisa
Vigência da autorização	Maio/2021 até Julho/2022
Espécie/Linhagem	*Canis lupus familiaris* (canino)
Número de animais	16
Peso/Idade	13,3kg – 15kg/5 anos e 9 meses
Sexo	Macho e fêmea
Origem	Laboratório de Estudos em Nutrição Canina da UFPR, Curitiba, Paraná, Brasil.

*A autorização para início da pesquisa se torna válida a partir da data de emissão deste certificado.

CERTIFICATE

We certify that the protocol number 018/2021, regarding the research project **"Intestinal functionality, immunity and inflammatory indicators in dogs fed with diets containing functional oils"** under **Ananda Portella Félix** – which includes the production, maintenance and/or utilization of animals from Chordata phylum, Vertebrata subphylum (except Humans), for scientific or teaching purposes – is in accordance with the precepts of Law nº 11.794, of 8 October 2008, of Decree nº 6.899, of 15 July 2009, and with the edited rules from Conselho Nacional de Controle da Experimentação Animal (CONCEA), and it was approved by the ANIMAL USE ETHICS COMMITTEE OF THE AGRICULTURAL SCIENCES CAMPUS OF THE UNIVERSIDADE FEDERAL DO PARANÁ (Federal University of Paraná, Brazil), with degree 2 of invasiveness, on April 29th, 2021.

Purpose	Research
Validity	May/2021 until July/2022
Specie/Line	*Canis lupus familiaris* (canine)
Number of animals	16
Weight/Age	29.2lb – 33.07lb/5 years and 9 months old
Sex	Male and female
Origin	Laboratory of Studies in Canine Nutrition of the UFPR, Curitiba, Paraná, Brazil.

*The authorization to start the research becomes valid from the date of issue of this certificate.

Curitiba, 29 de abril de 2021

Maity Zopollatto
Coordenadora pro-tempore
CEUA/AG/UFPR

Comissão de Ética no Uso de Animais do Setor de Ciências Agrárias - UFPR

APPENDIX II - DOCUMENT OF ARTICLE SUBMISSION (CHAPTER II)

Effects of dietary supplementation with a blend of functional oils to fecal microbiota, and inflammatory and oxidative responses, of dogs submitted to a periodontal surgical challenge

Renata Bacila Morais dos Santos de Souza [1] ✉, Nayara Mota Miranda Soares ✉, Taís Silvino Bastos ✉, Gislaine Cristina Bill Kaelle ✉, Simone Gisele de Oliveira ✉, Ananda Portella Félix ✉

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APPENDIX III – GUIDELINES FOR AUTHORS

The Chapter II was presented according to the Guidelines for Authors of the Journal in which the article was published. The instructions for authors can be accessed through the link below:

Animal Feed Science and Technology:

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